A Comparison of Glycemic Variability Associated With Insulin Glargine and Intermediate-Acting Insulin When Used as the Basal Component of Multiple Daily Injections for Adolescents With Type 1 Diabetes

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Objective—To compare the glucose variability associated with insulin glargine and NPH/Lente insulin used as the basal insulin component of a multiple daily injection (MDI) regimen in pediatric patients with type 1 diabetes.

Research design and methods—Continuous glucose monitoring data were collected from a subset of patients (n= 90) who agreed to use a continuous glucose monitoring system during an active-controlled, randomized, open-label study evaluating the safety and efficacy of insulin glargine and NPH/Lente insulin used with insulin lispro as part of an MDI regimen.

Results—Treatment with insulin glargine resulted in significant reductions in glucose variability as measured by the SD of glucose values (adjusted mean change from baseline to week 24, –13.4 mg/dL [–0.74 mmol/L]; P ≤0.05); mean amplitude of glycemic excursion (adjusted mean change from baseline to week 24, –34.4 mg/dL [–1.91 mmol/L]; P ≤0.0001); and M value (adjusted mean change from baseline to week 24, –9.6 mg/dL [–0.53 mmol/L]; P ≤0.03). The corresponding reductions in glucose variability for NPH/Lente were not significant.

Conclusions—Insulin glargine is associated with greater reductions in glucose variability than NPH/Lente insulin in pediatric patients with type 1 diabetes.
Improved glycemic control to prevent or delay microvascular complications is of paramount importance in children and adolescents with type 1 diabetes, but is often achieved at the price of increased hypoglycemia (1,2). Persistent wide fluctuations in plasma glucose in the presence of lower mean glucose and glycated hemoglobin A1C (A1C) values may be an important reason why intensive therapy, as practiced in the Diabetes Control and Complications Trial (DCCT), increases the risk of severe hypoglycemia (2,3). Several studies have suggested that glycemic variability may also play an independent role in the development of complications (4–8). Therefore, some investigators suggest that blood glucose variability, when combined with A1C levels, is an important indicator of glycemic control and the risk for long-term complications (9,10).

Insulin glargine (Lantus, sanofi-aventis U.S. LLC, Bridgewater, NJ) is a basal insulin with little or no pronounced action peak and limited site absorption variation (11). Its use as part of a multiple daily injection (MDI) regimen demonstrated good glucose control with less hypoglycemia than NPH insulin in adults with type 1 and type 2 diabetes (12,13). However, only one major randomized clinical trial in pediatric patients has examined the relative efficacy of insulin glargine–based MDI vs. MDI regimens utilizing intermediate-acting insulins, and this study did not examine glucose variability (14).

Consequently, we performed a large randomized clinical trial in adolescents with type 1 diabetes to compare these two approaches to intensive insulin therapy. A secondary aim of this trial was to compare the glucose variability using insulin glargine vs. intermediate-acting insulin (NPH or Lente) as the basal insulin component of an MDI regimen. Both patient groups received premeal insulin lispro (Humalog, Eli Lilly and Co., Indianapolis, IN). This paper reports the results of data analysis from a subset of patients who volunteered to use a continuous glucose monitoring system (CGMS) to assess glucose variability. Results from the entire randomized controlled trial are reported elsewhere (15).

RESEARCH DESIGN AND METHODS

Study design—The study design and methods have been described previously (15). Patients with type 1 diabetes (N=175) participated in this randomized study comparing insulin glargine and NPH/Lente insulin, each used with premeal insulin lispro in an MDI regimen. A subset of patients (glargine, n=74; NPH/Lente, n=75) volunteered to use the CGMS (Medtronic/MiniMed, Inc., Northridge, CA), which measures interstitial glucose concentrations every 5 minutes for 3 days via a glucose oxidase-based method, to compare variability in interstitial glucose levels across the two regimens. CGMS accuracy has been demonstrated to be similar from day to day (16). The median relative absolute difference between sensor and reference plasma glucose values in children with type 1 diabetes has been 11% during outpatient use (17). In this study, patients and the health care team were blinded to CGMS results, which were not used for diabetes management but only for the assessment of glycemic variability.

