Comparison of Insulin Glargine 300 Units/mL and 100 Units/mL in Adults With Type 1 Diabetes: Continuous Glucose Monitoring Profiles and Variability Using Morning or Evening Injections

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OBJECTIVE

The objective of this study was to compare glucose control in participants with type 1 diabetes receiving insulin glargine 300 units/mL (Gla-300) or glargine 100 units/mL (Gla-100) in the morning or evening, in combination with mealtime insulin.

RESEARCH DESIGN AND METHODS

In this 16-week, exploratory, open-label, parallel-group, two-period crossover study (clinicaltrials.gov identifier NCT01658579), 59 adults with type 1 diabetes were randomized (1:1:1:1) to once-daily Gla-300 or Gla-100 given in the morning or evening (with crossover in the injection schedule). The primary efficacy end point was the mean percentage of time in the target glucose range (80–140 mg/dL), as measured using continuous glucose monitoring (CGM), during the last 2 weeks of each 8-week period. Additional end points included other CGM glycemic control parameters, hypoglycemia (per self-monitored plasma glucose [SMPG]), and adverse events.

RESULTS

The percentage of time within the target glucose range was comparable between the Gla-300 and Gla-100 groups. There was significantly less increase in CGM-based glucose during the last 4 h of the 24-h injection interval for Gla-300 compared with Gla-100 (least squares mean difference −14.7 mg/dL [95% CI −26.9 to −2.5]; P = 0.0192). Mean 24-h glucose curves for the Gla-300 group were smoother (lower glycemic excursions), irrespective of morning or evening injection. Four metrics of intrasubject interstitial glucose variability showed no difference between Gla-300 and Gla-100. Nocturnal confirmed (<54 mg/dL by SMPG) or severe hypoglycemia rate was lower for Gla-300 participants than for Gla-100 participants (4.0 vs. 9.0 events per participant-year; rate ratio 0.45 [95% CI 0.24–0.82]).

CONCLUSIONS

Less increase in CGM-based glucose levels in the last 4 h of the 24-h injection interval, smoother average 24-h glucose profiles irrespective of injection time, and reduced nocturnal hypoglycemia were observed with Gla-300 versus Gla-100.

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Despite advances in basal insulin therapy, many people with type 1 diabetes still experience marked day-to-day differences in glucose levels as well as glucose excursions within the same day. These often unpredictable fluctuations in glucose levels make it difficult to optimize insulin doses and reach desired glycemic targets. It is also well recognized that hypoglycemia is a limiting factor when intensifying insulin therapy (1). Therefore, a basal insulin that leads to more stable glucose control with a reduced risk for hypoglycemia would provide a distinct clinical advantage.

A pharmacokinetic (PK)/pharmacodynamic (PD) euglycemic clamp study at steady state in people with type 1 diabetes showed that the basal insulin analog insulin glargine 300 units/mL (Gla-300) provides more consistent and prolonged insulin exposure compared with insulin glargine 100 units/mL (Gla-100), resulting in blood glucose control that lasts well beyond 24 h (2). A second euglycemic clamp study demonstrated predictable and stable 24-h glycemic coverage by Gla-300 as a result of low fluctuation and high reproducibility of insulin exposure (3). Continuous glucose monitoring (CGM), which records interstitial fluid glucose levels every 5 min throughout the day and night, is a valuable way to confirm whether the differences observed in the PK and PD properties of insulins under euglycemic clamp conditions translate to clinically relevant differences in their 24-h glucose profiles and other parameters of glycemic control, including hypoglycemia.

CGM was used in this study by 59 adult participants with type 1 diabetes over two successive 8-week periods to assess glucose control, safety, and tolerability of Gla-300 compared with Gla-100 when administered in the morning or evening.

RESEARCH DESIGN AND METHODS

Study Design

This exploratory, 16-week, open-label, phase II, parallel-group, two-period crossover study of participants with type 1 diabetes was conducted in three study centers in the U.S. from August 2012 to May 2013. After a 4-week screening phase, participants were randomized 1:1:1:1, using a remote telephone system, to receive treatment with Gla-300 or Gla-100 (both Sanofi, Paris, France) in the morning or evening during treatment period A (weeks 1–8); participants then crossed over to the alternate injection schedule (evening or morning) for treatment period B (weeks 9–16).

