New Insulin Glargine 300 Units/mL Versus Glargine 100 Units/mL in People With Type 1 Diabetes: A Randomized, Phase 3a, Open-Label Clinical Trial (EDITION 4)

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OBJECTIVE

Insulin therapy in type 1 diabetes still provides suboptimal outcomes. Insulin glargine 300 units/mL (Gla-300), with a flatter pharmacodynamic profile compared with insulin glargine 100 units/mL (Gla-100), is an approach to this problem.

RESEARCH DESIGN AND METHODS

People with type 1 diabetes, using a mealtime and basal insulin regimen, were randomized open-label to Gla-300 or Gla-100 and to morning or evening injection, continuing the mealtime analog, and followed for 6 months.

RESULTS

Participants (n = 549) were a mean age of 47 years and had a mean duration of diabetes of 21 years and BMI of 27.6 kg/m^2. The change in HbA$_{1c}$ (primary end point; baseline 8.1%) was equivalent in the two treatment groups (difference, 0.04% [95% CI −0.10 to 0.19]) (0.4 mmol/mol [−1.1 to 2.1]), and Gla-300 was thus noninferior. Similar results with wider 95% CIs were found for morning and evening injection times and for prebreakfast self-measured plasma glucose (SMPG) overall. Results were also similar for Gla-300 when morning and evening injection time was compared, including overlapping 8-point SMPG profiles. Hypoglycemia did not differ, except for the first 8 weeks of the study, when nocturnal confirmed or severe hypoglycemia was lower with Gla-300 (rate ratio 0.69 [95% CI 0.53–0.91]). Hypoglycemia with Gla-300 did not differ by time of injection. The basal insulin dose was somewhat higher at 6 months for Gla-300. The adverse event profile did not differ and was independent of the Gla-300 time of injection. Weight gain was lower with Gla-300.

CONCLUSIONS

In long-duration type 1 diabetes, Gla-300 provides similar glucose control to Gla-100, with a lower risk of hypoglycemia after transfer from other insulins, independent of time of injection, and less weight gain.

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Type 1 diabetes requires life-long insulin therapy, with consequences for quality of life (1). Accordingly, insulin administration should be convenient and support self-management by being adaptable to individual lifestyle. Current recommendations are generally basal plus mealtime insulin injections with insulin analogs, or pump

therapy, with the aim of optimal blood glucose levels with a minimum tolerable rate of hypoglycemia (2). However, despite advances in basal insulin therapy (3,4), blood glucose control often remains suboptimal, with HbA_{1c} above the normal range and clinically important rates of hypoglycemia, including nocturnal and severe hypoglycemia (5). There thus remains a need for the development of new insulins (6,7).

After subcutaneous injection in people with type 1 diabetes, new insulin glargine 300 units/mL (Gla-300) demonstrated more constant and prolonged pharmacokinetic (PK) and pharmacodynamic (PD) profiles compared with insulin glargine 100 units/mL (Gla-100), extending beyond 24 h (8). The longer duration of action and more consistent within-day profile of Gla-300 may also allow greater flexibility in injection timing compared with Gla-100, while providing equivalent glycemic control and perhaps less hypoglycemia. To evaluate whether the improved PK and PD profiles can provide clinical benefit, the efficacy and safety of Gla-300 have been investigated in populations of people with type 2 and type 1 diabetes in the phase 3a EDITION program. In type 2 diabetes, the EDITION 1 and 2 studies of people with type 2 diabetes already receiving insulin found Gla-300 was as effective as Gla-100 in terms of HbA_{1c}, with a reduction in nighttime hypoglycemia (9,10). Furthermore, a study of Japanese people with type 1 diabetes found similar HbA_{1c} with less hypoglycemia, particularly during the night and in the first 8 weeks (11).

The current study (EDITION 4) compared the efficacy, tolerability, and safety of Gla-300 and Gla-100 in an international population of people with type 1 diabetes and investigated whether these outcomes differed when injections were given in the morning or evening.

RESEARCH DESIGN AND METHODS

Study Design and Participants
EDITION 4 was a multicenter, randomized, four-arm, parallel-group, phase 3a study involving 549 participants with type 1 diabetes who were randomized (1:1:1:1) to once-daily Gla-300 or Gla-100 (both Sanofi, Paris, France), injected morning or evening, while continuing mealtime insulin (NCT01683266). The

main treatment period was 6 months, presented here, followed by a 6-month extension period. The study was approved by relevant review boards/ethics committees and was performed in accordance with the Declaration of Helsinki and the International Conference on Harmonisation guidelines. All participants provided written informed consent.

