Comparison of Insulin Detemir and Insulin Glargine in a Basal–Bolus Regimen, With Insulin Aspart as the Mealtime Insulin, in Patients with Type 1 Diabetes: A 52-Week, Multinational, Randomized, Open-Label, Parallel-Group, Treat-To-Target Noninferiority Trial

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ABSTRACT

Objective: The primary study objective was to determine whether insulin detemir (detemir) was noninferior to insulin glargine (glargine) as the basal insulin in a basal–bolus regimen, with insulin aspart as the mealtime insulin, in terms of glycemic control at the end of 52 weeks in patients with type 1 diabetes mellitus (T1DM).

Methods: This multinational, open-label, parallel-group, treat-to-target, noninferiority trial enrolled patients aged ≥18 years who had had T1DM for at least 12 months, had been taking a basal–bolus insulin regimen for at least 3 months, and had a glycosylated hemoglobin (HbA_{1c}) value ≤11.0%. Patients were randomized in a 2:1 ratio to receive either detemir given once or twice daily or glargine given once daily for 52 weeks. The basal insulin was initially administered once daily (in the evening) in both groups; if patients in the detemir group were achieving the PG target before breakfast but not before dinner, they were switched to twice-daily administration. Each patient attended 13 study visits and received 16 scheduled telephone calls from the trial site. The primary efficacy end point was glycemic control (HbA_{1c}) after 52 weeks of treatment. Secondary end points included the number of patients achieving an HbA_{1c} value ≤7.0%, with or without a major hypoglycemic episode in the last month of treatment; fasting plasma glucose (FPG); within-patient variation in self-monitored plasma glucose (SMPG) before breakfast and dinner; and 10-point SMPG profiles. The noninferiority margin was 0.4%, consistent with US Food and Drug Administration guidelines.

Results: Four hundred forty-three patients received study treatment (mean [SD] age, 42 [12] years; body mass index, 26.5 [4.0] kg/m^2; duration of diabetes, 17.2 [11.4]

years; HbA_{1c}, 8.1% [1.1%]). After 52 weeks, the estimated mean HbA_{1c} did not differ significantly between the detemir and glargine groups (7.57% and 7.56%, respectively; mean difference, 0.01%; 95% CI, –0.13 to 0.16), consistent with the noninferiority of detemir to glargine. The corresponding estimated changes in HbA_{1c} were –0.53% and –0.54%. In the 90 patients who completed the trial on once-daily and the 173 patients who completed the trial on twice-daily detemir, the estimated changes in HbA_{1c} were –0.45% and –0.56%, respectively. After 52 weeks, there were no significant differences in the proportion of those receiving detemir and glargine who achieved an HbA_{1c} value ≤7.0% without major hypoglycemia (31.9% and 28.9%, respectively). In addition, there were no significant differences in estimated mean FPG (8.58 and 8.81 mmol/L; mean difference, –0.23; 95% CI,–1.04 to 0.58) or in basal insulin doses. The basal insulin dose was numerically higher in patients receiving detemir twice rather than once daily (0.47 vs 0.33 U/kg, respectively). The relative risks for total and nocturnal hypoglycemia with detemir versus glargine were 0.94 and 1.12, respectively (both, *P* = NS). Six patients (2.0%) in the detemir group and 4 (2.8%) in the glargine group withdrew due to adverse events.

Conclusion: During 52 weeks of basal–bolus therapy in patients with T1DM, detemir was noninferior to glargine in terms of overall glycemic control (HbA_{1c}), occurrence of hypoglycemia, and tolerability when used according to the approved labeling. ClinicalTrials.gov Identifier: NN3034-1430. (*Clin Ther.* 2009:31:XXX-XXX) © 2009 Excerpta Medica Inc.

Key words: detemir, glargine, type 1 diabetes, basal insulin plus OAD, once daily.

INTRODUCTION

Neutral protamine Hagedorn (NPH) insulin has been reported to have substantial within-patient variability in both absorption and action (variability in glucose infusion rate–$AUC_{0–24}$, 59%; variability in C_{max}, 34%)[1] and a distinct "peak" 4 to 6 hours after injection.[1–4] This may make it difficult to achieve stable glycemic control over 24 hours, as both the variability and pronounced peak can result in unexpected hyperglycemia or hypoglycemia.

