New Insulin Glargine 300 Units/mL Versus Glargine 100 Units/mL in People With Type 2 Diabetes Using Oral Agents and Basal Insulin: Glucose Control and Hypoglycemia in a 6-Month Randomized Controlled Trial (EDITION 2)

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OBJECTIVE

To compare the efficacy and safety of new insulin glargine 300 units/mL (Gla-300) with glargine 100 units/mL (Gla-100) in people with type 2 diabetes using basal insulin (≥42 units/day) plus oral antihyperglycemic drugs (OADs).

RESEARCH DESIGN AND METHODS

EDITION 2 was a multicenter, open-label, two-arm study. Adults receiving basal insulin plus OADs were randomized to Gla-300 or Gla-100 once daily for 6 months. The primary end point was change in HbA_{1c}. The main secondary end point was percentage of participants with one or more nocturnal confirmed (≤3.9 mmol/L [≤70 mg/dL]) or severe hypoglycemic events from week 9 to month 6.

RESULTS

Randomized participants (n = 811) had a mean (SD) HbA_{1c} of 8.24% (0.82) and BMI of 34.8 kg/m^2 (6.4). Glycemic control improved similarly with both basal insulins; least squares mean (SD) reduction from baseline was −0.57% (0.09) for Gla-300 and −0.56% (0.09) for Gla-100 (mean difference −0.01% [95% CI −0.14 to 0.12]), with 10% higher dose of Gla-300. Less nocturnal confirmed (≤3.9 mmol/L [≤70 mg/dL]) or severe hypoglycemia was observed with Gla-300 from week 9 to month 6 (relative risk 0.77 [95% CI 0.61–0.99]; P = 0.038) and during the first 8 weeks. Fewer nocturnal and any time (24 h) hypoglycemic events were reported during the entire 6-month period. Weight gain was lower with Gla-300 than with Gla-100 (P = 0.015). No between-treatment differences in safety parameters were identified.

CONCLUSIONS

Gla-300 was as effective as Gla-100 and associated with a lower risk of hypoglycemia during the night and at any time of the day.

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Insulin glargine 100 units/mL (Gla-100) is a once-daily, long-acting basal insulin analog that induces less hypoglycemia than neutral protamine Hagedorn (NPH) insulin (1). Its efficacy in achieving and maintaining target glycemic control and safety profile in terms of cardiovascular risk and cancer is well documented (1–6). However, hypoglycemia continues to be observed even during Gla-100 treatment (1). Fears of hypoglycemia and other concerns, such as weight gain, are a barrier to people beginning or continuing insulin therapy and can impair adherence to the treatment regimen (7,8). To address this problem, a new insulin glargine (Gla-300), which contains 300 units/mL insulin glargine, has been developed. After subcutaneous injection, Gla-300 has been shown to have smoother, more stable, and prolonged pharmacokinetic and pharmacodynamic profiles than Gla-100, resulting from an extended release of glargine from the subcutaneous depot (9).

To determine whether these properties will translate into clinical benefits, Gla-300 is being compared with Gla-100 in the phase 3a EDITION program. EDITION 1, the first study in this program, showed that in people with type 2 diabetes receiving ≥42 units/day of basal insulin plus mealtime insulin, use of Gla-300 led to a similar improvement in glycemic control as Gla-100. Gla-300 was, however, associated with a 21% reduction in the relative risk (RR) of nocturnal confirmed or severe hypoglycemic events compared with Gla-100 (RR 0.79 [95% CI 0.67–0.93], P = 0.0045), without increases in overall or daytime events (10). Consistent reductions in hypoglycemia were observed during the first 8 weeks (titration phase) and across the entire 6-month treatment period. Here, we report results from EDITION 2, which compared the efficacy and safety of Gla-300 and Gla-100 in people with type 2 diabetes previously receiving basal insulin therapy in combination with oral antihyperglycemic drugs (OADs), but without injections of rapid-acting mealtime insulin.

RESEARCH DESIGN AND METHODS

Study Design and Participants

EDITION 2 was a multicenter, randomized, open-label, two-arm, parallel-group, phase 3a study conducted between 14 December 2011 and 26 April 2013, with 811 participants with type 2 diabetes. The study comprised a 2-week screening phase, followed by a 6-month treatment period and a 6-month safety extension period. The study also included a 4-week posttreatment follow-up period to monitor safety and efficacy during the transition back to a commercially available basal insulin. Results from the main 6-month treatment period will be presented here.

Participants were recruited as outpatients in 213 centers across 13 countries (Canada, Chile, Finland, France, Germany, Hungary, Mexico, Portugal, Romania, Russia, South Africa, Spain, and the United States of America). Local or national ethics committees approved the protocol, which was conducted according to Good Clinical Practice and the Declaration of Helsinki. All participants provided informed, written consent. Inclusion criteria comprised age ≥18 years with type 2 diabetes (World Health Organization definition [11]) for at least 1 year before screening and at least 6 months on basal insulin treatment, assessed as recent use within the last 4 weeks of ≥42 units/day of Gla-100 or NPH combined with OAD(s). Exclusion criteria included HbA_{1c} <7.0% or >10%; recent (within the past 3 months) use of premixed insulin, insulin detemir, or new glucose-lowering agents; recent (within the past 2 months) use of sulfonylurea; recent (>10 days in the past 3 months) use of human regular insulin or mealtime insulin; and rapidly progressing diabetic retinopathy (which may likely require laser/surgical treatment during the study), end-stage renal disease (defined as those participants requiring dialysis or transplantation [12]), or clinically significant cardiac, hepatic, or other systemic disease.