Participants were recruited in 124 centers in 12 countries (Supplementary Data). Key inclusion criteria included ≥18 years of age, type 1 diabetes for >1 year, and use of any mealtime insulin analog for ≥3 months. Exclusion criteria at screening included HbA_{1c} <7.0 and >10.0% (<53 and >86 mmol/mol); <1 year on a basal plus mealtime insulin regimen; insulin dose not stable (±20%) within 30 days; use of other mealtime, premix insulin, or other glucose-lowering medication within 3 months; and pump therapy within 6 months.

Education on use of self-measured plasma glucose (SMPG) and data recording in study diaries as well as on insulin dose titration was given at screening and randomization. Baseline measurements were at randomization (week 0). Other core measurements, including HbA_{1c} and laboratory-measured fasting plasma glucose (FPG) at a clinic visit were at week 12 and month 6, but hypoglycemia, insulin dose, SMPG (details in MEASUREMENTS AND BIOCHEMICAL ANALYSES), body weight, and adverse events (AEs) were also assessed at intermediate visits (weeks 2, 4, and 8, and month 4). Insulin dose–adjustment advice was provided at these visits and at telephone contacts (weeks 1, 3, 6, 10, and 22), with unscheduled contacts if required. Questionnaires were applied at baseline, month 3 (except Hypoglycemia Fear Survey II [HFS II]), and month 6. Blood samples for insulin antibodies were collected at baseline, at weeks 4 and 12, and at month 6.

Randomization
Randomization was to once-daily subcutaneous injection of Gla-300 (using a modified TactiPen pen injector [Sanofi]: 1.5-unit dose increments) or Gla-100 (SoloSTAR pen [Sanofi]: 1-unit dose increments) and as a morning or evening injection, using a central treatment system (voice or web). Stratification was by HbA_{1c} at screening (<8.0 or ≥8.0% [<64

or ≥64 mmol/mol] with ≥20% per stratum) and Japan/non-Japan.

Interventions
Morning injection time was between prebreakfast and prelunch (inclusive) and evening at the evening meal until bedtime. Basal insulin dose on day −1 was used to determine the starting dose, modulated by the median fasting SMPG of the last 3 days. Gla-300 or Gla-100 was titrated to a prebreakfast SMPG of 80–130 mg/dL (4.4–7.2 mmol/L). Change in dose was suggested as ≥10%, while not >4.5 units for Gla-300 or >4.0 units for Gla-100; the minimum dose step was 1.5 units for Gla-300 and 1.0 units for Gla-100. Dose adjustments of basal insulin were to be made weekly (no more than every 3–4 days). An Insulin-Dosing Supervision Committee independent of the study changes monitored insulin dose adjustment and could provide feedback. Mealtime insulin continued with a target range of 160 mg/dL (<8.9 mmol/L) for 2-h postprandial plasma glucose, adjusted at investigator discretion.

Outcomes
The primary efficacy end point was the overall change in HbA_{1c} from baseline to month 6, regardless of injection time. Primary and secondary end points were also analyzed by injection time. Secondary end points included percent to HbA_{1c} <7.0% (<53 mmol/mol) at month 6, change in preinjection SMPG, within-participant variability of preinjection SMPG, FPG, 8-point SMPG profile, and daily insulin doses. Percentages of participants experiencing at least one hypoglycemic event and annualized rates (events per person-year), as categorized by the American Diabetes Association (12), were assessed. The predefined definition was confirmed or severe hypoglycemia (all severe and all documented symptomatic and asymptomatic hypoglycemia). Documentation required a glucose measurement of ≤70 mg/dL (≤3.9 mmol/L), and a sensitivity analysis for <54 mg/dL (<3.0 mmol/L) was also preplanned. The periods of baseline to 8 weeks, and 9 weeks to 6 months, and these combined, were predefined as of interest. Nocturnal hypoglycemia was also predefined as of interest, and as episodes between midnight and 0559 h inclusive.

AEs, including injection site and generalized sensitivity reactions, were

systematically recorded at each visit, as was body weight.

Measurements and Biochemical Analyses

An Accu-Chek meter (type dependent on country) and reagent strips were used for SMPG measurement (Roche Diagnostics, Mannheim, Germany), supplied by the study sponsor. In addition to daily prebreakfast SMPG during dose titration and suggested for later weeks, 5-point profiles and preinjection SMPG were requested for at least 5 days before study visits, 8-point profiles at least once before each on-site visit, and a measurement upon possible symptoms of hypoglycemia. Results from diaries were transferred to study records at each visit. HbA_{1c} and clinic FPG were measured at central laboratories (Covance, Geneva, Switzerland, and Indianapolis, IN). Insulin antibodies were measured using validated binding assay methodology by a central laboratory (PAREXEL, Brandhof, South Africa).

