# Efficacy and Safety of Insulin Degludec in a Flexible Dosing Regimen vs Insulin Glargine in Patients With Type 1 Diabetes (BEGIN: Flex T1): A 26-Week Randomized, Treat-to-Target Trial With a 26-Week Extension

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**Objective:** This study investigated the efficacy and safety of insulin degludec (IDeg) once daily (OD), varying injection timing day to day in subjects with type 1 diabetes.

**Research Design and Methods:** This 26-week, open-label, treat-to-target, noninferiority trial compared IDeg forced flexible (Forced-Flex) OD (given in a fixed schedule with a minimum 8 and maximum 40 hours between doses) with IDeg or insulin glargine (IGlar) given at the same time daily OD. In the 26-week extension, all IDeg subjects were transferred to a free-flexible (Free-Flex) regimen, which allowed any-time-of-day dosing, and compared with subjects continued on IGlar.

**Results:** After 26 treatment weeks, mean glycosylated hemoglobin was reduced with IDeg Forced-Flex (−0.40%), IDeg (−0.41%), and IGlar (−0.58%). IDeg Forced-Flex noninferiority was achieved. Fasting plasma glucose reductions were similar with IDeg Forced-Flex and IGlar but greater with IDeg (−2.54 mmol/L) than IDeg Forced-Flex (−1.28 mmol/L) ($P = .021$). At week 52, IDeg Free-Flex subjects had similar glycosylated hemoglobin but greater fasting plasma glucose reductions than IGlar subjects (−1.07 mmol/L) ($P = .005$). Confirmed hypoglycemia rates (plasma glucose <3.1 mmol/L or severe hypoglycemia) were similar at weeks 26 and 52. Nocturnal confirmed hypoglycemia was lower with IDeg Forced-Flex vs IDeg (37%; $P = .003$) and IGlar (40%; $P = .001$) at week 26 and 25% lower with IDeg Free-Flex vs IGlar ($P = .026$) at week 52.

**Conclusions:** IDeg can be administered OD at any time of day, with injection timing varied without compromising glycemic control or safety vs same-time-daily IDeg or IGlar. This may improve basal insulin adherence by allowing injection-time adjustment according to individual needs. (***J Clin Endocrinol Metab*** **98: 1154–1162, 2013)**

ISSN Print 0021-972X ISSN Online 1945-7197
Printed in U.S.A.

Received August 31, 2012. Accepted January 2, 2013.
First Published Online February 7, 2013

Abbreviations: AE, adverse event; CI, confidence interval; ERR, estimated rate ratio; ETD, estimated treatment difference; ETS, extension trial set; FAS, full analysis set; FPG, fasting plasma glucose; $HbA_{1c}$, glycosylated hemoglobin; IAsp, insulin aspart; IDeg, insulin degludec; IGlar, insulin glargine; OD, once daily; PP, per protocol; PYE, patient-years of exposure; SAE, serious AE; SMPG, self-measured plasma glucose; T1DM, type 1 diabetes mellitus; T2DM, type 2 diabetes mellitus.

Long-acting insulin analogs have been developed to cover the basal requirements of patients with diabetes but current treatment options generally require same-time-daily (or even twice-daily) administration to ensure optimal glycemic control. This schedule is often in conflict with everyday variations in patients' lives and can be challenging for patients. Findings suggest that missing or delaying injections is relatively common and may result in deterioration of glycemic control (1–5). Many patients with diabetes report missing numerous injections, resulting in a significant association between self-reported noncompliance and higher glycosylated hemoglobin ($HbA_{1c}$) levels. Insulin omission frequency can be significantly affected by perceived burden of therapy (1, 6). Greater flexibility in daily injections may thus benefit all insulin-treated patients who often need to adjust dosing times.

Insulin degludec (IDeg) is a basal insulin in development for the treatment of type 1 (T1DM) and type 2 diabetes mellitus (T2DM). It has an ultralong duration of action and low variability, which produces a consistent glucose-lowering activity profile at steady state. Pharmacokinetic data have demonstrated that IDeg has a terminal half-life of approximately 25 hours, twice that of insulin glargine (IGlar), and a duration of action of more than 42 hours (7, 8). This suggests that IDeg injection time may be varied from day to day, offering patients greater convenience and flexibility, when needed.

A previous study in patients with T1DM confirmed that IDeg, administered at the same time once daily (OD), effectively reduced $HbA_{1c}$ and fasting plasma glucose (FPG), with lower risk for nocturnal hypoglycemia than IGlar (9). The aim of our study was to investigate whether greater flexibility in basal insulin injection timing could be achieved with IDeg in patients with T1DM without compromising efficacy or safety. We therefore designed a study to test the hypothesis that flexibly dosed IDeg would provide glycemic control comparable with conventional basal insulin regimens without compromising safety.

## Research Design and Methods

### Study design and participants

This was a 26+26-week, randomized, controlled, open-label, multinational, parallel-design, treat-to-target, noninferiority trial comparing the efficacy and safety of IDeg and IGlar, administered sc OD in basal-bolus therapy, with insulin aspart (IAsp) at mealtimes. The main study compared IDeg in a forced-flexible regimen (IDeg Forced-Flex) with IDeg and IGlar administered at the same time daily (3 treatment arms). An extension compared safety and efficacy of IDeg given in a free-flexible regimen (IDeg Free-Flex) with IGlar (2 treatment arms). For detail please see Supplemental Figure 1 Journals Online web site at http://jcem.endojournals.org. The trial was conducted in accordance with the Declaration of Helsinki (10) and good clinical practice guidelines (11). Informed consent was obtained separately for the main and extension periods. The protocol and consent form were approved by local independent ethics committees or institutional review boards before trial initiation.