Randomization and Masking

Participants were randomized (1:1) to once-daily injections of Gla-300 (using a modified SoloSTAR pen) or Gla-100 (Lantus, using a SoloSTAR pen). The precision of the modified SoloSTAR device was adequate for use with Gla-300 at starting doses at or above 42 units. Randomization used a centralized interactive voice or Internet response system (block size: 4) and was stratified by HbA_{1c} <8.0% (<64 mmol/mol) and ≥8.0% (≥64 mmol/mol) at screening. Owing to differences in the injection devices, this was an open-label study.

Interventions

Participants received a once-daily subcutaneous injection of Gla-300 or Gla-100, administered in the evening (i.e., immediately before the evening meal until bedtime) at the same time of the day throughout the study. Gla-300 or Gla-100 was titrated to a fasting self-monitored plasma glucose (SMPG) target of 4.4–5.6 mmol/L. For participants previously using Gla-100 or NPH once daily, the starting dose of Gla-300 or Gla-100 was the basal insulin dose before randomization; for those previously taking NPH more than once daily, the starting dose of the new basal insulin was reduced by ~20%. The insulin dose was adjusted once weekly, based on median fasting SMPG from the preceding three measurements, to be increased by 3 units if the median SMPG was above 5.6 but less than 7.8 mmol/L, and by 6 units if the median SMPG was ≥7.8 mmol/L. The dose was decreased by 3 units if fasting SMPG readings were <4.4 mmol/L or at the discretion of the investigator. Adjustments were restricted by protocol in both groups to changes divisible by 3 units, the smallest adjustment possible for Gla-300 because of the characteristics of the pen-injector. OAD therapy, with the exception of sulfonylureas, was continued at a stable dose. If the fasting plasma glucose (FPG) or HbA_{1c} measurements were above target values and there was no reasonable explanation for insufficient glucose control, or if appropriate action failed to decrease the levels to below threshold values, the investigator had the option to initiate rescue therapy. The choice of the rescue therapy was based on investigator's decision and local approved guidelines.

Study visits occurred at screening (week −2), baseline, weeks 2, 4, 8, and 12, and months 4 and 6. Interim telephone contacts were scheduled at weeks −1, 1, 3, 5–7, and 9–11. Samples for central measurement of HbA_{1c} and FPG concentrations were collected at baseline, week 12, and month 6. Eight-point SMPG profiles (before and 2 h after breakfast, lunch, and dinner, and at bedtime and 0300 h) were performed at baseline and before each study visit.

Outcomes

The primary end point was change in HbA_{1c} from baseline to month 6 or the last visit on treatment and without rescue therapy. The first main secondary efficacy end point was the percentage of participants with one or more confirmed (≤3.9 mmol/L [≤70 mg/dL]) or severe hypoglycemic events occurring during the night (termed nocturnal, 0000–0559 h), reported between the start of week 9 and month 6 or the last visit on treatment and without rescue therapy. Other main secondary end points included change from baseline in preinjection SMPG and change in variability of preinjection SMPG. Further secondary end points included change in FPG; percentage of participants attaining HbA_{1c} <7.0% (<53 mmol/mol) and ≤6.5% (≤48 mmol/mol) or FPG ≤6.7 mmol/L and <5.6 mmol/L; change in mean and variability of 24-h plasma glucose based on 8-point SMPG profiles; change in basal daily insulin dosages and in body weight. The percentages of participants with hypoglycemic events and the annualized event-rates for hypoglycemia, as categorized by the American Diabetes Association, were systematically recorded (13). Adverse events, including injection site reactions, were recorded at each visit. Treatment satisfaction was assessed using the validated Diabetes Treatment Satisfaction Questionnaire (DTSQ), completed on day 1, week 12, and month 6. The main secondary end point of nocturnal hypoglycemia was changed before participant enrollment to exclude self-reported nonsevere hypoglycemia episodes that were not confirmed by plasma glucose data (probable symptomatic hypoglycemia).

Data Analysis and Statistics

The modified intent-to-treat (mITT) population was defined as all randomized participants who received at least one dose of study insulin and had both a baseline and one or more postbaseline assessments. If a participant discontinued treatment prematurely or did not have an efficacy measurement at month 6, a last observation carried forward procedure was applied on rescue-free measurements. Safety analyses included all participants randomized and exposed to one dose or more of study insulin.

To assess noninferiority for the primary end point, the upper bound of the two-sided 95% CI of the least squares (LS) mean difference, estimated by an ANCOVA model, was compared with the predefined noninferiority margin (<0.40% HbA_{1c}). If noninferiority was demonstrated for HbA_{1c}, superiority was tested for HbA_{1c} (one-sided α = 0.025) and the main secondary efficacy end points according to a hierarchical testing procedure. Hypoglycemic event rates were analyzed using an overdispersed Poisson regression model. All continuous secondary efficacy variables (except for change in variability of plasma glucose) were analyzed using a similar ANCOVA model. Variability of preinjection SMPG was assessed from the mean coefficient of variation calculated using at least three SMPG readings from the preceding 7 days. Change in variability of preinjection SMPG was analyzed using an ANOVA model with treatment, strata of screening HbA_{1c} (<8.0% and ≥8.0%), and country as fixed effects. Categorical secondary efficacy variables (responder rates) were analyzed using a Cochran-Mantel-Haenszel method stratified according to screening HbA_{1c} (<8.0% [<64 mmol/mol] and ≥8.0% [≥64 mmol/mol]).

Role of the Funding Source

Sanofi was the sponsor, and designed and coordinated the study, monitored clinical sites, collected and managed the data, and performed statistical analyses. H.Y.-J., M.C.R., and R.B. took part in the protocol design, data interpretation, and manuscript writing. All authors had full access to the study data and had final responsibility to submit the article for publication.