Two basal insulin analogues, insulin glargine* (glargine) and insulin detemir† (detemir), have become available in recent years for use in the treatment of type 1 or type 2 diabetes mellitus. Both offer potential advantages over NPH insulin, including a flatter diurnal plasma glucose (PG) profile, a longer duration of action (up to 24 hours, depending on the dose),[5] and reduced within-patient variability.[1] However, only 1 study has directly compared the efficacy of these 2 basal insulins in patients with type 1 diabetes mellitus (T1DM).[6]

*Trademark: **Lantus®, Sanofi Aventis, Paris, France**

†Trademark: Levemir® **Levemir®, Novo Nordisk A/S, Copenhagen, Denmark**

In glargine, 2 arginine molecules have been added to the C-terminus of the insulin β chain, and the asparagine residue at position A21 has been replaced with glycine. The arginine molecules carry positive charges, and their presence shifts the

molecule's isoelectric point to a pH of ~6.4 to 6.6, reducing its solubility at physiologic pH.[7] This leads is associated with delayed absorption and a prolonged duration of action (~22 hours) in comparison with NPH.[7–9]

Detemir is engineered through covalent attachment of an acyl group to the amino acid sequence of human insulin. Its action profile is the result of increased self-association at the injection site, together with reversible albumin binding via a fatty acid side chain.[10] In clamp studies in patients with T1DM[1] and type 2 DM,[11] the amount of within-patient variability in the blood glucose–lowering action of detemir was reported to be significantly lower than that of NPH or glargine as measured by the coefficient of variation for glucose infusion rate, area under curve. For patients with T1DM, CV was 27% for detemir versus 59% for NPH and 46% for glargine[1], and for those with T2DM, CV was 47% versus 215% (detemir versus glargine)[2] ($p<0.001$ for all comparisons)

The primary purpose of the present trial was to determine whether detemir was noninferior to glargine with respect to the primary variable, glycosylated hemoglobin (HbA_{1c}), at the end of 52 weeks of treatment in patients with T1DM.

PATIENTS AND METHODS

Patients

Men and women aged ≥18 years who had had T1DM for at least 12 months, had been taking a basal–bolus insulin regimen for at least 3 months, and had an HbA_{1c} value ≤11.0% were eligible for the trial. Exclusion criteria included proliferative retinopathy or maculopathy requiring acute treatment within 6 months before the study; any recurrent major hypoglycemia; an anticipated change in any medication known to

interfere with glucose metabolism; impaired hepatic or renal function; and cardiac problems or uncontrolled hypertension believed to affect study participation.

Study Design and Procedures

This was a 52-week, multinational, randomized, open-label, parallel-group, treat-to-target, noninferiority trial comparing the efficacy and safety profiles of detemir and glargine as the basal insulin in a basal–bolus regimen, with insulin aspart as the mealtime insulin, in patients with T1DM. Each patient attended 13 study visits and received 16 scheduled telephone calls from the trial site. There was no active posttreatment follow-up.

All trial sites were reviewed and approved by an ethics committee or institutional review board, and all patients gave written informed consent. Before commencement of the trial, the protocol, informed consent form, and patient information sheet were reviewed and approved by local health authorities according to local regulations and by local independent ethics committees and/or institutional review boards. Novo Nordisk A/S, Bagsvaerd, Denmark, supplied the 2 trial drugs (but no other medications) and covered the cost of all treatment-related procedures.

Patients were randomized in a 2:1 ratio to receive detemir or glargine as the basal component of the insulin regimen. This ratio was chosen to provide increased information about the safety profile of detemir. Randomization was carried out using a telephone randomization system prepared by Clinical Supplies Coordination at Novo Nordisk A/S.

The basal insulin was initially administered once daily (in the evening) in both groups. If the basal insulin used before the trial had been administered once daily, patients were transferred to the same number of units as the equivalent basal insulin dose. If the pretrial basal insulin had been administered more frequently, the total daily basal insulin dose was reduced by 30% and given once daily, followed by dose titration.