Adults 18 years old or older with T1DM on basal-bolus therapy, with $HbA_{1c}$ 10.0% or less and body mass index 35.0 $kg/m^2$ or less participated. Basal insulin allowed at screening included IGlar, insulin detemir, or NPH insulin (as 1 or 2 daily injections) and 3 or more daily injections of bolus insulin (IAsp, insulin lispro, insulin glulisine, or human insulin); see Supplemental Data for inclusion/exclusion criteria.

### Randomization and masking

Eligible participants were randomized 1:1:1, using a central interactive voice/web response system, to receive IDeg (100 U/mL, 3 mL FlexPen; Novo Nordisk, Bagsvaerd, Denmark) (given in either the Forced-Flex regimen or at the same time daily) or IGlar (Lantus, 100 U/mL, 3 mL SoloStar; Sanofi, Paris, France), in combination with mealtime IAsp (NovoRapid/NovoLog, 100 U/mL, 3 mL FlexPen; Novo Nordisk). Trial-product masking was maintained for titration surveillance monitors and statistical and medical personnel until data were locked for analysis. Ongoing masked-data safety surveillance was performed by an internal Novo Nordisk Safety Committee and an independent, external committee adjudicated cardiovascular events in accordance with predefined classifications.

### Procedures

Eligible participants were switched to OD IDeg or IGlar with mealtime IAsp at randomization (week 0). If previous basal insulin was dosed OD, initial doses were transferred 1:1 for IDeg and IGlar. If previous basal insulin was dosed more than OD, total daily basal dose was calculated and transferred 1:1 for IDeg, with dose reduction considered by the investigator's judgment. For transfer to IGlar, a 20%–30% dose reduction was recommended, based on current prescribing information (12). Participants switched pretrial bolus insulin to IAsp 1:1 at the pretrial dose (Supplemental Data). At the end of the main and extension periods, basal insulin was switched to NPH insulin for 7 days to minimize interference with antibody detection at a follow-up visit performed 1 week later.

The trial was approximately 56 weeks including one screening week, two 26-week treatment periods, and two 7- to 12-day follow-up wash-out periods (Supplemental Figure 1). The main period compared IDeg Forced-Flex [IDeg administered on Monday, Wednesday, and Friday mornings and on Tuesday, Thursday, Saturday, and Sunday evenings; ie, at fixed intervals with a minimum of 8 and a maximum of 40 hours between injections (Supplemental Data)] with IDeg (given OD with the evening meal) and with IGlar (given OD at the same time daily). All participants randomized to IDeg in the main study were offered participation in the extension with instructions to take IDeg OD at any time of day (IDeg Free-Flex), provided they maintained a minimum of 8 and a maximum of 40 hours between doses. Patients randomized to IGlar in the main period who entered the extension continued the same-time-daily IGlar.

A treat-to-target approach was used for optimal glycemic target attainment. Basal insulin doses in all groups were to be self-adjusted on Mondays, Wednesdays, and Fridays based on mean prebreakfast self-measured plasma glucose (SMPG) values

of the preceding 2–3 days and titrated to a prebreakfast SMPG target of 4.0–5.0 mmol/L (titration algorithm details in Supplemental Data). Bolus doses were titrated to a mean premeal SMPG target of less than 5.0 mmol/L.

The primary end point was change in $HbA_{1c}$ from baseline after 26 weeks. Other efficacy assessments included laboratory-measured FPG and SMPG profiles. Glucose measurements were performed with drawn capillary blood automatically calibrated to plasma-equivalent glucose values. Safety variables included adverse events (AEs), hypoglycemic episodes, insulin dose, body weight, antibodies, and standard laboratory and clinical safety assessments. Confirmed hypoglycemia was defined as blood glucose measurements of less than 3.1 mmol/L or severe episodes requiring assistance (13). Hypoglycemic episodes occurring between 0001 and 0559 hours (inclusive) were classified as nocturnal.

Laboratory analyses were conducted at central laboratories (Quintiles Laboratories Europe, West Lothian, United Kingdom, and Quintiles Laboratories Limited, Marietta, Georgia). Antibody analyses were performed at Celerion Switzerland AG (Fehraltorf, Switzerland), using a validated RIA method (14, 15).

### Statistical analyses

The primary objective was to confirm the noninferiority of IDeg Forced-Flex to IGlar in $HbA_{1c}$ change from baseline to week 26. Noninferiority was confirmed if the upper limit of the 2-sided 95% confidence interval (CI) for the treatment difference for mean change in $HbA_{1c}$ was 0.4% or less, as recommended by regulatory guidelines (16). Sample size was determined on the basis of the primary objective under the assumption of a 1-sided *t* test of size 2.5%, a zero mean treatment difference, and standard deviation of 1.1% for $HbA_{1c}$. A total of 486 participants had to be randomized for 85% or greater power in the evaluation of the per-protocol (PP) analysis set to demonstrate noninferiority at 0.4%, after adjustment for a 15% dropout rate. The extension investigated long-term safety and efficacy of IDeg (given during the extension in a Free-Flex dosing regimen) vs IGlar.