CGM (using the Dexcom Seven Plus CGM system [Dexcom, San Diego, CA]) was performed throughout the 16-week treatment period. Participants were masked to their CGM data. Data from the last 2 weeks of each 8-week treatment period (A and B) were analyzed (weeks 7–8 and weeks 15–16 combined). The study design is summarized in Supplementary Fig. 1.

The study protocol was approved by the appropriate local or central independent ethics committees or institutional review boards, and the study was conducted according to Good Clinical Practice guidelines and the Declaration of Helsinki. All participants provided written informed consent.

Key Inclusion and Exclusion Criteria

Adult participants (≥18 and <70 years of age at screening) diagnosed with type 1 diabetes and receiving any basal insulin regimen and mealtime insulin analog for at least 1 year were eligible for inclusion. Exclusion criteria included HbA_{1c} >9.0% at screening; not taking a stable insulin dose in the 30 days before screening; use of an insulin pump within 6 months before screening; use of premixed insulin, human regular insulin as mealtime insulin, and/or any antihyperglycemic drugs other than an insulin analog at mealtime and basal insulin within 3 months before screening; and any contraindication to insulin glargine.

Interventions

Participants self-administered subcutaneous injections of Gla-300 or Gla-100 once daily, at the same time each day—either in the morning (immediately before breakfast until lunch) or evening (immediately before the evening meal until bedtime)—according to their assigned schedule in each treatment period. Injections were administered using commercially available insulin syringes because an insulin pen that could deliver the small volumes of Gla-300 required was not available when the study was conducted. All information pertaining to the time, dose, and location of the injection of basal insulin treatment as well as the time and dose of mealtime insulin were recorded daily in participant diaries.

Participants receiving basal insulin twice daily before study entry were changed to a once-daily regimen at screening (week −2). For treatment period A, the basal insulin dose on the day before randomization and the median fasting self-measured plasma glucose (SMPG) value before breakfast during the 3 days before baseline were used to calculate the starting dose. For treatment period B, the starting dose was calculated using the basal insulin dose on the day before the first study visit of treatment period B (week 9) and the SMPG before breakfast during the 3 days before week 9.

The basal insulin dose was titrated no more often than every 3 to 4 days during the first 6 weeks of each treatment period (A and B) to reach the target fasting SMPG of 80–130 mg/dL (4.4–7.2 mmol/L), and it was optimized by the investigators using CGM data (downloaded at the study visits). In each treatment period, the 6-week titration phase was followed by a 2-week maintenance phase (weeks 7–8 and weeks 15–16) in which basal insulin doses were to remain as constant as clinically possible (representing a steady-state scenario to better allow comparison of the two basal insulins), and in which most glycemic corrections were made using the mealtime insulin.

Each participant continued to use the same rapid-acting insulin analog used in the 3 months before screening, with adjustments to achieve a target 2-h postprandial SMPG of <160 mg/dL (<8.9 mmol/L). Glycemic targets were adapted for individual participants, if deemed necessary.

End Points

The primary end point was the mean percentage of time within the predefined CGM glucose range of 80–140 mg/dL (4.4–7.8 mmol/L) during the last 2 weeks of each treatment period. Secondary end points based on CGM included the mean percentage of time with glucose <80 mg/dL, the mean percentage of time with glucose >140 mg/dL, mean glucose levels, mean and variation in glucose profiles, and glucose variability metrics. Mean change in HbA_{1c} (NGSP units) from baseline to week 16 (analyzed by a central laboratory) and insulin dose (units per kilogram; total daily dose, basal dose, mealtime/bolus dose) were assessed.

Participant-reported hypoglycemic events were collected for the entire on-treatment study period and analyzed by categories as defined by the

American Diabetes Association (4); they were classified as occurring during the night (0000–0559 h) and at any time of day (24 h). The number of hypoglycemic events per participant-year were calculated using plasma glucose concentration cutoffs of ≤70 mg/dL (≤3.9 mmol/L) and <54 mg/dL (<3.0 mmol/L). To confirm a hypoglycemic event, participants were instructed to measure capillary plasma glucose levels (SMPG) before the administration of carbohydrates whenever symptomatic hypoglycemia was suspected, unless safety considerations required immediate glucose rescue before confirmation. Treatment-emergent adverse events (AEs), both nonserious and serious, were evaluated.