Eligibility criteria and baseline characteristics—Patients aged 9–17 years with type 1 diabetes (for ≥1 year) and at least Tanner stage 2 puberty, with A1C level ≥7.0% and ≤9.5% and using ≥2 insulin injections per day or continuous subcutaneous insulin infusion, were enrolled. Excluded were patients with diabetic ketoacidosis in the past 3 months or ≥2 episodes of severe hypoglycemia (i.e., an event requiring assistance of another person and accompanied by either a blood glucose level of <36 mg/dL.
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[<2.0 mmol/L] or prompt recovery after oral carbohydrate intake, intravenous glucose, or glucagon administration) in the past 12 months. Patients had to be willing to perform self-monitoring of blood glucose (SMBG) at least 4 times daily. The CGMS subgroup had to be willing to use the MiniMed CGMS for up to 3 consecutive days on 3 occasions.

Study medication—Patients were randomized to receive basal insulin glargine once daily before breakfast or intermediate-acting insulin (NPH or Lente) twice daily; starting doses were 40%-50% of the total daily insulin dose. Both groups received insulin lispro before each meal based on carbohydrate intake, with individualized correction doses based on the degree to which blood glucose levels deviate from the target glucose values.

Continuous glucose monitoring—Interstitial glucose was measured during 3 periods for 3 consecutive days each (week 0, week 12, and week 24). Patients were to enter at least four SMBG values daily to calibrate the CGMS and to record important events (e.g., insulin boluses, snacks, exercise).

Measures of glycemic control and glycemic variability—Glycemic control was assessed by A1C at baseline, 12 weeks, and 24 weeks, and by the time CGMS glucose values were <70, <50, and ≤40 mg/dL and ≥250 and ≥350 mg/dL (<3.89, <2.78, ≤2.22, ≥13.88, and ≥19.45 mmol/L) were calculated.

For CGMS data to be analyzable, each patient had to have a sufficient duration (i.e., 24 hours of sensor data for each day) of CGMS data and a date for CGMS data collection at the appropriate time in the study. Some patients in the insulin glargine (N=29) and the NPH/Lente (N=30) groups were excluded from the analysis due to discrepancies between CGMS and SMBG values recorded by the same patient; unfamiliarity with the mechanics of the CGMS; and occurrence of technical problems during CGMS measurement. Forty-five patients in each group had analyzable data at baseline and at any endpoint; and 33 patients in the glargine group and 36 in the NPH/Lente group had data at baseline and week 24.

RESULTS

Primary study results—Study results from the overall trial are reported elsewhere (15). In summary, change in A1C level from baseline to 24 weeks was –0.25% ± 0.14% for the glargine group (N =76) and –0.05% ± 0.13% for the NPH/Lente group (N =81); these changes were not significant (P=0.1725). However, repeated-measures analysis showed a greater reduction in A1C level associated with the use of insulin glargine in patients who had higher baseline A1C values (for median and 90th percentile values, P <0.05 between groups). Rates of glucose readings (per patient-year) <70 mg/dL (3.88 mmol/L) were 116.1 and 93.8 in the glargine and the NPH/Lente group, respectively (P=0.030); whereas rates of glucose <50 mg/dL (2.78 mmol/L) (21 in
glargine group vs. 20 in NPH/Lente group; P=0.81) and <36 mg/dL ([2.0 mmol/L] (1.2 vs. 1.7, respectively; P=0.32), severe hypoglycemia (0.20 vs. 0.09, respectively; P=0.18), and treatment-emergent adverse events (17.6% vs. 8.9%, respectively; P=0.12) did not differ significantly between groups.

Patient characteristics at baseline—
There were no significant differences in baseline characteristics between patients who used the CGMS and the entire study population (Table 1). There was also no significant difference between the main study group and CGMS subgroup with respect to changes in A1C level during the trial (Table 1).

Glycemic Outcomes—In the CGMS subgroup, the adjusted mean change in A1C level from baseline to endpoint was –0.12% and –0.10% for the glargine vs. NPH/Lente subgroup (P=0.9250). A1C outcomes and hypoglycemia rates (events per patient-year, determined by glucose meter measurements) in the CGMS subgroup paralleled those in the overall study (15).