Patients measured their fasting PG (FPG) before breakfast and dinner on the 3 days before each study visit using standard glucose meters (Lifescan OneTouch) **OneTouch® (Lifescan, United States)** and test strips calibrated to PG levels. The mean of each patient's FPG measurements and a predefined algorithm (**Table I**) were used to individually titrate the basal insulin doses to achieve and maintain a PG target of ≤6.0 mmol/L (≤108 mg/dL) before breakfast and dinner, with no episodes of significant hypoglycemia. If patients in the detemir arm were achieving the PG target before breakfast but not before dinner, a second daily dose (initially 4 U) administered in the morning was added to the usual evening dose.Any titration of the morning dose was performed according to the treatment algorithm. In the glargine arm, the dose was administered once daily regardless of the predinner PG measurement, in accordance with its FDA-approved labeling.

All patients received insulin aspart at main meals. The initial dose of mealtime insulin aspart was based on the previous mealtime insulin dose or on local practice, and was adjusted to achieve a 90-minute postprandial PG target of ≤9.0 mmol/L (≤162 mg/dL).[12] However, because the focus of the study was comparison of the basal insulins, titration of the basal insulin dose took precedence over optimizing the mealtime bolus doses.

All patients were asked to record a 10-point self-monitored PG (SMPG) profile on a typical day during the weeks before the randomization visit, the 24-week visit, and the 52-week visit. The 10-point SMPG profile included values recorded before and 90 minutes after each main meal, at bedtime, twice during the night, and before breakfast the next day.

Efficacy Measures

The primary efficacy end point was glycemic control (HbA_{1c}) after 52 weeks of treatment. Secondary variables included the number of patients reaching an HbA_{1c} ≤7.0%, with or without a major hypoglycemic episode in the last month of treatment; FPG; within-patient variation in prebreakfast and predinner SMPG; and 10-point SMPG profiles. The within-patient variation in SMPG at 24 and 52 weeks was calculated from the 6 recorded values, along with 2 FPG measurements and 1 predinner PG measurement recorded in the week before the visit.

In addition to SMPG, FPG was also determined by laboratory analysis of blood samples collected on the morning of randomization and after 12, 24, 36, and 52 weeks. The central laboratory was Laboratorium für Klinische Forschüng GmbH, Schwentinental, Germany, which provided all sites with a manual describing the procedures for collecting, preparing, storing, and shipping blood samples.

Safety Measures

Safety measures included episodes of hypoglycemia; weight; adverse events (AEs); standard laboratory safety tests (hematology, biochemistry, lipids, pregnancy

testing for women); vital signs; physical examinations; and fundoscopy/fundus photography. AEs were defined as *treatment emergent* if they arose on or after the first day of treatment with study medication and no later than 7 days after the last day of treatment. Hypoglycemic episodes were defined as *major* (the patient could not treat the episode by himself/herself), *minor* (the patient could treat himself/herself and the measured PG value was <3.1 mmol/L), or *symptoms only* (the patient could treat himself/herself and no PG measurement was taken or the measured PG value was ≥3.1 mmol/L).

Hypoglycemic episodes were further categorized by time period: overall (every episode over a 24-hour period) and nocturnal (episodes occurring from 11 PM up to but not including 6 AM). Episodes of nocturnal hypoglycemia were analyzed separately, as the effect of the basal insulin may be easier to differentiate from the effect of the bolus injection of rapid-acting insulin analogue at night. Hypoglycemia was classified as a serious AE if the incident was considered life threatening and/or required hospitalization.

Statistical Analysis

The sample size was determined for 2:1 (detemir:glargine) randomization and based on a 1-sided *t* test at a 2.5% significance level. Assuming an SD of 1.0% for HbA_{1c} and a dropout rate of 15%, a sample size of 435 patients gave 95% power to demonstrate noninferiority.