Data Analysis and Statistics

No formal sample size estimation was performed for this first-of-its-kind head-to-head comparison of basal insulins using CGM in a crossover exploratory study. Assuming a 15% withdrawal rate, we planned to enroll approximately 56 participants to achieve 48 evaluable participants.

Unless otherwise specified, the efficacy results were analyzed using CGM data from the last 2 weeks of each treatment period (weeks 7–8 and weeks 15–16, when basal insulin doses were to remain as constant as possible and most glycemic corrections were made using mealtime insulin) by treatment group overall (i.e., pooled morning and evening injection schedules); some end points were also analyzed by treatment group and injection schedule (morning vs. evening).

The modified intent-to-treat (mITT) population included all randomized participants who received at least one dose of study medication and had at least one efficacy assessment after the baseline. The primary efficacy population (the CGM population) included all participants from the mITT population who had evaluable CGM data after the baseline. The safety population was defined as all randomized participants who received at least one dose of study medication.

All summaries and statistical analyses were generated using SAS software, version 9.2. The efficacy analyses are presented using last-observation-carried-forward imputation. The primary end point was analyzed using a mixed model with repeated measurements, with treatment and period as fixed effects and participant as the random effect. The model was fitted to all the data simultaneously, and from this model the relevant treatment differences were estimated as least squares (LS) means with SEs. Statistical comparisons were performed using a two-sided test with a nominal 5% significance level. Mean glucose levels and 24-h glucose profiles were generated by calculating the mean CGM-based glucose level pooled across all participants within each treatment group, reported overall and (for 24-h glucose profiles) by injection schedule. CGM-detected hypoglycemic events were defined as one or more continuously measured interstitial glucose value either ≤70 or <54 mg/dL.

Post Hoc Analyses

To confirm the more stable and prolonged duration of the glucose-lowering activity of Gla-300, the mean and SD of the change per participant (Δ) in CGM-based glucose level in the last 4 h of the 24-h injection interval was calculated for the last 2 weeks of each treatment period, compared between Gla-300 and Gla-100 overall (using mixed model with repeated measurements analysis), and described by treatment group for morning and evening injections (Δ = glucose level 0–5 min before injection − glucose level 4 h before injection).

Intrasubject glucose variability metrics were analyzed by treatment group. Metrics assessed included total SD of all glucose values over all days and times (SD_T), within-day SD (SD_w; averaged over all days), SD of daily means (SD_{dm}), and SD between days (SD_b) for any specified time of day (5). Each variability metric is presented by treatment group as the mean of the SD for all participants in each group.

RESULTS

Study Population

Of 85 participants with type 1 diabetes enrolled in the study, 59 were randomized to treatment with Gla-300 (n = 30) or Gla-100 (n = 29) and included in the mITT population; 29 (97%) in the Gla-300 group and 26 (90%) in the Gla-100 group completed the study (Supplementary Fig. 2). Of the four participants who discontinued the study, one (1.7%) in the Gla-300 group was discontinued because of pregnancy (details are provided in the ADVERSE EVENTS section), and three (5.1%) in the Gla-100 group were discontinued because of "other" non-safety-related reasons. Baseline characteristics were similar across treatment groups. Characteristics of the entire study population were mean age 44.2 years; mean duration of diabetes 22.1 years; mean HbA_{1c} 7.46% (58.0 mmol/mol); and prior total daily insulin dose 0.6 units/kg/day (Supplementary Tables 1 and 2).