RESULTS

Study Population

A total of 811 participants were randomized to Gla-300 (n = 404) or Gla-100 (n = 407; Supplementary Fig. 1). One participant in each group did not receive treatment, and one participant in the Gla-100 group had no baseline or postbaseline HbA_{1c} measurements; therefore, 403 and 405 participants, respectively, formed the mITT population. Treatment was discontinued by 36 participants (8.9%) in the Gla-300 group and by 38 (9.3%) in the Gla-100 group. The most common reason for discontinuation was participant's request. Baseline characteristics were similar between treatment groups (Table 1). Mean duration of diabetes was 13 years (SD 7); BMI 34.8 kg/m^2 (6.4); HbA_{1c} 8.24% (0.82) or 66.6 mmol/mol (9.0); FPG 8.03 mmol/L (2.83) or 145 mg/dL (51); and basal insulin dose 0.67 units/kg/day (0.24). The most common concomitant medication at randomization was metformin, which was used by 94.8% of participants in the Gla-300 group and by 93.6% in the Gla-100 group (Table 1). Less than 5% of all participants had used sulfonylureas, which were to be discontinued 2 months before randomization according to protocol. Eight participants in the Gla-300 group and two in the Gla-100 group were still receiving concomitant sulfonylurea medication at randomization, and one further participant in each group commenced sulfonylurea treatment during the study, representing protocol violations. During the 6-month on-treatment period, rescue therapy was initiated in 23 (5.7%) and 20 (4.9%) Gla-300 and Gla-100 participants, respectively (Supplementary Fig 1). The most frequent type of rescue therapy used was rapid-acting insulin analogs (19 [4.7%] in the Gla-300 group and 18 [4.4%] in the Gla-100 group).

Glycemic Responses and Insulin Dosage

The decrease in HbA_{1c} from baseline to month 6 was comparable for both groups (Fig. 1*A*). The mean HbA_{1c} at month 6 was 7.57% (59.2 mmol/mol) in the Gla-300 group and 7.56% (59.1 mmol/mol) in the Gla-100 group. The LS mean (SE) change was −0.57% (0.09) or −6.2 mmol/mol (1.0) for Gla-300 and −0.56% (0.09) or −6.1 mmol/mol (1.0) for Gla-100, with a mean (SE) difference of −0.01% (0.07; 95% CI −0.14 to 0.12) or −0.1 mmol/mol (0.8; 95% CI −1.5 to 1.3). Because the upper CI limit was lower than the predefined noninferiority margin of 0.4%, Gla-300 demonstrated noninferiority for glycemic control.

Similar reductions in FPG from baseline were observed in both treatment groups (Supplementary Fig. 2 and Supplementary Table 1). Similar proportions of participants reached target HbA_{1c} <7.0% (<53 mmol/mol) and ≤6.5% (≤48 mmol/mol); 30.6% and 14.5% with Gla-300, and 30.4% and 14.8% with Gla-100,

Table 1—Baseline demographics (randomized population)

	Gla-300 *n* = 404	Gla-100 *n* = 407
Age, years	57.9 (9.1)	58.5 (9.2)
Sex (male), *n* (%)	187 (46.3)	185 (45.5)
Ethnic group, *n* (%)		
Caucasian	378 (93.6)	383 (94.1)
Black	20 (5.0)	16 (3.9)
Asian/Oriental	3 (0.7)	7 (1.7)
Other	3 (0.7)	1 (0.2)
Body weight, kg	98.7 (22.3)	98.0 (20.8)
BMI, kg/m^2	34.8 (6.6)	34.8 (6.1)
Duration of diabetes, years	12.7 (7.1)	12.5 (7.0)
Duration of basal insulin treatment, years	3.78 (3.73)	3.83 (3.34)
Previous basal insulin dose		
units/kg/day	0.66 (0.22)	0.68 (0.25)
units/day	64.07 (25.59)	65.69 (26.14)
Previous basal insulin, *n* (%)		
Insulin glargine	301 (74.9)	332 (82.8)
NPH	101 (25.1)	69 (17.2)
Previous basal insulin injections, *n* (%)		
Once daily	315 (78.4)	322 (80.1)
Twice daily	83 (20.6)	76 (18.9)
More than twice daily	4 (1.0)	4 (1.0)
Prior use of insulin glargine, *n* (%)	304 (75.2)	337 (82.8)
OAD treatment*, *n* (%)		
Biguanides	383 (94.8)	381 (93.6)
Dipeptidyl peptidase 4 inhibitors	31 (7.7)	51 (12.5)
Sulfonylureas	8 (2.0)	2 (0.5)
Thiazolidinediones	6 (1.5)	14 (3.4)
Combinations of OADs	5 (1.2)	10 (2.5)
Other	11 (2.7)	16 (3.9)
HbA_{1c}		
%	8.26 (0.86)	8.22 (0.77)
mmol/mol	66.8 (9.4)	66.3 (8.4)

Data are mean (SD) unless otherwise specified. *OAD treatment was continued at stable doses during the study on-treatment period, with the exception of sulfonylureas, which were to be stopped 2 months before randomization according to protocol. Eight participants in the Gla-300 group and two participants in the Gla-100 group did not discontinue sulfonylurea treatment at randomization, and a further one participant in each group commenced sulfonylurea treatment during the study, representing protocol violations.

respectively (Supplementary Table 1). The proportions of participants attaining FPG ≤6.7 or <5.6 mmol/L were similar between treatment groups (48.7 and 29.4% for Gla-300 vs 54.1 and 33.6% for Gla-100).