Statistical analyses of efficacy end points, hypoglycemia, and body weight included all randomized participants [full analysis set (FAS)], following the intention-to treat principle. All other safety end points were evaluated in participants exposed to treatment (safety analysis set). Missing values were imputed using last observation carried forward (16). Comparisons between IDeg Forced-Flex and IGlar and between IDeg Forced-Flex and IDeg were made after 26 treatment weeks. IDeg Free-Flex and IGlar were compared after 52 weeks of treatment.

Baseline characteristics, demographics, AEs, and hypoglycemic episodes were presented using descriptive statistics. Treatment differences in $HbA_{1c}$, FPG, SMPG, and body weight after 26 and 52 weeks were estimated by ANOVA with treatment, insulin therapy at screening, sex, and region as fixed factors and age and relevant baseline value as covariates. The robustness of results for change in $HbA_{1c}$ was explored by additional analyses including analysis on the PP set. Estimated rate ratios (ERRs) of hypoglycemic episodes were made using a negative binomial regression model including the same fixed factors with age as covariate and using the log of exposure time as offset, using all reported treatment-emergent episodes in randomized subjects. A mixed-effect model was fitted to 9-point SMPG profile data with treatment, time, interaction between treatment and time, insulin therapy at screening, sex, and region as fixed factors; age as covariate; and subject as random effect. Analyses were repeated for $HbA_{1c}$, treatment-emergent hypoglycemic episodes, antibodies, and central laboratory parameters at 52 weeks using the extension trial set (ETS; subjects who attended the first visit of the extension trial) to assess stability of key results. Data were reported using a 95% CI and *P* values for 2-sided testing at $\alpha = .05$.

This trial is registered at www.clinicaltrials.gov: NCT01079234.

## Results

Of the 493 randomized participants, 490 (99.4%) received trial drug, and most [84.1% (138 of 164) IDeg Forced-Flex, 84.2% (139 of 165) IDeg, and 92.7% (152 of 164) IGlar] completed the main trial. The percentage of participants withdrawn during the main trial from the IDeg Forced-Flex (15.9%) and IDeg (15.8%) groups was higher than from the IGlar group (7.3%); see Supplemental Figure 2 and Supplemental Table 1 for details. More withdrawal-related AEs, including hypoglycemic episodes, occurred among IDeg-treated subjects, although the numbers overall were low. Slightly more IDeg-treated subjects met withdrawal criteria as specified in the protocol or were withdrawn for reasons classified as "Other". Of 277 IDeg-treated main trial completers, 239 entered the extension into the IDeg Free-Flex arm and 67.8% (223 of 329) of those randomized in the main trial completed the extension. Of 152 IGlar-treated main trial completers, 133 entered the extension and 74.4% (122 of 164) of those randomized in the main trial completed the extension. The pattern and the percentage of participants withdrawn during the extension were similar with IDeg Free-Flex (4.9%) and IGlar (6.7%).

Baseline characteristics were representative of a T1DM population with moderate glycemic control (mean $HbA_{1c}$ 7.7%, Table 1). Treatment groups were well matched at baseline. The pretrial insulin regimen of most participants [70.6% (348 of 493)] comprised once-daily basal injection with 3 or more bolus doses daily. IGlar and IAsp were used by 63.7% (314 of 493) and 50.9% (251 of 493) of participants, respectively, before entering the trial. The following proportions of subjects took basal insulin OD and more than OD, respectively, at screening: IDeg Forced-Flex, 68.3% (112 of 164) and 31.7% (52 of 164), IDeg, 70.9% (117 of 165) and 29.1% (48 of 165), and IGlar, 72.6% (119 of 164) and 27.4% (45 of 164).

Consistent with the treat-to-target methodology, the observed mean decrease in $HbA_{1c}$ from baseline to week 26 was similar among IDeg Forced-Flex (−0.40% points), IDeg (−0.41% points), and IGlar (−0.58% points; Figure 1A) groups. The primary objective of the trial was met because IDeg Forced-Flex was shown to be noninferior to

**Table 1.** Demographics and Baseline Characteristics: Full Analysis Set

| Characteristic | IDeg Forced-Flex + IAsp[a] | IDeg + IAsp[a] | IGlar + IAsp |
|---|---|---|---|
| Participants in the FAS, n | 164 | 165 | 164 |
| Female/male, n (%) | 62 (37.8)/102 (62.2) | 71 (43.0)/94 (57.0) | 76 (46.3)/88 (53.7) |
| Race: white/black/Asian/other, n (%) | 158 (96.3)/5 (3.0)/ 1 (0.6)/0 (0.0) | 161 (97.6)/3 (1.8)/ 0 (0.0)/1 (0.6) | 162 (98.8)/1 (0.6)/ 1 (0.6)/0 (0.0) |
| Age, y | 42.6 (13.4) | 44.5 (13.1) | 44.1 (12.6) |
| Body weight, kg | 81.7 (15.5) | 79.5 (15.5) | 80.4 (15.6) |
| Duration of diabetes, y | 17.3 (12.2) | 20.0 (12.5) | 18.2 (11.9) |
| $HbA_{1c}$, % | 7.7 (1.0) | 7.7 (0.9) | 7.7 (0.9) |
| FPG, mmol/liter | 9.6 (4.1) | 10.0 (4.0) | 9.7 (4.2) |
| Antidiabetic treatment regimen at screening, n (%) | | | |
| Basal-bolus therapy | 163 (99.4%) | 165 (100.0%) | 164 (100.0%) |
| Basal TID + bolus TID or more | 1 (0.6%) | | |
| Basal BID + bolus TID or more | 50 (30.5%) | 48 (29.1%) | 44 (26.8%) |
| Basal OD + bolus TID or more | 112 (68.3%) | 117 (70.9%) | 119 (72.6%) |
| Basal OD + premix TID[b] | | | 1 (0.6%)[b] |
| Other[c] | 1 (0.6%) | | |
| Premix BID[c] | 1 (0.6%)[c] | | |
| Insulin at screening, n (%) | | | |
| Basal | 163 (99.4%) | 165 (100.0%) | 164 (100.0%) |
| Insulin glargine | 107 (65.2%) | 107 (64.8%) | 100 (61.0%) |
| Insulin detemir | 44 (26.8%) | 43 (26.1%) | 47 (28.7%) |
| NPH insulin | 11 (6.7%) | 14 (8.5%) | 17 (10.4%) |
| Insulin detemir + NPH insulin | 1 (0.6%) | | |
| Human insulin | | 1 (0.6%) | |
| Bolus | 163 (99.4%) | 165 (100.0%) | 163 (99.4%) |
| Insulin analog (aspart, lispro, glulisine) | 149 (90.9%) | 159 (96.4%) | 156 (95.1%) |
| Human insulin | 14 (8.5%) | 6 (3.6%) | 7 (4.3%) |
| Premix | 1 (0.6%)[c] | | 1 (0.6%)[b] |