Continuous glucose monitoring values—Mean glucose value: There were no between-group differences in mean 24-hour glucose concentrations (Table 2, Figure 1) or the glucose concentrations analyzed in 6-hour intervals throughout the day (data not shown).

Variability—Standard deviation of glucose. Subjects using insulin glargine showed a significant reduction in glucose variability (as measured by SD) from baseline (P < 0.0001 for each time point) and a significantly greater reduction compared to those using NPH/Lente at week 24 (P=0.0147) (Table 2; Figure 2A). Those using NPH/Lente had a trend for reduction in SD from baseline at week 12 (P=0.0503) but not at week 24 (P=0.4286) (Table 2; Figure 2A).

Mean amplitude of glucose excursion. MAGE was significantly reduced in the insulin glargine group at weeks 12 (P=0.0001) and 24 (P <0.0001) compared with baseline (Table 2). The adjusted mean change from baseline in MAGE for NPH/Lente-treated patients was not significant at weeks 12 (P=0.1139) or 24 (P=0.7459). The between-group difference in mean adjusted change in MAGE from baseline favored glargine at week 12 and was significant at week 24 (P=0.0055) (Figure 2B).

M Value. Although between-group differences in the adjusted mean reduction in M value were not statistically significant (Figure 2C), insulin glargine-treated patients experienced significant reductions from baseline at weeks 12 (P=0.0309) and 24 (P=0.0048) (Table 2). The mean adjusted change from baseline in the NPH/Lente group was not significant (P=0.8440 and P=0.7360, at 12 and 24 weeks, respectively).

Hypoglycemia and hyperglycemia as determined by CGMS—Compared with NPH/Lente, insulin glargine therapy reduced the time spent at glucose levels <70, <50, and ≤40 mg/dL (<3.89, <2.78, and ≤2.22 mmol/L) between baseline and week 24 (Table 3). Differences in mean adjusted change from baseline were statistically significant for insulin glargine for glucose levels of <50 mg/dL (<2.78 mmol/L; P=0.0198) and ≤40 mg/dL (≤2.22 mmol/L; P=0.0130). Insulin glargine also significantly reduced the time spent at glucose levels of ≥250 and ≥350 mg/dL (≥13.88 and ≥19.43 mmol/L) between baseline and week 12 (P=0.0220 and P=0.0126, respectively); at week 24, time spent ≥250 mg/dL (≥13.88 mmol/L) was also significantly reduced (P=0.0347), but the time spent ≥350 mg/dL (≥19.43 mmol/L; P=0.0709) was not. For NPH/Lente, time spent ≥350 mg/dL (≥19.43 mmol/L) or ≥250 mg/dL (≥13.88 mmol/L) were not reduced at 12 or 24 weeks, and there were no between-group differences (P’s= 0.1214-0.5523).

DISCUSSION
The most important finding of this substudy was that pediatric patients receiving insulin glargine appeared to experience less variability in glucose levels, as assessed by SD and MAGE, than did patients receiving NPH/Lente insulin. Reductions in glycemic variability may have important clinical implications, including tighter glycemic control with less risk of hypoglycemia and a reduction in vascular complications (3,19). Cox and colleagues found that high glucose variability precedes severe hypoglycemia,(20) suggesting that reducing glucose fluctuations may reduce the risk for severe hypoglycemia. Hypoglycemia limits the ability to control blood glucose and A1C levels in insulin-treated diabetes (21). Increased glycemic variability, independent of average blood glucose and A1C levels, is believed by some to contribute to vascular complications (22,23). Thus, information on variability of blood glucose may become increasingly important to clinicians and patients in the future; CGMS may serve as a valuable tool for assessing the overall level of glycemic control beyond what can be determined by measuring A1C levels alone. The CGMS with masked 5-minute sampling used in this study provides a better estimate of the magnitude of glucose excursions than the fixed-point-in-time 8-point testing procedures used in other studies (3).