Overall, glucose measurements of the 8-point profile showed a comparable decrease in SMPG for both Gla-300 and Gla-100 (Fig. 1*B*). However, the mean prebreakfast SMPG was lower with Gla-100 than with Gla-300 during the first 8 weeks, and a more gradual decrease in prebreakfast SMPG was observed with Gla-300 than with Gla-100 (Fig. 1*C*). At month 6, a similar average prebreakfast SMPG was reached in both groups (6.59 mmol/L or 119 mg/dL for Gla-300 and 6.28 mmol/L or 113 mg/dL for Gla-100; Fig. 1*C*). Comparable results were observed between Gla-300 and Gla-100 for change in preinjection SMPG and variability in preinjection SMPG (Supplementary Table 1).

The daily basal insulin dose increased from baseline to the end point (month 6) in both groups, mainly during the first 12 weeks (Fig. 1*D*). The daily basal insulin dose increased from 0.64 units/kg/day (SD 0.22) at baseline to 0.92 units/kg/day (0.31) (corresponding to 91 units/day [37]) at the end of the 6-month treatment period with Gla-300, and from 0.66 units/kg/day (0.23) to 0.84 units/kg/day (0.28) (82 units/day [31]) with Gla-100. There was a slight but significant difference in insulin dose between treatment groups at month 6 (LS mean difference 11 units/day [95% CI 8–14]), with those in the Gla-300 group requiring 10% more basal insulin (units/kg/day) than those receiving Gla-100.

Hypoglycemia

Nocturnal Hypoglycemia (0000–0559 h)

During the 6 months of treatment, 123 participants (30.5%) in the Gla-300 group experienced 379 nocturnal hypoglycemic events, and 169 participants (41.6%) in the Gla-100 group experienced 766 nocturnal hypoglycemic events (Supplementary Tables 2 and 3).

Confirmed (≤3.9 mmol/L [≤70 mg/dL]) or Severe Hypoglycemia. A significantly lower percentage of participants reported at least one nocturnal confirmed (≤3.9 mmol/mol [≤70 mg/dL]) or severe hypoglycemic event (0000–0559 h) from week 9 to month 6 with Gla-300 (21.6%) compared with Gla-100 (27.9%) (mITT population). Analysis of this prespecified main secondary end point demonstrated superiority of Gla-300 over Gla-100 (RR 0.77 [95% CI 0.61–0.99], $P = 0.038$). The risk of nocturnal confirmed or severe hypoglycemia was also reduced with Gla-300 compared with Gla-100 during the 6-month study period (RR 0.71 [95% CI 0.58–0.86]) and in the first 8 weeks (RR 0.53 [95% CI 0.39–0.72]) (Fig. 2*A*).

Curves displaying the cumulative mean number of nocturnal confirmed or severe hypoglycemic events per participant during the course of treatment are shown in Fig. 2*B*. Consistent reductions were observed when considering the annualized rates of hypoglycemia (events per participant-year). During the 6-month study period, the annualized rates of nocturnal confirmed (≤3.9 mmol/mol [≤70 mg/dL]) or severe hypoglycemia were 1.89 for Gla-300 and 3.68 for Gla-100 (RR 0.52 [95% CI 0.35–0.77], $P = 0.0010$). Reductions in hypoglycemic events per participant-year were also observed across the first 8 weeks as well as during the maintenance period (Supplementary Table 3).

When assessed as a function of the value of HbA_{1c} at end point, the number of events per participant-year of nocturnal confirmed or severe hypoglycemia from week 9 to month 6 was lower in the Gla-300 group compared with the Gla-100 group ($P = 0.010$). Overall, consistently low rates of nocturnal events