Abbreviations: BID, twice daily; TID, 3 times daily. Data are presented as mean (SD) unless stated otherwise.

[a] Subjects randomized to the IDeg Forced-Flex and IDeg treatment arms during the main trial period had the opportunity to continue in the IDeg Free-Flex arm after 26 weeks of treatment.

[b] One subject was randomized to IGlar, although her antidiabetic treatment regimen at screening was basal OD plus premix insulin TID. She was withdrawn from the study.

[c] One subject was randomized to IDeg Forced-Flex, although his antidiabetic treatment regimen at screening was BID premix insulin; he was not withdrawn because this deviation was discovered late in the trial. He was included in the FAS but was ineligible to enroll in the extension.

IGlar in reducing $HbA_{1c}$ [estimated treatment difference (ETD) ($IDeg_{Forced\text{-}Flex}$-IGlar): 0.17% points (0.04; 0.30)$_{95\%CI}$]. The robustness of the primary analysis was further supported by PP and additional sensitivity analyses (Supplemental Table 2). There was no difference in observed mean decrease in $HbA_{1c}$ from baseline to week 26 between IDeg Forced-Flex (−0.40% points) and IDeg (−0.41% points); ETD [$IDeg_{Forced\text{-}Flex}$-IDeg]: 0.01% points [−0.13; 0.14]$_{95\%CI}$.

Laboratory-measured FPG decreased from baseline to week 26 (IDeg Forced-Flex, −1.28; IDeg, −2.54; IGlar, −1.33 mmol/L), with the most pronounced decline occurring during the first 12 weeks (Figure 1B). No significant difference was seen with IDeg Forced-Flex vs IGlar (Supplemental Table 2), but a greater reduction was seen with IDeg than with IDeg Forced-Flex [ETD ($IDeg_{Forced\text{-}Flex}$-IDeg): 0.95 mmol/L (0.15; 1.75)$_{95\%CI}$, $P = .021$]. After 26 weeks, observed 9-point SMPG means appeared similar among groups. Despite varying dosing times with IDeg Forced-Flex, the only difference in SMPG vs IGlar was before lunch [ETD ($IDeg_{Forced\text{-}Flex}$-IGlar): 0.85 mmol/L (0.12; 1.57)$_{95\%CI}$, $P = .022$]. The proportion of participants who attained prebreakfast SMPG target less than 5.0 mmol/L at week 26 was 11.3% (IDeg Forced-Flex), 23.8% (IDeg), and 18.4% (IGlar). The median time to achieving the prebreakfast titration target for the first time was 7 weeks (IDeg Forced-Flex), 4 weeks (IDeg), and 6 weeks (IGlar).

Although mean $HbA_{1c}$ values increased slightly from 26-week levels during the extension, they remained below baseline at week 52; −0.13% points from baseline to 7.6% (IDeg Free-Flex) and −0.21% points from baseline to 7.5% (IGlar). IDeg Free-Flex was not significantly different from IGlar in lowering $HbA_{1c}$ in the FAS or ETS at week 52, with an upper 95% CI limit below a predefined noninferiority mark of 0.4% (Supplemental Table 2). Mean FPG decreased from baseline to week 52 with IDeg Free-Flex (−1.73 mmol/L) and IGlar (−0.61 mmol/L),