The primary analysis of whether glycemic control with detemir was noninferior to that with glargine after 52 weeks of treatment used a noninferiority margin of 0.4%,

consistent with FDA guidance.[13] The hypothesis was tested by fitting an ANCOVA model to the primary end point, with treatment and country as fixed factors and baseline (randomization) HbA_{1c} as a covariate. A 95% CI was calculated based on a 2-sided *t* test for the treatment difference in the model for the intent-to-treat (ITT) analysis set, which consisted of all patients randomized and exposed to study treatment with at least 1 postbaseline HbA_{1c} observation. Statistical analyses were performed in accordance with International Conference on Harmonisation guidelines.[14] Detemir would be considered noninferior to glargine if the upper limit of the 95% CI was <0.4%.

FPG, weight, and dose were analyzed using an ANCOVA similar to that used for the primary end point.[15] The within-patient variation for each treatment was estimated by fitting a mixed-effect model with patient as a random effect and treatment and country as fixed factors. The within-patient variation for the 2 groups was compared using the likelihood ratio test, in which the mixed-effect was compared with a model in which a common residual variance was fitted.

The 10-point SMPG profiles were used to investigate the treatment-by-time interaction and examine whether the treatment effects were constant over time (ie, whether the profiles could be regarded as parallel). A mixed-effect model was fitted to the data with patient as a random effect and treatment, country, time, and treatment–time interaction as fixed factors. The residual variance structure was modeled as unstructured for each patient, whereas independence was assumed across patients.

Hypoglycemic episodes were compared between treatment groups by estimating the hazard (instantaneous risk) ratio for having a hypoglycemic episode in the detemir

group compared with the glargine group. For this purpose, episodes were analyzed as recurrent events using a gamma frailty model.[16]

All tests, except for the analysis of the primary end point, were 2 sided. *P* values <0.05 were considered statistically significant. Summary statistics and 95% CIs are presented based on estimates from the statistical models used. Analyses were based on the ITT analysis set.

Additional ANCOVA analyses were carried out on dose data for the glargine group and on the subgroups of patients who completed the trial on once- and twice-daily detemir. Self-monitored PG values after 2 weeks were also examined for all patients, including those who were randomized to receive glargine, to determine whether they met the protocol-defined PG criterion for a switch from once- to twice-daily dosing of detemir.

Withdrawn patients were accounted for in the statistical analyses using the last-observation-carried-forward approach. This technique was used to estimate values for missing data in cases where treatment had been initiated, and where the endpoint under consideration had been measured on >1 occasion.

RESULTS

Demographic Characteristics and Patient Disposition

Four hundred forty-three patients (mean [SD] age, 42 [12] years; body mass index, 26.5 [4.0] kg/m^2; duration of disease, 17.2 [11.4] years; HbA_{1c}, 8.1% [1.1%]) received study treatment. The 2 treatment groups were similar with respect to demographic and baseline characteristics (**Table II**). Both groups included numerically

more men than women, and most patients were white. Before the trial, 54.2% of patients were receiving an insulin regimen consisting of 1 basal and 3 bolus injections daily, 14.9% were receiving 2 basal and 3 bolus injections daily, and 13.3% were receiving 1 basal and 4 bolus injections daily. Glargine, the most common basal insulin before the trial, had been used by 288 patients (65.0%), 25 (8.7%) of whom used it twice daily (an off-label use). Detemir had been used by 3 patients, 1 of whom used it twice daily. Other basal insulins (mainly NPH) had been used once daily by 71 patients (16.0%) and twice daily by 77 patients (17.4%). All patients using detemir at baseline were randomized to the detemir group.

The flow of patients through the study is illustrated in **Figure 1**. The primary reasons for withdrawal in the detemir group were noncompliance with the protocol (15 [5.0%]), as determined by the patient's physician, and other reasons (10 [3.3%]) that included gastroparesis, withdrawal of consent, weight gain, relocation, recommencement of the pretrial regimen, and incorrect dispensing of study drug. The most common reason for noncompliance that was considered likelyto have a potential impact on patient outcomes was >3 consecutive days without study medication in the last 8 weeks of the trial (7 patients in the detemir group, 1 in the glargine group). The most common reasons for withdrawal in the glargine group were ineffective therapy (5 [5%]) and other reasons (12 [8.2%]) that included incorrect dispensing of study drug, off-label use of glargine (twice daily), patient's perception that the study was too time consuming, patient's decision not to continue glargine, patient's dissatisfaction with treatment, withdrawal of consent, and pregnancy.