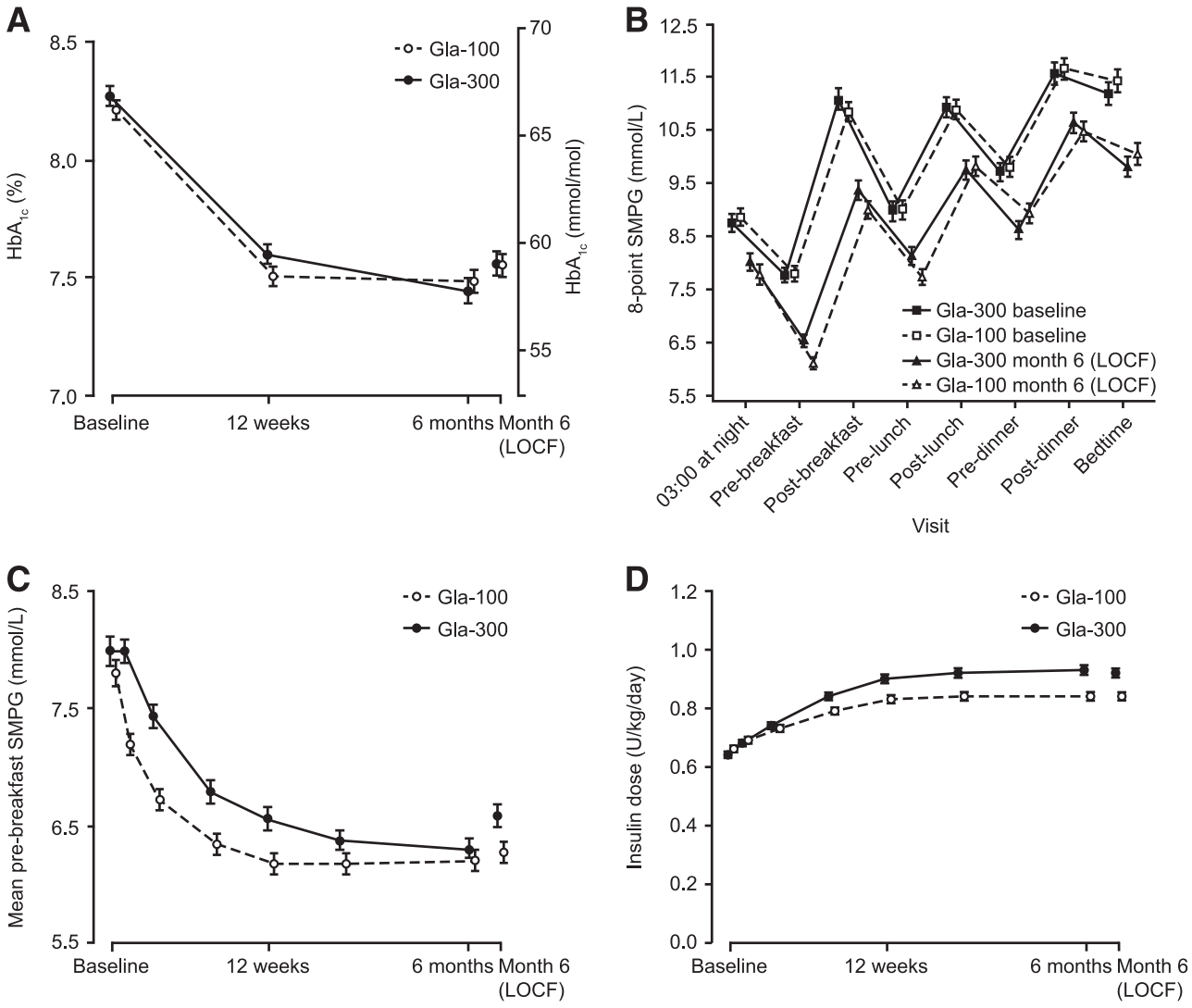


Figure 1—*A*: HbA_{1c} during treatment. *B*: Eight-point SMPG profile. *C*: Mean prebreakfast SMPG profiles (mmol/L). Data are shown as mean ± SE. *D*: Insulin dose (units/kg/day). Data for mITT population. LOCF, last observation carried forward.

were found with Gla-300 and Gla-100 over the entire range of HbA_{1c} (Fig. 2*C*).

Other Categories of Hypoglycemia. When considering nocturnal documented symptomatic hypoglycemia (≤3.9 mmol/L [≤70 mg/dL]) and hypoglycemia across other definitions, a lower percentage of participants experienced one or more events with Gla-300 compared with Gla-100 during the 6-month study period, and during the first 8 weeks (Fig. 2*A* and Supplementary Table 2).

Hypoglycemia at Any Time (24 h)

During the main 6-month treatment period, 288 participants (71.5%) treated with Gla-300 and 322 participants (79.3%) treated with Gla-100 reported one or more hypoglycemic events (any hypoglycemia; Supplementary Table 2). In total, 2,750 hypoglycemic events were reported in the Gla-300 group and 3,675 in the Gla-100 group (Supplementary Table 3).

Confirmed (≤3.9 mmol/L [≤70 mg/dL]) or Severe Hypoglycemia. The percentage of participants who experienced one or more confirmed (≤3.9 mmol/L [≤70 mg/dL]) or severe hypoglycemic events at any time (24 h) was lower with Gla-300 (70.0%) than with Gla-100 (77.3%) during the 6-month study period (RR 0.90 [95% CI 0.83–0.98]). Similarly, fewer participants reported a confirmed or severe hypoglycemic event in the first 8 weeks (titration period) (RR 0.78 [95% CI 0.69–0.89]; Fig. 2*A* and Supplementary Table 2).

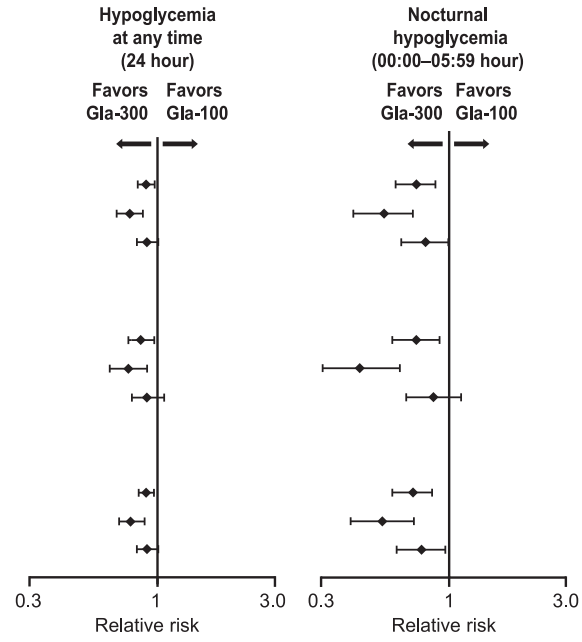
Curves displaying the cumulative mean number of confirmed or severe hypoglycemic events per participant at any time (24 h) show continued between-group divergence during the 6-month treatment period (Fig. 2*D*).

Consistent with the percentage of participants experiencing one or more events, the annualized event rate for confirmed or severe hypoglycemia was statistically significantly lower with Gla-300 than with Gla-100 at 6 months (14.01 vs 18.14; RR 0.77 [95% CI 0.63–0.96], $P = 0.0175$) and showed a more pronounced reduction during the first 8 weeks (RR 0.67 [95% CI 0.51–0.86]).