Glycemic Control (as Measured by CGM)

The mean percentage of time within the predefined target glycemic range of 80–140 mg/dL during the last 2 weeks of treatment (primary end point) was comparable between the Gla-300 and Gla-100 groups (LS mean [SE] 31.8% [1.5] vs. 31.0% [1.6], respectively; LS mean difference 0.75% [95% CI −3.61 to 5.12]; P = 0.73) (Fig. 1). There was also no difference between the Gla-300 and Gla-100 treatment groups in the mean percentage of time in the target range when the injection was in the morning (mean [SE] 31.6% [1.8] vs. 31.5% [1.7]) or in the evening (32.0% [1.7] vs. 30.5% [1.8]). There was no meaningful difference between treatment groups in terms of

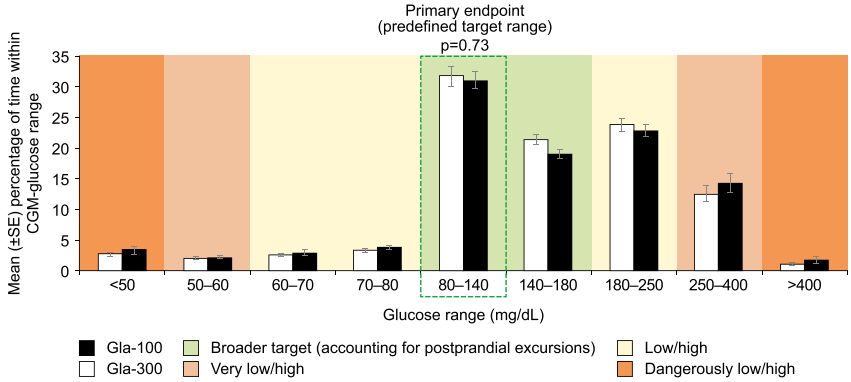


Figure 1—Mean percentage of time within glucose ranges during the last 2 weeks of each treatment period overall among the CGM population.

the percentage of time spent at values <80 mg/dL (LS mean difference −1.6% [95% CI −4.61 to 1.36]; $P = 0.28$) or >140 mg/dL (LS mean difference 0.87% [95% CI −5.22 to 6.96]; $P = 0.78$).

CGM-detected low interstitial glucose values during the entire on-treatment period in the Gla-300 and the Gla-100 groups are shown in Supplementary Fig. 3*A* (at either threshold [≤70 and <54 mg/dL] and by injection time) and Supplementary Fig. 3*B*.

24-h Glucose Profile

Figure 2 shows the mean 24-h glucose profiles obtained by CGM during the last 2 weeks of each treatment period for participants receiving Gla-300 and Gla-100, pooled across participants in each treatment group. The profiles were smoother with Gla-300, showing smaller differences in glucose levels throughout the 24-h period than with Gla-100 (difference between the daily minimum and maximum values: Gla-300, 14 mg/dL; Gla-100, 28 mg/dL) (Fig. 2*A*). This was particularly evident when comparing by injection time: profiles of the Gla-300 morning and evening injection groups were almost able to be superimposed (Fig. 2*B*), whereas there were larger glycemic excursions in the Gla-100 morning injection group (minimum/maximum values, 149/189 mg/dL) compared with the evening injection group (minimum/maximum values, 162/183 mg/dL) (Fig. 2*C*).

Glycemic Control in the Last 4 h of the 24-h Injection Interval

In a post hoc sensitivity analysis, the mean (SD) change (Δ) in glucose level during the last 4 h of each participant's 24-h injection interval showed significantly less increase for Gla-300 than for Gla-100 (10.9 [24.5] vs. 26.5 [21.0] mg/dL, respectively; LS mean difference between groups, −14.7 mg/dL [95% CI −26.9 to −2.5]; $P = 0.0192$). The difference in favor of Gla-300 was observed regardless of injection time.