In the CGMS subpopulation in this study, despite similar reductions in A1C (−0.12% vs. −0.10%), the adjusted mean difference from baseline at 24 weeks in time spent at glucose levels of ≤40 and <50 mg/dL (<2.22 and <2.78) by patients using insulin glargine was significantly less than time spent by those using NPH/Lente (13.4 vs. 39.8 min/day, \(P=0.0198\) for glucose <50 mg/dL [<2.78]; 3.0 vs. 23.8 min/day, \(P=0.013\) for glucose ≤40 mg/dL [<2.22]). The time spent <70 mg/dL was similar between groups (64.2 vs. 85.3 minutes/day, \(P=0.1163\)) (Table 3). In both groups there was an initial trend for an increase in time at each hypoglycemia threshold at week 12, followed by a reduction by week 24, as noted above. This increase may reflect the initial up titration of insulin doses at the start of the study, followed by stabilization of doses. There were too few severe hypoglycemic events to allow identification of differences between groups. No other clinical correlates were evaluated.

Although the CGMS subgroup in the current study was similar to the overall study population in terms of demographics, one limitation of this analysis is the possibility that the CGMS subgroup may have been different from the overall population, based on unmeasured variables, such as motivation, conscientiousness, and other behavioral differences that can affect disease management. While all patients had to have at least Tanner stage 2 pubertal development to enter the study, the impact of different stages of pubertal development on glycemic control and glucose variability could not be determined from the data collected.

**CONCLUSION**

The results of this study suggest that the use of insulin glargine as the basal component of a multiple injection regimen appears to be associated with a reduction in glycemic variability. In addition, to the extent to which reduced glycemic variability may contribute to a decrease in diabetes-related complications, the use of insulin glargine may be beneficial.

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REFERENCES

1. The Diabetes Control and Complications Trial Research Group: The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. *N Engl J Med* 329:977-986, 1993

2. Diabetes Control and Complications Trial Research Group: Effect of intensive diabetes treatment on the development and progression of long-term complications in adolescents with insulin-dependent diabetes mellitus: Diabetes Control and Complications Trial. *J Pediatr* 125:177-188, 1994

3. Fiallo-Scharer R: Eight-point glucose testing versus the continuous glucose monitoring system in evaluation of glycemic control in type 1 diabetes. *J Clin Endocrinol Metab* 90:3387-3391, 2005

4. Monnier L, Mas E, Ginet C, Michel F, Villon L, Cristol JP, Colette C: Activation of oxidative stress by acute glucose fluctuations compared with sustained chronic hyperglycemia in patients with type 2 diabetes. *JAMA* 295:1681-1687, 2006

5. Temelkova-Kurktschiev TS, Koehler C, Henkel E, Leonhardt W, Fuecker K, Hanefeld M: Postchallenge plasma glucose and glycemic spikes are more strongly associated with atherosclerosis than fasting glucose or HbA1c level. *Diabetes Care* 23:1830-1834, 2000

6. Esposito K, Giugliano D, Nappo F, Marfella R: Regression of carotid atherosclerosis by control of postprandial hyperglycemia in type 2 diabetes mellitus. *Circulation* 110:214-219, 2004

7. Ceriello A, Cavarape A, Martinelli L, Da Ros R, Marra G, Quagliaro L, Piconi L, Assaloni R, Motz E: The post-prandial state in Type 2 diabetes and endothelial dysfunction: effects of insulin aspart. *Diabet Med* 21:171-175, 2004

8. Brownlee M: The pathobiology of diabetic complications: a unifying mechanism. *Diabetes* 54:1615-1625, 2005

9. Hirsch, I. B. and Parkin, C. G. Is AIC the best measure of glycemic control? US Endocrine Review, 22-24. 2005.

10. Brownlee M, Hirsch IB: Glycemic variability: a hemoglobin A1c-independent risk factor for diabetic complications. *JAMA* 295:1707-1708, 2006

11. Lepore M, Pampanelli S, Fanelli C, Porcellati F, Bartocci L, Di Vincenzo A, Cordoni C, Costa E, Brunetti P, Bolli GB: Pharmacokinetics and pharmacodynamics of subcutaneous injection of long-acting human insulin analog glargine, NPH insulin, and ultralente human insulin and continuous subcutaneous infusion of insulin lispro. *Diabetes* 49:2142-2148, 2000