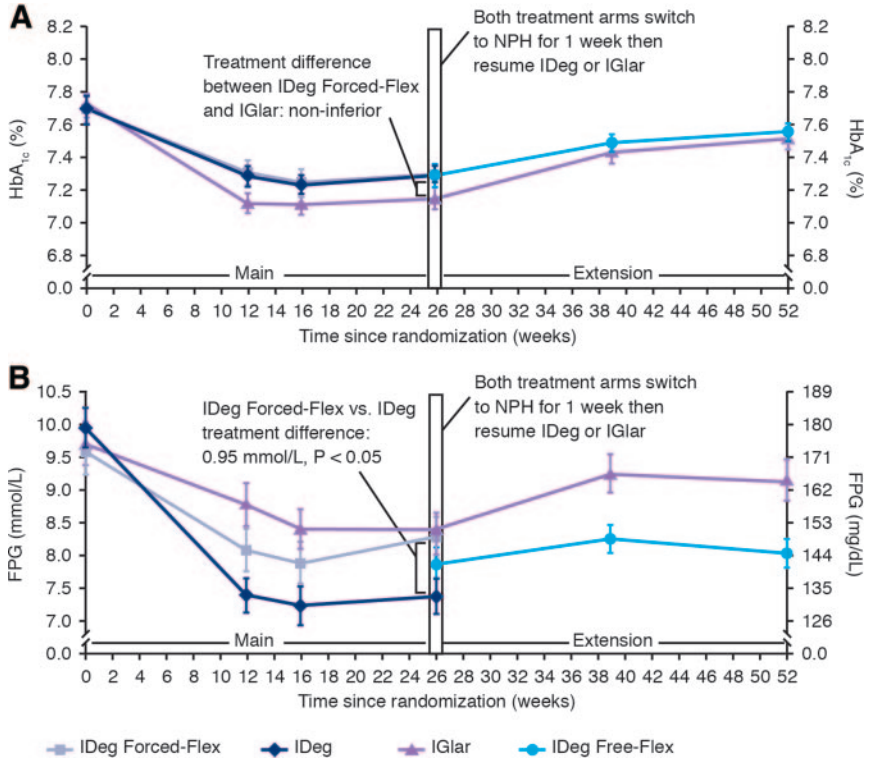


**Figure 1.** Glycemic efficacy: mean $HbA_{1c}$ ± SEM over time (A) and mean FPG ± SEM over time (B). Plotted data are reported mean values for all randomized participants (FAS). Estimated treatment differences are based on FAS. Last observation carried forward is used for each postbaseline time point in A and B. Subjects randomized to the IDeg Forced-Flex and IDeg treatment arms during the main trial period had the opportunity to continue in the IDeg Free-Flex arm after 26 weeks of treatment.

with significantly greater reduction observed with IDeg Free-Flex [ETD ($IDeg_{Free\text{-}Flex}$-IGlar): −1.07 mmol/L (−1.82; −0.32)$_{95\%CI}$, $P$ = .005]. Mean 9-point SMPG profiles decreased from baseline to week 52 in both groups. At week 52, SMPG profiles were similar at all time points except at 90 minutes after the main evening meal, when it was significantly lower with IDeg Free-Flex [ETD ($IDeg_{Free\text{-}Flex}$-IGlar): −0.82 mmol/L (−1.53; −0.12)$_{95\%CI}$, $P$ = .022]. The proportion of participants who attained prebreakfast SMPG < 5.0 mmol/L at week 52 was 17.9% (IDeg Free-Flex) and 13.8% (IGlar).

Mean basal doses increased slightly during weeks 0–26 with IDeg Forced-Flex and IGlar. However, basal doses remained stable with IDeg during weeks 0–26 and in the IDeg Free-Flex and IGlar groups from week 27 to week 52. Mean daily IAsp doses increased slightly during the main period in the IGlar group. At week 52, mean daily basal, bolus, and total insulin doses were lower by 4%, 18%, and 11%, respectively, with IDeg Free-Flex vs IGlar. The greater mean total daily insulin dose with IGlar vs IDeg Free-Flex was due mainly to a decrease in mean daily bolus insulin dose with IDeg Free-Flex (0.39 to 0.35 U/kg) and an increase with IGlar (0.40 to 0.42 U/kg; Table 2).

Overall, confirmed and severe hypoglycemia rates were similar across groups at week 26 (Figure 2 and Supplemental Table 3). The nocturnal confirmed hypoglycemia rate was significantly lower with IDeg Forced-Flex than IGlar [by 40%; ERR ($IDeg_{Forced\text{-}Flex}$/IGlar): 0.60 (0.44; 0.82)$_{95\%CI}$, $P$ = .001] and IDeg [by 37%; ERR ($IDeg_{Forced\text{-}Flex}$/IDeg): 0.63 (0.46; 0.86)$_{95\%CI}$, $P$ = .003]. Nocturnal confirmed hypoglycemia rates were generally lower with IDeg Forced-Flex than with IGlar and IDeg, regardless of the day of the week (Supplemental Table 4). No significant difference in overall confirmed hypoglycemia was seen at week 52 between IDeg Free-Flex and IGlar in the FAS or ETS. Although the number of events was small, the severe hypoglycemia rate was numerically lower in the FAS and significantly lower by 53% [ERR ($IDeg_{Free\text{-}Flex}$/IGlar): 0.47 (0.23; 0.94)$_{95\%CI}$, $P$ = .033] in the ETS with IDeg Free-Flex. Nocturnal confirmed hypoglycemia rates were significantly lower with IDeg Free-Flex by 25% [ERR ($IDeg_{Free\text{-}Flex}$/IGlar): 0.75 (0.58; 0.97)$_{95\%CI}$, $P$ = .026] in the FAS and by 27% [ERR ($IDeg_{Free\text{-}Flex}$/IGlar): 0.73 (0.54; 0.98)$_{95\%CI}$, $P$ = .035] in the ETS.

Rates for AEs were 443 (IDeg Forced-Flex), 550 (IDeg), and 527 (IGlar) per 100 patient-years of exposure (PYE) from week 0 to week 26 and 447 (IDeg Free-Flex) and 481 (IGlar) per 100 PYE from week 0 to week 52. Most AEs were mild or moderate and considered unrelated to basal insulin, with no treatment-specific patterns observed (Supplemental Tables 5 and 6). Injection-site reaction rates were low over 52 weeks, with 6 (IDeg Free-Flex) and 4 (IGlar) events per 100 PYE; no reactions were classified as serious. Mean weight gain from baseline to week 26 and during the extension was modest, with no between-group differences at week 52 (IDeg Free-Flex, 1.3 kg; IGlar, 1.9 kg; Supplemental Table 2).