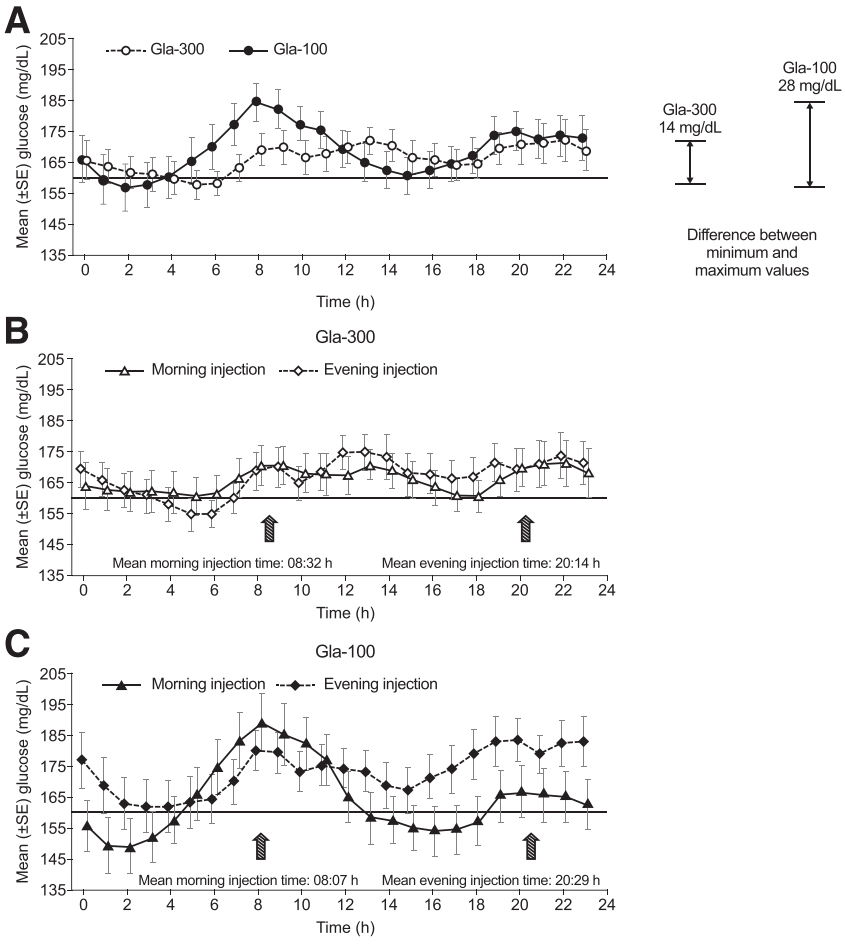


Figure 2—Mean glucose profile over 24 h during the last 2 weeks of each treatment period, pooled across participants in the CGM population: Gla-300 vs. Gla-100 overall (*A*); Gla-300 by injection schedule (*B*); Gla-100 by injection schedule (*C*). Data displayed are mean hourly glucose values by time of day, pooled across all participants within each treatment group and time of administration. The postprandial SMPG target used in this study (160 mg/dL) is represented by a horizontal black line to better enable comparisons between panels. Arrows represent the mean time of morning and evening injections.

Mean Glucose

Mean interstitial glucose levels decreased over the 16-week treatment period in the Gla-300 group, from 182.1 mg/dL at baseline to 165.0 mg/dL at week 16 (mean change from baseline −13.2 mg/dL), and in the Gla-100 group, from 172.6 mg/dL at baseline to 169.3 mg/dL at week 16 (mean change from baseline −2.7 mg/dL).

Glucose Variability Metrics

All metrics assessing the intrasubject CGM glucose variability, whether within days or between days (SD_T, SD_W, SD_{dm}, and SD_b), showed no statistical difference in glucose measurements for those receiving Gla-300 compared with those receiving Gla-100 during the last 2 weeks of each treatment period (Fig. 3).

HbA_{1c}

At baseline, mean HbA_{1c} was similar in both treatment groups (Gla-300, 7.51%; Gla-100, 7.41%). The mean change from baseline to week 16 was −0.44% (95% CI −0.64 to −0.24) in the Gla-300 group, a statistically significant decrease, and −0.22% (−0.45 to 0.01) in the Gla-100 group.

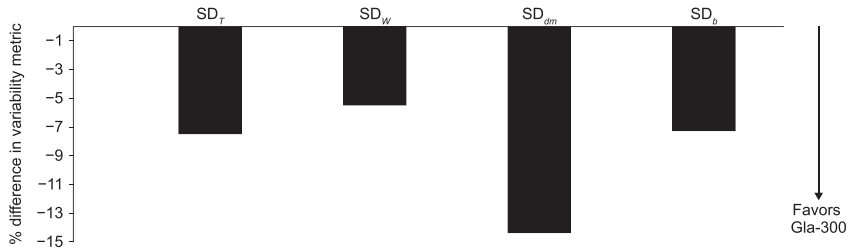
Daily Insulin Dose

The total (basal + mealtime) daily insulin dose throughout the study remained relatively stable in both groups (Gla-300 group: baseline, 0.68 units/kg and week 16, 0.67 units/kg; Gla-100 group: baseline, 0.59 units/kg and week 16, 0.63 units/kg). The daily basal insulin dose increased slightly in both groups from baseline to week 16 (Gla-300 group: baseline, 0.30 units/kg and week 16, 0.35 units/kg; Gla-100 group: baseline, 0.30 units/kg and week 16, 0.33 units/kg) (Supplementary Table 2).