12. Hershon KS, Blevins TC, Mayo CA, Rosskamp R: Once-daily insulin glargine compared with twice-daily NPH insulin in patients with type 1 diabetes. *Endocr Pract* 10:10-17, 2004

13. Fonseca V, Bell DS, Berger S, Thomson S, Mecca TE: A comparison of bedtime insulin glargine with bedtime neutral protamine hagedorn insulin in patients with type 2 diabetes: subgroup analysis of patients taking once-daily insulin in a multicenter, randomized, parallel group study. *Am J Med Sci* 328:274-280, 2004

14. Schober E, Schoenle E, Van Dyk J, Wernicke-Panten K: Comparative trial between insulin glargine and NPH insulin in children and adolescents with type 1 diabetes mellitus. *J Pediatr Endocrinol Metab* 15:369-376, 2002
15. Chase HP, Arslanian S, White NH, Tamborlane WV: Insulin Glargine Versus Intermediate-Acting Insulin as the Basal Component of Multiple Daily Injection Regimens for Adolescents with Type 1 Diabetes Mellitus. *J Pediatr* 153:547-53, 2008
16. Diabetes Research in Children Network (DIRECNET) Study Group: The accuracy of the CGMS in children with type 1 diabetes: results of the diabetes research in children network (DirecNet) accuracy study. *Diabetes Technol Ther* 5:781-789, 2003
17. Tansey MJ, Beck RW, Buckingham BA, Mauras N, Fiallo-Scharer R, Xing D, Killman C, Tamborlane WV, Ruedy KJ: Accuracy of the modified Continuous Glucose Monitoring System (CGMS) sensor in an outpatient setting: results from a diabetes research in children network (DirecNet) study. *Diabetes Technol Ther* 7:109-114, 2005
18. Service FJ, Molnar GD, Rosevear JW, Ackerman E, Gatewood LC, Taylor WF: Mean amplitude of glycemic excursions, a measure of diabetic instability. *Diabetes* 19:644-655, 1970
19. Service FJ, O'Brien PC, Rizza RA: Measurements of glucose control. *Diabetes Care* 10:225-237, 1987
20. Cox DJ, Gonder-Frederick L, Ritterband L, Clarke W, Kovatchev BP: Prediction of severe hypoglycemia. *Diabetes Care* 30:1370-1373, 2007
21. Cryer PE: Hypoglycemia risk reduction in type 1 diabetes. *Exp Clin Endocrinol Diabetes* 109 Suppl 2:S412-S423, 2001
22. Feringa HH, Karagiannis SE, Vidakovic R, Elhendy A, Schouten O, Boersma E, Bax JJ, Poldermans D: Glycemic control, lipid-lowering treatment, and prognosis in diabetic patients with peripheral atherosclerotic disease. *Ann Vasc Surg* 21:780-789, 2007
23. Hirsch IB, Brownlee M: Should minimal blood glucose variability become the gold standard of glycemic control? *J Diabetes Complications* 19:178-181, 2005
24. White NH, Tamborlane WV, Usiskin K: Less variability in blood glucose values with insulin glargine versus intermediate-acting insulin (NPH/LENTE) in adolescents with Type 1 diabetes (Abstract). *Diabetes* 55(Suppl. 1):A139, 2006
Figure legends

Figure 1. Mean (±1 SE) CGMS curves in patients with at least one 24-hour CGMS recording at the following time points: baseline (A), week 12 (B), and week 24 (C) for those in the glargine group (green) and the NPH/Lente group (blue).

Figure 2. Adjusted mean change from baseline in measures of glucose variability associated with insulin glargine (black bars) and intermediate-acting insulin (NPH/Lente) (open bars); standard deviation (A), mean amplitude of glycemic excursion (B), and M value (C).
1A. 

1B.
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1C.
2A

![Graph showing change in SD for Insulin glargine and NPH/Lente]

-1.11  -0.833  -0.555  -0.278  0

Week 12  Week 24

-13.9*  -13.4*

P = 0.0509  P = 0.0147

*P ≤ 0.05 from baseline.
†P = 0.0503 from baseline.