When assessed as a function of the value of HbA_{1c} at end point, the rates of confirmed or severe hypoglycemia from week 9 to month 6 were lower in the Gla-300 group compared with the Gla-100 group (Fig. 2*C*); however, the difference was not statistically significant ($P = 0.159$).

A

	Hypoglycemia at any time (24 hour)		Nocturnal hypoglycemia (00:00–05:59 hour)	
	RR	95% CI	RR	95% CI
Any hypoglycemia				
Baseline to month 6	0.90	0.83–0.98	0.73	0.61–0.88
Baseline to week 8	0.77	0.68–0.88	0.54	0.40–0.71
Week 9 to month 6	0.91	0.82–1.01	0.80	0.63–1.00
Documented symptomatic hypoglycemia (≤3.9 mmol/L [≤70 mg/dL])				
Baseline to month 6	0.86	0.76–0.98	0.73	0.58–0.92
Baseline to week 8	0.76	0.63–0.92	0.43	0.30–0.63
Week 9 to month 6	0.91	0.78–1.07	0.86	0.66–1.13
Confirmed (≤3.9 mmol/L [≤70 mg/dL]) or severe hypoglycemia				
Baseline to month 6	0.90	0.83–0.98	0.71	0.58–0.86
Baseline to week 8	0.78	0.69–0.89	0.53	0.39–0.72
Week 9 to month 6	0.91	0.82–1.02	0.77	0.60–0.97



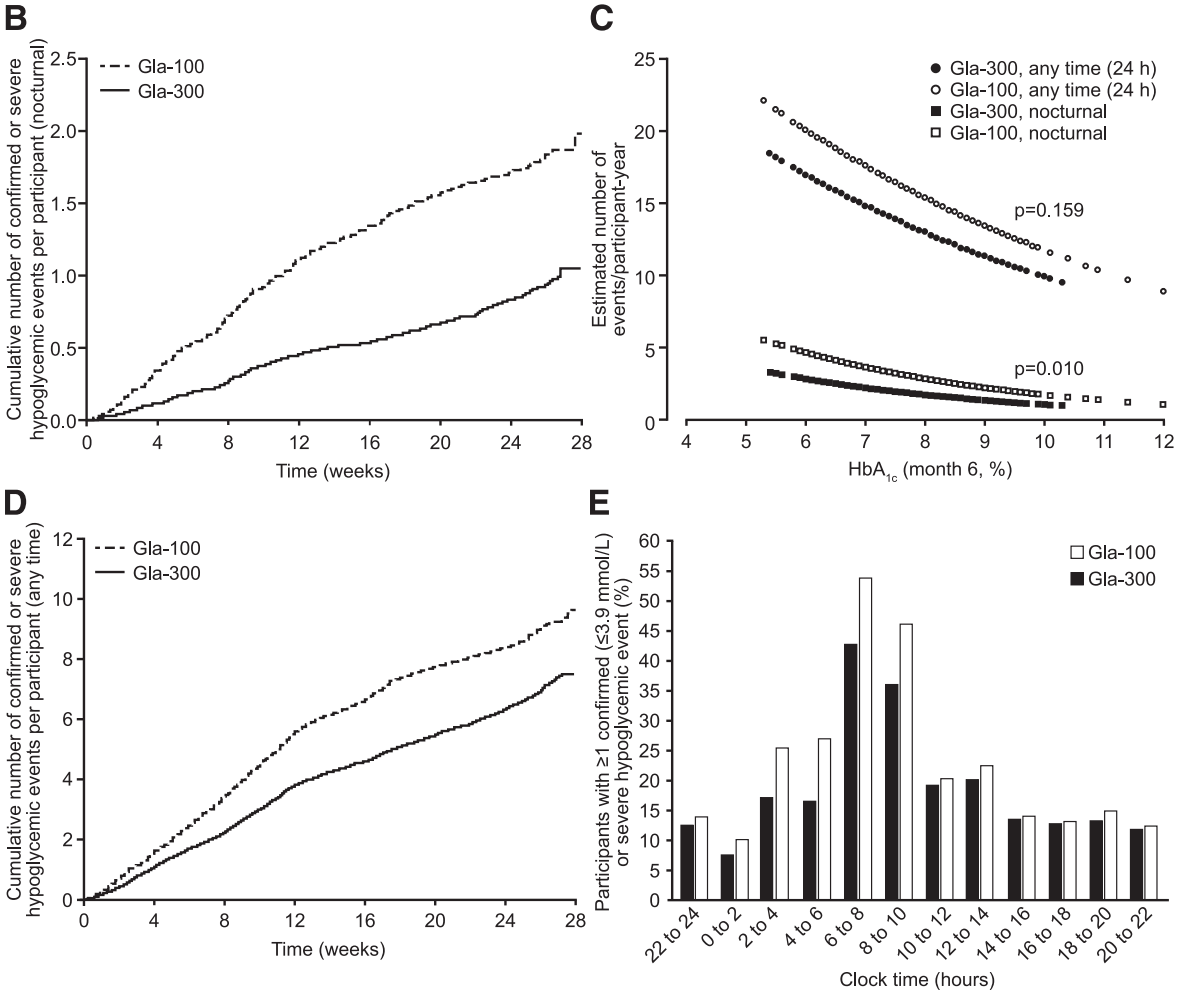


Figure 2—*A*: Relative risk of experiencing one or more hypoglycemic events per participant at any time (24 h) and during the night (0000–0559 h) for Gla-300 vs. Gla-100 during the 6-month treatment period. *B*: Cumulative mean number of nocturnal confirmed (≤3.9 mmol/L [≤70 mg/dL]) or severe hypoglycemic events per participant during the 6-month treatment period. *C*: Estimated number of confirmed (≤3.9 mmol/L [≤70 mg/dL]) or severe events per participant-year from week 9 to month 6 according to HbA_{1c} at month 6. *D*: Cumulative mean number of confirmed (≤3.9 mmol/L [≤70 mg/dL]) or severe hypoglycemic events per participant at any time (24 h) during the 6-month treatment period. *E*: Percentage of participants with one or more confirmed or severe hypoglycemic events by time of day during the 6-month treatment period. Data for safety population.