Serious AEs (SAEs) were reported by 5.5% (IDeg Forced-Flex), 4.2% (IDeg), and 5.0% (IGlar) of participants from week 0 to week 26 and by 7.6% (IDeg Free-Flex) and 7.5% (IGlar) of participants in total from week 0 to week 52 (Supplemental Table 5). Of randomized subjects who did not enter the extension, 10.0% (5 of 50) IDeg Forced-Flex, 2.5% (1 of 40) IDeg, and 6.5% (2 of 31) IGlar-treated subjects reported SAEs during the main period. Of randomized subjects who entered the extension,

**Table 2.** Mean Daily Insulin Dose (SD): Safety Analysis Set

| Main Period (Wks 0–26) | IDeg Forced-Flex (U/kg) | IDeg (U/kg) | IGlar (U/kg) | Mean Ratio (U/kg)[a] |
|---|---|---|---|---|
| Participants, n | 164 | 165 | 161 | |
| Basal | | | | |
| Week 1 | 0.35 (0.18) | 0.34 (0.14) | 0.35 (0.14) | N/A |
| Week 26 | 0.42 (0.25) | 0.38 (0.23) | 0.42 (0.23) | $IDeg_{Forced-Flex}$/IGlar: 1.01<br>$IDeg_{Forced-Flex}$/IDeg: 1.11 |
| Bolus | | | | |
| Week 1 | 0.41 (0.39) | 0.36 (0.24) | 0.40 (0.18) | N/A |
| Week 26 | 0.35 (0.15) | 0.33 (0.23) | 0.42 (0.46) | $IDeg_{Forced-Flex}$/IGlar: 0.83<br>$IDeg_{Forced-Flex}$/IDeg: 1.08 |
| Total daily insulin dose (basal + bolus) | | | | |
| Week 1 | 0.75 (0.45) | 0.70 (0.30) | 0.75 (0.23) | N/A |
| Week 26 | 0.77 (0.33) | 0.70 (0.39) | 0.84 (0.61) | $IDeg_{Forced-Flex}$/IGlar: 0.92<br>$IDeg_{Forced-Flex}$/IDeg: 1.10 |
| Basal/bolus split of total daily insulin dose | | | | |
| Week 1 | 46/54 | 49/51 | 47/53 | N/A |
| Week 26 | 54/46 | 53/47 | 50/50 | N/A |
| **Main and Extension Period (wks 0–52)** | **IDeg Free-Flex (U/kg)** | | **IGlar (U/kg)** | **Mean Ratio (U/kg)[a]** |
| Participants, n | 329 | | 161 | |
| Basal | | | | |
| Week 1 | 0.35 (0.16) | | 0.35 (0.14) | N/A |
| Week 52 | 0.40 (0.25) | | 0.42 (0.24) | $IDeg_{Free-Flex}$/IGlar: 0.96 |
| Bolus | | | | |
| Week 1 | 0.39 (0.32) | | 0.40 (0.18) | N/A |
| Week 52 | 0.35 (0.19) | | 0.42 (0.41) | $IDeg_{Free-Flex}$/IGlar: 0.82 |
| Total daily insulin dose (basal + bolus) | | | | |
| Week 1 | 0.73 (0.38) | | 0.75 (0.23) | N/A |
| Week 52 | 0.73 (0.36) | | 0.81 (0.60) | $IDeg_{Free-Flex}$/IGlar: 0.89 |
| Basal/bolus split of total daily insulin dose | | | | |
| Week 1 | 47/53 | | 47/53 | N/A |
| Week 52 | 54/46 | | 50/50 | N/A |

Abbreviation: N/A, not applicable. Subjects randomized to the IDeg Forced-Flex and IDeg treatment arms during the main trial period had the opportunity to continue in the IDeg Free-Flex arm after 26 weeks of treatment. The data for IDeg Forced-Flex and IDeg arms from the first 26 weeks were pooled into the IDeg Free-Flex arm in this table.

[a] Mean ratio is the unadjusted ratio between mean doses at last treatment visit, in which missing data are imputed using last observation carried forward. Values are observed mean (SD) for the safety analysis set.

3.5% (4 of 114) IDeg Forced-Flex, 4.8% (6 of 125) IDeg, and 4.5% (6 of 133) IGlar-treated subjects reported SAEs during the main period. SAEs were distributed similarly among groups; few were considered related to the trial product and the most frequently reported SAEs were related to hypoglycemia (Supplemental Table 7). Three AEs were adjudicated as major adverse cardiovascular events; none was fatal. One death, suicide by assumed-intentional insulin overdose, occurred in an IDeg-treated female participant 158 days after starting the trial drug.

Concentrations of IDeg-specific antibodies and antibodies cross-reacting between IDeg and human insulin were low during the main and extension periods (Supplemental Table 8), with no apparent association between the development of antibodies and $HbA_{1c}$ or insulin dose (data not shown). No clinically relevant treatment-related differences were noted in physical examination findings, vital signs, electrocardiograms, funduscopy, or laboratory measurements.