Satisfaction with treatment and perception of occurrence of hypo- and hyperglycemia were assessed with the Diabetes Treatment Satisfaction Questionnaire (DTSQ), and health-related quality of life was assessed with the EQ-5D (13,14). Behaviors and worries related to hypoglycemia were assessed with the HFS II (15).

Data Analysis

A sample size of 500 participants (125 for each randomization group) was chosen to ensure with 99% power that the upper bound of the two-sided 95% CI for the mean difference between Gla-300 and Gla-100 (modified intent-to-treat [mITT] population) would not exceed 0.40%-units (4.4 mmol/mol) HbA_{1c}, assuming a SD of change of 1.0% (10.9 mmol/mol), if the insulins were truly identical. If noninferiority was demonstrated, the superiority of Gla-300 (one-sided α = 0.025) could be assessed as the upper bound of the two-sided 95% CI for the same difference being <0.00%-units (<0.0 mmol/mol).

The mITT population was defined as all randomized participants who received one or more doses of study insulin and had a baseline and one or more postbaseline assessments. Analyses used SAS 9.2 software (SAS Institute, Inc., Cary, NC). The primary and continuous secondary end points were analyzed using a mixed model with

repeated measures (MMRM) approach, with treatment, time of injection (morning, evening), screening HbA_{1c} (<8.0% or ≥8.0%), visit, and geographical region (Japan/non-Japan) as fixed effects and baseline value as the covariate. Categorical variables were analyzed using a Cochran–Mantel–Haenszel method stratified according to injection time, screening HbA_{1c}, and geographical region. If a participant discontinued treatment prematurely or had absent measurement at month 6, assessments up to and including premature end of treatment were included in the MMRM analyses.

The safety population was defined as all participants randomized and exposed to at least one dose of either treatment. Hypoglycemia and body weight assessments used this population. Annualized rates of hypoglycemia used a 365.25-day year.

RESULTS

Study Population

A total of 846 people with type 1 diabetes were screened, with 274 randomized to Gla-300 and 275 to Gla-100; all received treatment and thus formed the

safety population (Supplementary Fig. 1). One and two people had no further data, so the mITT population was 273 receiving each insulin; 136 and 137 on Gla-300 were in the morning and evening injection groups, and 135 and 138 similarly for Gla-100. Missing HbA_{1c} data at week 12 and month 6 meant 47 further participants could not contribute to the MMRM calculation.

Insulin was discontinued before 6 months in 43 people (16%) in the Gla-300 group versus 39 (14%) from the Gla-100 group. The most common reason for treatment discontinuation given was "other reasons" (26 [9%] and 30 [11%] participants), usually stating personal, family, or job-conflict reasons (13 and 19 participants).

The population studied (Table 1) was middle-aged (mean 47 [SD 14] years), with a long diabetes duration of 21 (13) years, and a BMI of 27.6 (5.1) kg/m². Most participants transferred from insulin glargine once daily, with some imbalance between groups (Table 1). Baseline HbA_{1c} was 8.1 (0.8)% (65 [9] mmol/mol), with poor baseline prebreakfast SMPG. Fasting C-peptide was above detection levels (≥0.023 nmol/L) in 26% of participants,

Table 1—Baseline characteristics by allocated study insulin of the people with type 1 diabetes studied (randomized and safety population)

	Insulin glargine	
	300 units/mL *n* = 274	100 units/mL *n* = 275
Age (years)	46.4 (13.9)	48.2 (13.4)
Duration of diabetes (years)	20.5 (12.7)	21.4 (13.1)
≥10 years, *n* (%)	216 (78.8)	215 (79.0)
Male sex, *n* (%)	149 (54.4)	164 (59.6)
Body weight (kg)	81.9 (20.4)	81.8 (16.8)
BMI (kg/m²)	27.6 (5.5)	27.6 (4.7)
eGFR ≤60 mL/min, *n* (%)	33 (12.0)	34 (12.4)
Fasting C-peptide, *n* (%)		
≥0.023 nmol/L	80 (29.4)	63 (23.2)
≥0.20 nmol/L	19 (6.9)	19 (6.9)
HbA_{1c} (mmol/mol)	65.1 (8.4)	65.4 (8.6)
HbA_{1c} (%)	8.11 (0.77)	8.14 (0.79)
Previous basal insulin type, *n* (%)		
Insulin glargine	210 (85.0)	193 (78.5)
Insulin detemir	32 (13.0)	45 (18.3)
NPH insulin	6 (2.4)	9 (3.7)
Basal insulin twice daily	33 (15.2)	39 (17.8)
Prior daily insulin dose (units/kg)*		
Basal	0.38 (0.17)	0.37 (0.15)
Mealtime	0.34 (0.19)	0.33 (0.17)
Total	0.71 (0.28)	0.72 (0.25)