Looking at events by time of day, a lower risk of hypoglycemia was shown during the night and beyond the predefined nocturnal (0000–0559 h) period (Fig. 2*E*).

Other Categories of Hypoglycemia. Documented symptomatic hypoglycemia (≤3.9 mmol/L [≤70 mg/dL]) and hypoglycemia at any time (24 h) across other definitions was consistently lower with Gla-300 compared with Gla-100 during the 6-month study period and during the first 8 weeks (Fig. 2*A* and Supplementary Table 2).

Severe Hypoglycemia

During the 6-month treatment period, the numbers of participants experiencing severe hypoglycemia at any time (24 h) were low for both groups: four (1.0%) for Gla-300 and six (1.5%) for Gla-100 (Supplementary Table 2). No participants in the Gla-300 group and two (0.5%) in the Gla-100 group experienced severe hypoglycemia during the night (Supplementary Table 2).

Table 2—Most frequent (>5%) TEAEs and serious adverse events

	Gla-300 (*n* = 403)		Gla-100 (*n* = 406)	
	TEAEs *n* (%)	SAEs *n* (%)	TEAEs *n* (%)	SAEs *n* (%)
Any class	237 (58.8)	15 (3.7)	206 (50.7)	15 (3.7)
Infections and infestations	133 (33.0)	2 (0.5)	129 (31.8)	7 (1.7)
Nasopharyngitis	39 (9.7)	0	27 (6.7)	0
Upper respiratory tract infection	17 (4.2)	0	28 (6.9)	1 (0.2)
Nervous system disorders	47 (11.7)	1 (0.2)	38 (9.4)	3 (0.7)
Gastrointestinal disorders	44 (10.9)	1 (0.2)	34 (8.4)	0
Musculoskeletal and connective tissue disorders	44 (10.9)	0	41 (10.1)	1 (0.2)
General disorders and administration site conditions	29 (7.2)	1 (0.2)	29 (7.1)	0
Injury, poisoning, and procedural complications	34 (8.4)	1 (0.2)	21 (5.2)	0

SAE, serious adverse event. Other SAEs, number reported (Gla-300 and Gla-100): benign, malignant, and unspecified neoplasms, including cysts and polyps (1 and 1); metabolism and nutrition disorders (0 and 1); cardiac disorders (6 and 1); vascular disorders (0 and 1); respiratory, thoracic, and mediastinal disorders (1 and 0); skin and subcutaneous tissue disorders (1 and 1); renal and urinary disorders (0 and 1).

Treatment Satisfaction

Mean treatment satisfaction scores collected by the DTSQ corresponded to high satisfaction of participants throughout the study and increased from baseline to month 6 in most participants: 64% with Gla-300 and Gla-100. The LS mean change in total treatment satisfaction score from baseline to month 6 was similar in both groups. The perceived frequency of hypoglycemia, as captured by item 3 of the DTSQ, was also similar between groups.

Changes in Body Weight

Participants treated with Gla-300 did not gain weight (mean change from baseline 0.08 kg [SD 3.45]), whereas weight gain was observed with Gla-100 (0.66 kg [3.01]). Weight gain was significantly less in participants treated with Gla-300 than in those treated with Gla-100 ($P = 0.015$). The mean change in body weight throughout the study is shown in Supplementary Fig. 3.

Adverse Events

The most common adverse events in the Gla-300 and Gla-100 groups were infections (33.0% vs. 31.8%), nervous system disorders (11.7% vs. 9.4%), gastrointestinal events (10.9% vs. 8.4%), and musculoskeletal complaints (10.9% vs. 10.1%). These were equally distributed between the treatment groups (Table 2). Overall, the percentage of patients who had treatment-emergent adverse events (TEAEs) considered related to study insulin was lower in the Gla-300 (1.7%) than in the Gla-100 group (3.7%). The most frequently reported TEAEs considered related to study insulin treatment were injection site reactions (0.7% in the Gla-300 group and 2.7% in the Gla-100 group). Serious TEAEs were reported by 15 participants (3.7%) on Gla-300 and 15 (3.7%) on Gla-100 (Table 2). The most frequently reported serious TEAEs in the Gla-300 and Gla-100 groups were infections (2 [0.5%] and 7 [1.7%]) and cardiac disorders (6 [1.5%] and 1 [0.2%]); none of the cardiac events were considered related to the study medication. TEAEs led to withdrawal from the study of six participants (1.5%) in the Gla-300 group and four (1.0%) in the Gla-100 group. Two participants in the Gla-300 group and one in the Gla-100 group died during the main 6-month period; none of the deaths were considered related to the study medication. Hypersensitivity reactions were reported in 13 participants (3.2%) in the Gla-300 group and in 16 (3.9%) in the Gla-100 group.

CONCLUSIONS

During this phase 3a study, Gla-300 was shown to confer similar glycemic control to that provided by Gla-100 in people with type 2 diabetes using basal insulin in combination with OADs. These data are similar to those reported for the EDITION 1 study, which compared Gla-300 and Gla-100 in people with type 2 diabetes using basal bolus insulin treatment (10).