## Discussion

Intensive insulin therapy in clinical trials is associated with lower rates of diabetes complications versus nonintensive therapy in people with T1DM and is presently considered the standard of care (13). Basal-bolus regimens with insulins designed to closely mimic a physiologic profile allow many patients to reach glycemic targets. However, issues related to variability of action (leading to unexpected hypoglycemia), and the need to adapt one's lifestyle to the action profile of a prescribed insulin, can prevent the achievement of good glycemic control in a safe manner. IDeg's duration of action exceeds 42 hours, providing full 24-hour basal insulin coverage and offering a consistent glucose-lowering effect, thus potentially allowing administration within a broader dosing window (7, 8).

In the present study, the aim was to evaluate whether IDeg dosed in a flexible regimen would be safe and effective in patients with T1DM. The prebreakfast titration

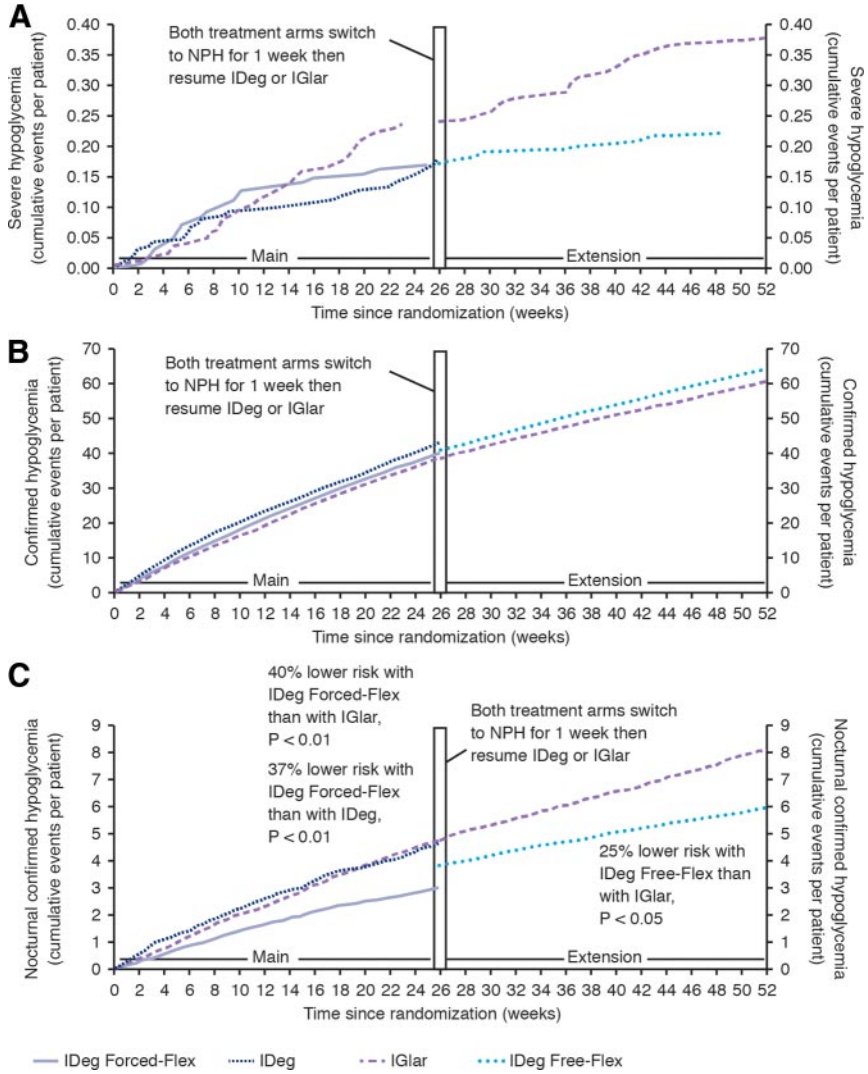


**Figure 2.** Hypoglycemia over time, weeks 0–52: severe hypoglycemia (A); overall confirmed hypoglycemia (B); and nocturnal confirmed hypoglycemia (C). Cumulative event rates are based on safety analysis set. Percentage risk reductions refer to delta risks based on estimated rate ratios (FAS). Subjects randomized to the IDeg Forced-Flex and IDeg treatment arms during the main trial period had the opportunity to continue in the IDeg Free-Flex arm after 26 weeks of treatment.

target 4.0–5.0 mmol/L was narrower than targets described in some other intensive T1DM basal-bolus trials (17); however, given that the pharmacokinetic profile of IDeg shows potential to lower hypoglycemic risk compared with current therapies (8, 18) and other recent trials in patients with T2DM and T1DM have investigated comparably low titration targets (19–23), an ambitious target was considered appropriate and the ultimate decision regarding insulin dose was the investigator's.

This was a novel trial both for investigators and participants because it challenged deeply ingrained habits by asking people with long-standing T1DM to inject basal insulin at varying daily time points while simultaneously aiming for the ambitious FPG targets considered attainable given IDeg's pharmacokinetic profile. Over 26 weeks, the Forced-Flex regimen proved effective (noninferior) compared with IGlar and IDeg and, even more importantly, proved safe. Flexibly dosed IDeg demonstrated lower rates of nocturnal hypoglycemia than IGlar, reaffirming findings of previous phase 2 and 3 trials (9, 24). However, this trial was unique in that it captured daily 4-point SMPG, which may partially explain higher overall hypoglycemia rates observed in this study vs a previous trial that compared OD IDeg and IGlar in patients with T1DM (9). Analysis between IDeg and IGlar OD at 26 weeks was not a prespecified end point within this trial, and thus, no statistical analysis was performed, although observed efficacy and safety data are presented for each of the 3 treatment arms through week 26. This comparison has been evaluated in other studies in patients with T1DM (9) and T2DM (25).