Glycemic Control

At the end of the trial, glycemic control did not differ significantly between detemir and glargine (HbA_{1c}, 7.57% and 7.56%, respectively; mean difference, 0.01%; 95% CI, –0.13 to 0.16), consistent with the noninferiority of detemir. The estimated change in HbA_{1c} in the 2 groups was –0.53% and –0.54% (**Figure 2**).

Glycemic control was improved with both detemir and glargine after 52 weeks; 33.0% and 30.4%, respectively, achieved an HbA_{1c} value ≤7% (*P* = NS). This goal was achieved without major hypoglycemia during the last month of treatment in 31.9% and 28.9% of the 2 groups (*P* = NS). The change in HbA_{1c} in the 90 patients who finished the trial on once-daily detemir was –0.45%; in the 173 patients who finished the trial on twice-daily detemir, the change was –0.56%.

There was no significant difference in estimated mean FPG between detemir and glargine after 52 weeks (8.58 and 8.81 mmol/L, respectively; mean difference, –0.23 mmol/L; 95% CI, –1.04 to 0.58) (**Figure 3**).

After 52 weeks of treatment, the mean 10-point SMPG profiles had shifted downward from baseline in both treatment groups (**Figure 4**). The mean 10-point SMPG profiles differed between the basal insulins,as the 2 profiles crossed at several time points. However, there were no significant differences between treatment groups at any individual time point.

After 52 weeks of treatment, the within-patient variation (SD) in prebreakfast PG was 2.55 for detemir and 2.39 for glargine (*P* = NS). The within-patient variation in predinner PG was 2.89 and 2.96, respectively (*P* = NS).

Insulin Regimens and Dose

After 52 weeks of treatment, 90 (34.2%) of 263 completing patients were receiving once-daily detemir and 173 (65.8%) were receiving twice-daily detemir.

Although the protocol specified once-daily administration of glargine, 7 patients (4.8%) in that group moved to a twice-daily regimen at some time during the trial. Data from these patients were included in the ITT analysis. Based on self-measured PG values, 91.6% of detemir recipients and 88.2% of glargine recipients met the predefined PG criterion for switching from a once- to twice-daily basal insulin regimen

At the end of the trial, the total basal doses were 0.40 U/kg in the detemir group and 0.33 U/kg in the glargine group (*P* = NS). The daily basal dose was 0.33 U/kg (bolus dose, 0.37 U/kg) in patients finishing the trial on a once-daily detemir regimen and 0.47 U/kg (bolus dose, 0.30 U/kg) in those finishing the trial on a twice-daily detemir regimen. In glargine recipients, the daily basal dose was 0.33 U/kg (bolus dose, 0.31 U/kg).

Weight Change

There was no significant difference between the detemir and glargine groups with respect to the estimated mean change in body weight (+0.36 and +0.42 kg, respectively; mean difference, –0.06; 95% CI, –0.84 to 0.73).

Hypoglycemic Episodes

The percentage of patients experiencing hypoglycemic episodes during the treatment period was similar in the detemir and glargine groups (97.3% and 97.2%,

respectively). The rate of all hypoglycemic episodes was 53.6 and 57.3 episodes per patient-year in the 2 groups (*P* = NS) (**Table III**). The mean rate of hypoglycemic episodes decreased over the study period in both groups (**Figure 5**).

The overall risk of having a hypoglycemic episode during the treatment period did not differ significantly between the detemir and glargine groups (relative risk [RR], detemir/glargine = 0.94; 95% CI, 0.74–1.18). In addition, there were no significant differences between groups in the risk of having a nocturnal hypoglycemic episode (RR = 1.12; 95% CI, 0.87–1.44) or a major nocturnal hypoglycemic episode (RR = 1.36; 95% CI, 0.58–3.32).