In addition to providing similar efficacy in glycemic control, use of Gla-300 resulted in a significant 23% reduction in the risk of at least one nocturnal confirmed or severe hypoglycemic event from week 9 to the end of treatment (prespecified main secondary efficacy end point; $P = 0.038$). Overall, reductions in nocturnal hypoglycemia were observed consistently with Gla-300 during the entire study period. The RR reduction was more pronounced during the first 8 weeks of study treatment, corresponding to the time when basal insulin dose titration occurs. This reduction is of clinical relevance because it may enable more reliable insulin titration and thus effective glucose control with less fear of nocturnal hypoglycemia.

Similarly, when looking at the annualized rate of confirmed (≤3.9 mmol/L [≤70 mg/dL]) or severe hypoglycemia across the 6-month study period, significant rate reductions were seen during the night (48%, $P = 0.0010$) and at any time (24 h; 23%, $P = 0.0175$). A more pronounced reduction in the annualized rate of hypoglycemia at any time (24 h) was also shown during the first 8 weeks of study treatment (33%).

Reductions in hypoglycemia were observed with Gla-300 across all nonsevere glycemic categories. Severe

hypoglycemia was infrequent in both groups, with only 10 participants in total reporting one or more severe events with Gla-300 and Gla-100. Owing to the low number of severe hypoglycemic events, the reported rates of the nocturnal confirmed or severe category of hypoglycemia were mainly driven by nonsevere hypoglycemic events. Differences of study design and populations preclude direct comparison of the present findings with other studies of longer-acting insulin. Nevertheless, these data resemble reported differences in hypoglycemia between degludec and glargine 100 units/mL (14) and those comparing PEGylated insulin lispro (LY2605541) and glargine 100 units/mL (15).

Despite differences in treatment regimens, the results of EDITION 1 (basal and mealtime insulin) and EDITION 2 (basal insulin plus OADs) were consistent. In both studies, Gla-300 showed a similar improvement in glycemic control compared with Gla-100, with the decreases in HbA_{1c} comparable in the two studies, as well as a consistently lower risk of hypoglycemia across study periods and hypoglycemia categories compared with Gla-100.

Of note, the EDITION 1 and EDITION 2 studies both showed an increase in insulin dose during the study period, most of which occurred in the first 8 weeks of treatment (10). A slightly greater increase in insulin dose was observed in the Gla-300 group compared with the Gla-100 group; by month 6 of the EDITION 2 study, the daily insulin dose was 10% higher with Gla-300 than with Gla-100. This dose difference is consistent with the lower 24-h exposure of Gla-300 compared with Gla-100 observed under steady-state conditions in pharmacokinetic and pharmacodynamic studies (9). This observation suggests a somewhat lower bioavailability of Gla-300 due to increased residence time in the subcutaneous depot, resulting in additional exposure to tissue peptidases.

Body weight increased slightly but significantly less with Gla-300 than with Gla-100, and Gla-300 was associated with decreases in body weight during the first 12 weeks of treatment. This finding is consistent with results of EDITION 1, where the magnitude was comparable with that observed previously in studies comparing glargine and detemir insulins (16,17). Given that glycemic control and oral agents were comparable between the groups, these factors were not responsible for the difference. Further analyses are warranted to establish whether hypoglycemia or other factors contributed to the difference in changes in body weight.

Similarly to EDITION 1, strengths of this study include a closely supervised titration scheme to optimize basal insulin delivery; the consistency of the findings with different categories of hypoglycemia and different intervals of time in the study; the absence of prandial insulin and sulfonylurea as a confounding factor, allowing the results to be more clearly attributed to basal insulin use; and the demonstration of Gla-300 benefit in a hard-to-treat population with long duration of diabetes, high BMI, and long-term prior insulin use.

Limitations include the unavoidable open-label nature of the protocol, relatively short duration, and limited generalizability to the whole population of people with diabetes. Although almost one-third of patients reached a target HbA_{1c} level $<7.0\%$ with systematic titration of basal insulin, many of those who did not would in clinical practice be candidates for further intensification of treatment by addition of therapy targeting persistent daytime (postprandial) hyperglycemia. Thus, in this challenging population of patients with relatively long duration of diabetes, optimally titrated basal insulin may serve as a platform for further modification of treatment, as necessary. Completion of additional EDITION studies will extend observations to the use of Gla-300 in people with type 2 diabetes who are insulin-naïve (EDITION 3), and to Japanese people with type 2 diabetes using basal insulin in combination with OADs (EDITION JP2). Further EDITION studies (EDITION 4 and JP1) will investigate Gla-300 in people with type 1 diabetes.

In summary, the EDITION 2 study, comparing the efficacy and safety of Gla-300 and Gla-100 in people with type 2 diabetes using basal insulin plus OADs, has shown that Gla-300 offers a similar improvement in glycemic control as Gla-100 but with a lower risk of hypoglycemia during the night as well as at any time (24 h) across the study periods, with particular reduction during the titration period. Clinical implications of these results center on the lower rate of hypoglycemia, which may help to overcome a major obstacle to the initiation and maintenance of insulin therapy, and consequently improve diabetes management.

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Author Contributions. Sanofi was the sponsor of the study and was responsible for the design and coordination of the trial. Sanofi monitored the clinical sites, collected and managed the data, and performed all statistical analyses. H.Y.-J. participated in the design of the study protocol and in the writing of the manuscript. R.B. and M.C.R. participated in the design of the study program and the study protocol, and in the writing, reviewing, and editing of the manuscript. M.Z., M.W., I.M.-B., and E.B. reviewed and edited the manuscript. H.Y.-J. 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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