Full-year results confirmed findings from the 26-week main trial, with the extension allowing all IDeg subjects the option to dose more flexibly than at same time daily. This is important because such an option would positively impact patients' abilities to lead the type of modern, hectic lives typical of people with T1DM, including travel, dining out, changing bedtimes, etc, without compromising glucose control or safety.

Limitations of this study include a smaller population size compared with previous IDeg studies; the relatively short time frame of the Forced-Flex regimen; and different recommendations for transferring subjects on more-than-OD basal insulin to IDeg and IGlar at the study's start (total basal dose was transferred 1:1 for IDeg, as is standard for switching long acting insulins, but reduced 20%–30% for IGlar [12]). More IDeg- than IGlar-treated participants withdrew from the trial during the main period; the rates of withdrawal could be related to the demanding nature of the study (particularly in the Forced-Flex arm), including frequent blood glucose measurement requirements and study visits. However, reasons for withdrawal among the 3 treatment arms were sufficiently varied that no clear explanation for the higher rate in the IDeg arms could be identified.

Data were not collected on dosing times during the extension; therefore, it is unknown how many IDeg Free-Flex participants varied dosing times. This was an open-label trial, and investigators may have been more alert in their management and documentation of the IDeg Forced-Flex arm than the IDeg or IGlar arms; caution on the part of investigators and subjects may partially explain some differences (such as in FPG and nocturnal confirmed hypoglycemia) in study results between IDeg Forced-Flex and IDeg. Additionally, the 2 insulins tested used different delivery devices and unavailability of placebo-filled devices precluded double-dummy masking (although such a design may be considered unethical in patients with T1DM due to the 8 or more daily injections required).

The authors do not advocate stretching insulin-dose timing to these limits in clinical practice, but this study has important implications for patients with T1DM and may herald a departure from restrictive dosing regimens. This trial demonstrates that IDeg's ultralong duration of action allows variation of daily administration times without compromising efficacy or safety in patients with T1DM who require multiple daily injections. It offers patients and clinicians insight into using this new basal insulin to assist patients in reaching glycemic targets despite ever-changing daily lifestyles.

## Acknowledgments

We thank the investigators, trial staff, and participants for their participation (see Supplemental Data for principal investigators). We also thank Lisa Bonk, PharmD, MBA, Charlotte Yap, MSc, and Carolynne Van Houten (employees of Novo Nordisk, Inc, Princeton, New Jersey), for providing medical writing and editorial assistance, and colleagues at Watermeadow Medical (sponsored by Novo Nordisk) for copy editing, preparation of artwork, and submission assistance.

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This work was supported by Novo Nordisk (Bagsvaerd, Denmark).

This study was registered under the Clinical Trials number NCT01079234. This full article has not been previously published, nor is it currently submitted for consideration for publication elsewhere. The data have been presented as abstracts at annual meetings of the American Diabetes Association, European Association for the Study of Diabetes, and International Diabetes Federation in 2011 and 2012. A list of the principal trial investigators and the completed Consolidated Standards of Reporting Trials checklist can be found in the Supplemental Data. The sponsor of this study, Novo Nordisk, was responsible for the design, conduct, and reporting of the study. All authors had access to trial data, full responsibility for manuscript content, and final responsibility for the decision to submit for publication.

Disclosure Summary: C.M. or the institution at which she works has received consulting fees from Novo Nordisk; is an advisory board member and consultant and has participated in speaker's bureaus for Novo Nordisk, Sanofi, Eli Lilly, Abbott, Pfizer, Novartis, Merck Sharp & Dohme, AstraZeneca, Roche, Janssen, Bristol-Myers Squibb, and Boehringer Ingelheim. P.H. or the institution at which she works has received research and grant support from Novo Nordisk and Pfizer; is an advisory board member for Novo Nordisk, Merck, Pfizer, and Orexigen; and is a consultant for Merck, Pfizer, and Bristol-Myers Squibb. B.M.-P. or the institution at which she works has received research and grant support from Novo Nordisk, Pfizer and Boehringer Ingelheim. J.C. has participated in speaker's bureaus for Novo Nordisk, Sanofi, Eli Lilly, Novartis, Merck Sharp & Dohme, and AstraZeneca. E.F. has served on advisory boards for Boehringer Ingelheim, Bioton, Eli Lilly, Bristol-Myers Squibb, Novo Nordisk, and Polpharma and has received speaker fees from Boehringer Ingelheim, Bioton, Eli Lilly, Merck Sharp & Dohme, Novo Nordisk, Polpharma, Bristol-Myers Squibb, and Servier. D.R.-J. receives research funding/lecture honoraria and advisory board honoraria from Eli Lilly, Sanofi Aventis, Novo Nordisk, Novartis, Pfizer, Boehringer Ingelheim, and Roche. J.L. and S.C.T. are employed by and hold shares in Novo Nordisk A/S. S.C.B. or the institution at which he works has been a consultant for Novo Nordisk, Eli Lilly, Boehringer Ingelheim, AstraZeneca, Bristol-Myers Squibb, GlaxoSmithKline, Takeda, Merck Sharp & Dohme, Sanofi, and Diartis; has participated in speaker's bureaus for Boehringer Ingelheim, Eli Lilly, GlaxoSmithKline, Merck Sharp & Dohme, Novartis, Novo Nordisk, Pfizer, Sanofi, Servier, and Takeda; has received payment for development of educational presentations for Doctors.net, Onmedica, Omnia-Med, Medscape Education, and Cardiff University.

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