Adverse Events

In the detemir and glargine groups (ITT population), 277 of 299 patients (92.6%) reported a total of 1508 AEs and 129 of 144 patients (89.6%) reported a total of 550 AEs, respectively. The rate of AEs (events per patient-year) in the 2 groups was ~5 and ~4. In the detemir group, 35 patients (11.7%) reported a total of 52 serious AEs during the treatment period; in the glargine group, 7 patients (4.9%) reported a total of 9 serious AEs. Twelve of the serious AEs in the detemir group and 1 of the serious AEs in the glargine group were considered probably or possibly related to the basal insulin. All the serious AEs judged probably or possibly related to the basal insulin consisted of major hypoglycemic episodes. Six patients (2.0%) in the detemir group and 4 (2.8%) in the glargine group were withdrawn from the trial due to AEs.

Of all AEs classified as probably or possibly related to the basal insulin, injection-site reactions were the most common, occurring more frequently in the detemir group

than in the glargine group (24 patients [8.0%] with 32 events vs 2 patients [1.4%] with 2 events, respectively). However, the injection-site reactions were generally mild or moderate in severity and none were judged serious with the exception of 3 patients in the insulin detemir group, one of whom withdrew from the trial Of these 3 patients, 2 had mild events considered unlikely to be related to the study insulin, and 1 had a moderate event that was considered possibly related to the study insulin.

Other Tolerability End Points

After 52 weeks of treatment, there were no clinically relevant differences between groups in terms of clinical laboratory tests, vital signs, physical examinations, or fundoscopy/fundus photography.

DISCUSSION

In this trial, 52 weeks of treatment with either basal detemir or glargine in combination with mealtime insulin aspart was associated with clinically significant and statistically similar improvements in glycemic control, consistent with the noninferiority of detemir to glargine. These comparable improvements were achieved despite the fact that glargine was the basal insulin in the basal–bolus regimen of 65.0% of patients at study entry. There was no significant difference in FPG between detemir and glargine at the end of the trial. Despite the reductions in HbA_{1c}, the mean rate of hypoglycemic episodes decreased throughout the trial in both groups. These results are consistent with findings from previous studies comparing detemir[17,18] and glargine[19] with NPH insulin in T1DM,

in which basal–bolus therapy with either insulin analogue was associated with improved tolerability (reduced risk of hypoglycemia) at comparable levels of glycemic control.

The present trial included a post hoc analysis comparing glycemic control in patients who completed the trial on once- and twice-daily detemir. The results of this analysis suggested that patients who switched to a twice-daily regimen did not achieve greater improvements in HbA_{1c} compared with those who remained on a once-daily regimen. Although patients were not randomized to once- or twice-daily dosing of the basal insulin, a recent 4-month study (ADAPT [Assessment of Detemir Administration in Progressive Treat-to-Target Trial]) in which patients with T1DM were randomized to receive detemir either once or twice daily as part of a basal–bolus regimen found no difference in HbA_{1c} reduction between the 2 groups (baseline-adjusted difference = 0.14%; 95% CI, 0–0.28; statistical power of our post hoc analysis, 85% with 95% CI).[20] These results are compatible with those of the present study, in which patients who completed the trial on twice-daily detemir had similar HbA_{1c} values to those who completed the trial on once-daily detemir (7.59% and 7.60%, respectively). In this trial, switching from once- to twice-daily detemir was associated with an increase in the insulin dose without a proportional improvement in glycemic control compared with remaining on once-daily detemir. A review by DeVries et al[21] reached a similar conclusion. Studies of glargine have reported that twice-daily administration of this basal insulin also tends to increase the dose.[22,23]

The post hoc analysis in this trial suggested that similar proportions of patients in the 2 treatment groups met the protocol-defined criterion for a switch from a once- to twice-daily regimen (in the detemir group only). Thus, had this been mandated by the

protocol, the proportion of the glargine group completing the trial on a twice-daily regimen would have been similar to that in the detemir group (88.2% and 91.6%, respectively). This supports the findings of a review of clamp studies by Heise et al,[5] who reported that detemir and glargine had similar durations of action in both T1DM and T2DM.