2B

![Graph showing change in MAGE for Insulin glargine and NPH/Lente]

-2.78  -2.22  -1.67  -1.11  0

Week 12  Week 24

-31.2*  -34.4*

P = 0.1051  P = 0.0055

*P ≤ 0.0001 from baseline.

MAGE, mean amplitude of glycemic excursion.
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*P ≤ 0.04 from baseline.
| Characteristic                     | Study population (n = 85) | CGMS subpopulation (n = 90) | Insulin glargine | NPH Lente | Insulin glargine | NPH/Lente |
|-----------------------------------|---------------------------|-----------------------------|-----------------|-----------|-----------------|-----------|
| **Age (years)**                   |                           |                             |                 |           |                 |           |
| Mean (SD)                         | 13.1 (2.4)                | 13.4 (2.4)                  | 13.2 (2.3)      | 13.4 (2.5) |
| **Sex (female), n (%)**           | 45 (53.6)                 | 44 (52.4)                   | 23 (51.1)       | 19 (42.2)  |
| **Race, n (%)**                   |                           |                             |                 |           |                 |           |
| White                             | 71 (84.5)                 | 68 (81.0)                   | 41 (91.1)       | 40 (88.9)  |
| African American                  | 0 (0.0)                   | 7 (8.3)                     | 9 (0.0)         | 0 (0.0)    |
| Asian                             | 2 (2.4)                   | 2 (2.4)                     | 0 (0.0)         | 2 (4.4)    |
| Hispanic                          | 7 (8.3)                   | 2 (4.8)                     | 3 (6.7)         | 2 (4.4)    |
| Multiracial                       | 2 (2.4)                   | 1 (1.2)                     | 1 (2.2)         | 0 (0.0)    |
| Other                             | 2 (2.4)                   | 2 (2.4)                     | 0 (0.0)         | 1 (2.2)    |
| **Weight (kg)**                   |                           |                             |                 |           |                 |           |
| Mean (SD)                         | 57.2 (14.8)               | 59.1 (18.1)                 | 57.9 (15.1)     | 57.8 (19.4) |
| **BMI (kg/m^2)**                  |                           |                             |                 |           |                 |           |
| Mean (SD)                         | 22.6 (3.8)                | 22.9 (5.0)                  | 22.6 (0.8)      | 22.6 (0.9) |
| **Age at onset (years)**          |                           |                             |                 |           |                 |           |
| Mean (SD)                         | 8.5 (3.5)                 | 8.5 (3.7)                   | 8.3 (3.7)       | 9.0 (3.5)  |
| **Duration of diabetes (years)**  |                           |                             |                 |           |                 |           |
| Mean (SD)                         | 5.1 (3.4)                 | 5.4 (3.7)                   | 5.4 (3.7)       | 4.9 (3.6)  |
| **A1C (%)**                       |                           |                             |                 |           |                 |           |
| Baseline Mean (SD)                | 7.8 (0.8)                 | 8.0 (0.8)                   | 7.9 (0.9)       | 8.0 (0.8)  |
| Adjusted Mean – at study end in relation to baseline values | | | | |
| Baseline A1C 10\(^{th}\) Percentile | 7.28 | 7.12 | 7.28 | 6.95 |
| Baseline A1C Median               | 7.74 | 7.86 | 7.82 | 7.84 |
| Baseline A1C 90\(^{th}\) Percentile | 8.32 | 8.79 | 8.51 | 8.97 |
| **Baseline fasting SMBG (mg/dL)** |                             |                             |                 |           |                 |           |
| Mean (SD)                         | 188.5 (54.4)              | 203.0 (52.1)                | 187.4 (62.5)    | 203.4 (42.3) |

A1C, glycosylated hemoglobin A1C; CGMS, continuous glucose monitoring system; SMBG, self-monitoring of blood glucose.