Safety

Hypoglycemia (by Participant-Recorded SMPG)

Throughout the 16-week study, the rate of confirmed (<54 mg/dL) or severe hypoglycemia was lower during the nocturnal interval (0000–0559 h) with Gla-300 versus Gla-100 (Gla-300: 4.0 events per participant-year, Gla-100: 9.0 events per



Absolute values; mean (SE) (mg/dL)	SD$_T$	SD$_W$	SD$_{dm}$	SD$_b$
Gla-100	76.1 (2.7)	61.4 (1.8)	41.4 (2.5)	72.7 (2.8)
Gla-300	70.5 (2.4)	58.1 (2.1)	35.5 (1.7)	67.5 (2.3)
P-value	0.126	0.229	0.052	0.157

Figure 3—Glucose variability metrics during the last 2 weeks of each treatment period for the CGM population, showing the relative difference between Gla-300 and Gla-100.

participant-year; rate ratio 0.45 [95% CI 0.24–0.82]) (Fig. 4). Rates of such events at any time of day (24 h) were comparable between the Gla-300 and Gla-100 groups. When assessing hypoglycemia at the less stringent glycemic threshold (≤70 mg/dL), rates of confirmed or severe events, both at any time of day (24 h) and during the nocturnal interval (0000–0559 h), were comparable between the Gla-300 and Gla-100 groups. There were no consistent differences between morning and evening injection within each treatment group (data not shown).

One participant (3.3%) receiving Gla-300 and three participants (10.3%) receiving Gla-100 each reported one severe hypoglycemic event (defined as requiring assistance from another person). The participant in the Gla-300 group experienced confusion and was treated with glucagon; the three participants in the Gla-100 group received oral carbohydrate.

Adverse Events

In total, 24 participants (80%) receiving Gla-300 and 19 participants (66%) receiving Gla-100 reported one or more treatment-emergent AE. The most commonly reported AEs were nasopharyngitis, headache, pyrexia, and influenza (Supplementary Table 3). One participant in the Gla-300 group who had a history of repeated abdominal obstruction experienced a serious treatment-emergent AE (intestinal obstruction), which was not considered to be related to the study treatment and resolved following treatment. Another participant in the Gla-300 group was withdrawn from the study owing to a treatment-emergent AE of pregnancy. At the time the database was locked, the pregnancy was continuing without any reported abnormalities. A healthy child was prematurely delivered at 33 weeks' gestation.

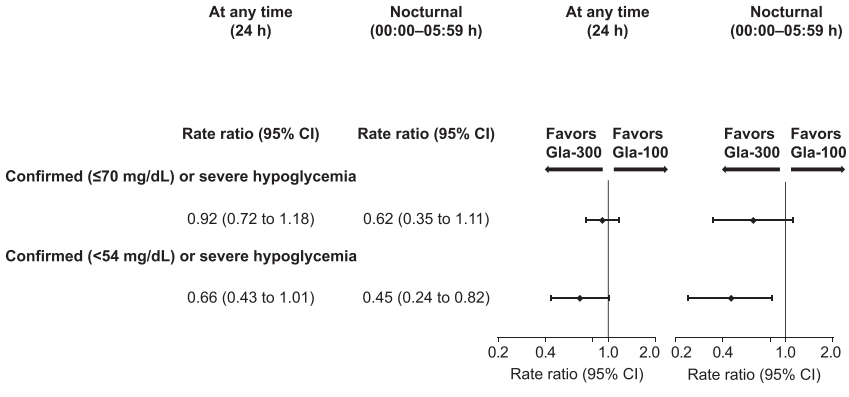


Figure 4—Ratios of annualized rates (events per participant-year) of confirmed (≤70 and <54 mg/dL) or severe hypoglycemia (based on case report form data) among the safety population.