As with all clinical trials, the strict inclusion and exclusion criteria used in this study mean that the conclusions are restricted to the population studied. Additional limitations were the open-label design and the complication of determining twice-daily treatment,as in a small number of instances, physicians chose to split the glargine dose to a BD administration contravening the current label. These patients were included in the ITT analysis, although this may have introduced some biasinto the glargine data set.

CONCLUSIONS

The results of this study in patients with T1DM suggest that intensive titration, close monitoring, and the use of a fairly simple insulin-dosing algorithm were effective tools for improving glycemic control in these patients previously receiving basal–bolus insulin therapy. When used according to the approved labeling in basal–bolus therapy, detemir was noninferior to glargine in terms of the primary end point (HbA_{1c}), with no significant differences on most secondary end points. Thus, the 2 long-acting insulin analogues had comparable clinical effects in these patients with T1DM.

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Table I. Dose-titration algorithm used to achieve and maintain plasma glucose (PG) targets without significant hypoglycemia.*

Mean PG	Change in Basal Insulin Dose
Target: ≤6.0 mmol/L (≤108 mg/dL)	No adjustment
6.1–10.0 mmol/L (109–180 mg/dL)	+2 U
10.1–15.0 mmol/L (181–270 mg/dL)	+4 U
>15.0 mmol/L (>270 mg/dL)	+6 U

*This algorithm was used only if there were no major hypoglycemic episodes or unexplained PG values ≤4 mmol/L. In the case of either of the latter events, the dose was reduced. Mean prebreakfast PG values were used for titration of the evening dose; mean predinner PG values were used for titration of the morning dose.

Table II. Demographic and baseline characteristics. Values are mean (SD), unless otherwise specified.

Characteristic	Insulin Detemir (n = 299)	Insulin Glargine (n = 144)	Total (n = 443)
Sex, no. (%)*			
Male	167 (55.9)	81 (56.3)	248 (56.0)
Female	132 (44.1)	63 (43.8)	195 (44.0)
Age, y	42 (13)	41 (12)	42 (12)
Weight, kg†	79.6 (14.9)	78.9 (15.4)	79.4 (15.1)
BMI, kg/m^2	26.5 (4.0)	26.3 (3.9)	26.5 (4.0)
Diabetes duration, y	17.2 (11.7)	17.3 (10.7)	17.2 (11.4)
HbA_{1c}, %†	8.1 (1.1)	8.1 (1.2)	8.1 (1.1)
FPG, mmol/L†	10.3 (4.3)	10.1 (4.6)	10.2 (4.4)

BMI = body mass index; HbA_{1c} = glycosylated hemoglobin; FPG = fasting plasma glucose.

*Percentages may not total 100 due to rounding.

†Last available value before randomization.

Table III. Hypoglycemic episodes.*

	Insulin Detemir			Insulin Glargine		
Hypoglycemic Episodes (mean)	No. of Events	Episodes/ Patient-Year (n = 278 Patient-Years)	Episodes/ Patient (n = 299 Patients)	No. of Events	Episodes/ Patient-Year (n = 131 Patient-Years)	Episodes/ Patient (n = 144 Patients)
All	14,895	53.6	49.8	7501	57.3	52.1
Major	146	0.5	0.5	53	0.4	0.4
Nocturnal	2756	9.9	9.2	1166	8.9	8.1
Major nocturnal	51	0.2	0.2	17	0.1	0.1
Episodes classified as serious AEs	12	<0.1	<0.1	2	<0.1	<0.1

AEs = adverse events.

*There were no significant differences between groups.

FIGURE LEGENDS

Figure 1. Flow of patients through the study.

Figure 2. Mean (SD) change in glycosylated hemoglobin (HbA_{1c}).

Figure 3. Mean (SD) change in fasting plasma glucose (FPG).

Figure 4. Mean (SD) 10-point self-monitored plasma glucose (PG) profiles at (A) baseline and (B) the end of the trial. *Before breakfast the following morning.

Figure 5. Mean monthly rates of all treatment-emergent hypoglycemic episodes (major, minor, and symptoms only).