*No significant differences between groups who did or did not participate in CGMS.
## Table 2—Mean CGMS sensor values and variability measures at baseline and weeks 12 and 24

| Time point | N | Sample mean (mg/dL) | P vs. baseline | N | Sample mean (mg/dL) | P vs. baseline | P value |
|------------|---|---------------------|---------------|---|---------------------|---------------|---------|
| **Mean CGMS sensor values** | | | | | | | |
| Baseline | 45 | 190.6 | | 45 | 197.1 | | | |
| Week 12 | 39 | 177.3 | 0.0728 | 35 | 195.4 | 0.6759 | 0.3516 |
| Week 24 | 33 | 181.8 | 0.2228 | 36 | 195.3 | 0.6371 | 0.5745 |
| **Standard deviation** | | | | | | | |
| Baseline | 45 | 77.4 | | 45 | 73.9 | | | |
| Week 12 | 39 | 63.8 | < 0.0001 | 35 | 71.2 | 0.0503 | < 0.0509 |
| Week 24 | 33 | 64.2 | < 0.0001 | 36 | 74.3 | 0.4286 | 0.0147 |
| **MAGE** | | | | | | | |
| Baseline | 45 | 188.5 | | 45 | 177.7 | | | |
| Week 12 | 39 | 154.7 | 0.0001 | 35 | 173.6 | 0.1139 | 0.1051 |
| Week 24 | 33 | 152.0 | < 0.0001 | 36 | 182.0 | 0.7459 | 0.0055 |
| **M value** | | | | | | | |
| Baseline | 45 | 43.5 | | 45 | 43.2 | | | |
| Week 12 | 39 | 36.8 | 0.0309 | 35 | 43.7 | 0.8440 | 0.1768 |
| Week 24 | 33 | 34.2 | 0.0048 | 36 | 42.3 | 0.7360 | 0.0631 |

*Difference in adjusted mean change between groups.

GLAR, insulin glargine; CGMS, continuous glucose monitoring system; MAGE, mean amplitude of glycemic excursion.
Table 3—Adjusted mean change from baseline in time spent above or below specified sensor glucose levels in CGMS subset

| Glucose Level | Insulin glargine | NPH/Lente | Difference [GLAR-NPH] |
|---------------|-----------------|-----------|----------------------|
|               | Time point      | N Sample  | P vs. baseline | N Sample  | P vs. baseline | Adjusted mean | P value |
| <70 mg/dL (<3.89 mmol/L) | | | | | | | |
| Baseline      | 45 119.0        | 45 75.5   |           |           |           |           |          |
| Week 12       | 39 141.0        | 35 94.8   | 0.1067    | 36 85.3   | 0.5931    | -46.6      | 0.4040  |
| Week 24       | 33 64.2         | 36        | 0.0983    |           |           |           |          |
| <50 mg/dL (<2.78 mmol/L) | | | | | | | |
| Baseline      | 45 25.1         | 45 18.2   |           |           |           |           |          |
| Week 12       | 39 54.0         | 35 38.6   | 0.0288    | 36 39.8   | 0.0083    | -38.2     | 0.0198  |
| Week 24       | 33 13.4         | 36        | 0.5246    |           |           |           |          |
| ≤40 mg/dL (≤2.22 mmol/L) | | | | | | | |
| Baseline      | 45 12.7         | 45 6.9    |           |           |           |           |          |
| Week 12       | 39 27.4         | 35 21.6   | 0.0832    | 36 23.8   | 0.0092    | -26.9     | 0.0130  |
| Week 24       | 33 3.0          | 36        | 0.3597    |           |           |           |          |
| ≥250 mg/dL (≥13.88 mmol/L) | | | | | | | |
| Baseline      | 45 397.3        | 45 415.4  |           |           |           |           |          |
| Week 12       | 39 289.9        | 35 408.3  | 0.0220    | 36 409.9  | 0.7453    | -93.8     | 0.1756  |
| Week 24       | 33 302.1        | 36        | 0.0347    |           |           |           |          |
| ≥350 mg/dL (≥19.43 mmol/L) | | | | | | | |
| Baseline      | 45 107.0        | 45 106.9  |           |           |           |           |          |
| Week 12       | 39 54.4         | 35 109.2  | 0.0126    | 36 87.9   | 0.2916    | -18.1     | 0.5523  |
| Week 24       | 33 66.6         | 36        | 0.0709    |           |           |           |          |

GLAR, insulin glargine; CGMS, continuous glucose monitoring system.