CONCLUSIONS

A fundamental goal of type 1 diabetes management is to maintain glucose levels within a target range and to minimize vulnerability to hypoglycemic or hyperglycemic events that can lead to short- and/or long-term health complications (6–8). To achieve this, the "ideal" basal insulin should provide stable glucose-lowering activity over an entire 24-h period and help maintain target glucose levels in the fasting state and before meals (9). The basal insulin can then be paired with a rapid-acting insulin before a meal that is adjusted to optimize glycemic control after the meal (10). The first generation of basal insulin analogs have substantially improved glucose management, offering a prolonged duration of action and a lower risk of hypoglycemia, particularly overnight, compared with NPH insulin (11). However, only a small percentage of individuals with type 1 diabetes who use these first-generation analogs achieve glycemic targets, and excursions into clinically dangerous hypoglycemic and hyperglycemic states are common (12).

The results of these CGM analyses consistently demonstrated a more even distribution of glucose-lowering activity throughout the entire 24-h injection interval with Gla-300 compared with Gla-100 based on glucose profiles pooled across individuals. Although there was no difference between Gla-300 and Gla-100 regarding the time spent in the predefined target glycemic range of 80–140 mg/dL during weeks 7–8 and weeks 15–16 combined (Gla-300: 31.8%; Gla-100: 31.0%), the relatively low percentage of time in the target glycemic range in both treatment groups may be attributed to the upper limit being defined as 140 mg/dL, which is lower than the postprandial target of 160 mg/dL used in this study and considerably lower than the 180 mg/dL after-meal upper limit set by the American Diabetes Association (7).

The mean 24-h glucose profile, averaged for all participants on CGM in each group by time of day, showed a narrower range of daily interstitial glucose levels for Gla-300 than for Gla-100. This difference in profile was even more evident when morning and evening injection groups were compared; the glucose profiles of Gla-300 morning and evening

injections are nearly superimposable, whereas larger excursions were seen in the morning injection group compared with the evening injection group for Gla-100. The increase in glucose levels from 0200−0800 h in the Gla-100 morning injection group may be more pronounced than any glucose increases seen in the evening injection group as a result of the basal insulin waning toward the end of the 24-h dosing interval, which is not masked by the use of rapid-acting insulin during this early morning period. While glucose variability metrics were smaller for Gla-300 than Gla-100, consistent with the 24-h glucose profiles, there were no statistically significant differences in these metrics.

Evidence of the more prolonged glucose-lowering activity of Gla-300 versus Gla-100 is most apparent toward the end of the daily injection interval, as shown by a significantly smaller increase in glucose within the last 4 h of the injection interval for Gla-300 than for Gla-100. These observations indicate that Gla-300 has a more sustained glucose-lowering action and provide clinical evidence of this prolonged glycemic control over an entire 24-h period. These results are consistent with previous findings from euglycemic clamp studies (2,3).

Rates of hypoglycemia detected using SMPG values were consistent with the interstitial glucose values detected by CGM. The annualized event rates for SMPG-confirmed or severe hypoglycemia were lower in the Gla-300 than Gla-100 group during the nocturnal period (0000–0559 h), which showed a risk reduction of 55% for confirmed (<54 mg/dL) or severe hypoglycemia. During the nocturnal period, mealtime insulin would be expected to have minimal effect as a contributory factor, allowing a more reliable comparison of the effects of basal insulin. There were no consistent within-treatment differences in terms of hypoglycemia risk between the morning and evening injection groups for either of the insulin preparations. The phase IIIa EDITION 4 study also investigated Gla-300 versus Gla-100 in people with type 1 diabetes and observed an increase in SMPG with Gla-300 before breakfast in the initial weeks of the study that might have affected the risk of hypoglycemia. In the current study, however, mean 24-h glucose profiles do not provide any indication of glucose levels being higher with Gla-300 than with Gla-100 at a time that might be considered "before breakfast." In addition, the hypoglycemia results presented here could be influenced by the fact that mean interstitial glucose levels were higher with Gla-300 than Gla-100 at baseline, although this was likely offset by the greater decrease in glucose over the study period with Gla-300 and the lower final mean glucose in that group.

The similar findings in the morning and evening injection groups for Gla-300 suggest the potential for flexibility to select an injection time (morning or evening) without compromising clinical benefits, and should enable people with diabetes to select their insulin injection schedule according to their lifestyle to reduce the burden of therapy (e.g., a morning dosing time would not be emphasized to avoid the nocturnal hypoglycemia that occurred in some patients given Gla-100 at bedtime) (13). The consistent 24-h insulin activity with Gla-300 suggests there would be value in a clinical trial exploring whether people currently using Gla-100 twice daily could be adequately controlled with Gla-300 once daily.

The safety profile of both treatments in this study was consistent with that reported previously (13–16), with similar numbers of participants in each group experiencing AEs. Both treatments were well tolerated.

The phase IIIa EDITION 4 study also compared morning versus evening injection times (13). This 6-month treat-to-target study demonstrated comparable glucose control with Gla-300 and Gla-100, in terms of HbA_{1c} and fasting plasma glucose, which did not differ between the morning and evening injection groups. Hypoglycemia rates were generally similar between treatment groups, except for lower nocturnal hypoglycemia with Gla-300 than Gla-100 in the first 8 weeks of the study. Neither hypoglycemia nor the AE profile differed by time of injection.

This exploratory CGM study has limitations: the open-label study design, which was unavoidable because of the different injection volumes of Gla-300 and Gla-100, and the use of commercial syringes that are not approved for use with Gla-300 in clinical practice and are suboptimal for delivery of an insulin with a concentration of 300 units/mL. Future studies could be enhanced by using the recently approved Gla-300 pen injector; the use of syringes with Gla-300 might be expected to increase glucose variability in the Gla-300 group, although an increase in variability was not seen in this study. This study also used a short duration of treatment (two 8-week periods), although a 2-week period of CGM (weeks 7–8 in this study) is considered to be representative of the longer-term pattern of glucose levels (17). A modest number of participants were enrolled, with crossover of the injection schedule (morning to evening or vice versa), so group size was limited, with a low power to detect differences between treatments—that is, the percentage of time within the glucose range of 80–140 mg/dL (the primary end point), glucose variability metrics, and post hoc analyses. This exploratory study involved participants with type 1 diabetes with relatively good glycemic control at baseline (HbA_{1c} 7.5% in the Gla-300 group and 7.4% in the Gla-100 group), which might have limited the improvement of the quality of glycemic control. Nevertheless, consistent differences were noted between Gla-300 and Gla-100 in terms of the average glucose profiles pooled across individuals, CGM-detected low and high interstitial glucose values, SMPG-documented nocturnal hypoglycemia (0000−0559 h), and CGM-determined glucose levels during the last 4 h of each participant's injection interval.

Recording interstitial glucose levels continuously throughout the day and night is a valuable tool for comparing new therapies and an important way to confirm whether observed PK/PD differences between insulins can be translated to clinically relevant differences in 24-h glucose profiles. CGM is also particularly useful for evaluating hypoglycemia and glucose variability, measures that are very difficult to capture accurately or to compare between treatments using intermittent SMPG data.

In conclusion, in people with moderately well-controlled type 1 diabetes, CGM findings are consistent with previously reported PK/PD analyses, demonstrating that Gla-300 offers improved glycemic control over a full 24-h period, with less fluctuation in glucose levels, compared with Gla-100. These results imply that Gla-300 should improve the flexibility of the injection

schedule (morning or evening) without compromising glycemic control.

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Author Contributions. R.M.B. was the principal investigator of this study. R.M.B., M.Z., and I.M.-B. designed the protocol, analyzed and interpreted data, and wrote the manuscript. T.S.B. and A.J.A. were investigators, saw participants at designated visits, monitored participants during the trial, and reviewed and revised the manuscript. D.R. guided several aspects of the statistical analysis of glucose metrics and reviewed and revised the manuscript. H.G. performed the statistical analysis of the data and reviewed and revised the manuscript. All authors had access to relevant study data and interpreted data, reviewed and commented on several drafts of the manuscript, and had the final responsibility to submit the article for publication. R.M.B. is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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