Mean (SD) unless otherwise stated. eGFR, estimated glomerular filtration rate. *The 7-day average before randomization.

but only 38 (7%) were above ≥0.20 nmol/L. Prebreakfast SMPG and clinic laboratory–measured FPG showed a similar imbalance between randomized treatment groups (Table 2). No notable differences were observed in baseline characteristics by timing of injection (morning vs. evening) across either treatment group.

Insulin Doses

Prior daily basal insulin dose was 0.38 (SD 0.17) units/kg/day for the Gla-300 group and 0.37 (0.15) units/kg/day for Gla-100. At 6 months, the corresponding figures were 0.47 (0.22) and 0.40 (0.18) units/kg/day (Table 2 and Fig. 1). In the morning injection groups, the basal insulin dose at month 6 was 0.49 (0.22) units/kg/day with Gla-300 and 0.45 (0.19) units/kg/day with Gla-100 (Supplementary Table 1), and for the evening injection was 0.45 (0.21) and 0.36 (0.16) units/kg/day. For the Gla-300 group, mealtime insulin doses were relatively stable, but for Gla-100, there was some fall in the morning group and a rise in the evening group (Supplementary Table 1).

Blood Glucose Control

A similar decrease in HbA_{1c} from baseline to month 6 was observed in the two overall treatment groups (Table 2 and Fig. 1). The upper bound of the 95% CI least squares (LS) mean difference (0.19% [4.4 mmol/mol]) was within the prespecified margin of 0.40% (LS mean difference 0.04% [95% CI −0.10 to 0.19], 0.4 mmol/mol [−1.1 to 2.1]). The time course of change of HbA_{1c} appeared similar. A similar percentage of participants in each overall group achieved HbA_{1c} <7.0% (<53 mmol/mol) at month 6, 16.8% for Gla-300 and 15.0% for Gla-100.

For any time point, data were available in the SMPG 8-point profile for 69–90% of readings, in general being most complete for prebreakfast (76–90%), for nighttime (0300 h) (75–85%), and for Gla-300 (74–87%). Although baseline levels of prebreakfast SMPG, which guided basal insulin dose titration, were somewhat higher on Gla-100, levels at 6 months were similar (Table 2 and Fig. 1). A similar situation pertained with laboratory-measured clinic FPG, which decreased to 175.5 (SD 71.4) mg/dL on Gla-300 and 173.5 (69.4) mg/dL on Gla-100 (Fig. 1). No relevant differences were observed in the change from baseline to month 6 in preinjection or within-participant variability of preinjection SMPG and the average of the 8-point SMPG estimations (Table 2). Inspection of the SMPG profiles reveals that the numerical mismatch at baseline in prebreakfast levels is more marked for 0300 h nighttime measurements (Fig. 1). This however disappears between the two insulin groups by 6 months, where the profiles appear similar from 0300 h to after lunch, and then lower on Gla-100.

In the morning injection groups, the change from baseline in HbA_{1c} was similar (Gla-300: LS mean [SE] change −0.48 [0.07] %-units, −5.2 [0.8] mmol/mol; Gla-100: −0.41 [0.07] %-units, −4.5 [0.8] mmol/mol), as it was also for the evening injection groups (−0.32 [0.07] %-units and −0.48 [0.07] %-units, −3.5 [0.8] mmol/mol and −5.2 [0.8] mmol/mol) (Supplementary Fig. 2). Similarly, no effect of injection time was seen on laboratory-measured clinic FPG (Supplementary Fig. 2). For Gla-300 the 8-point SMPG profiles with morning and evening injection look similar, whereas for Gla-100, a difference appears prebreakfast (Supplementary Fig. 2).

Hypoglycemia

Over 6 months, 255 people (93%) in the Gla-300 group had one or more

Table 2—Measures of insulin dose and blood glucose control (mITT population) in those randomized to Gla-300 or Gla-100

| | Insulin glargine | | | |
| | 300 units/mL | | 100 units/mL | |
	Baseline or prior*	6 months	Baseline or prior*	6 months
Total insulin dose (units/kg/day)	0.71 (0.28)	0.81 (0.32)	0.73 (0.25)	0.73 (0.27)
Basal insulin dose (units/kg/day)	0.38 (0.17)	0.47 (0.22)	0.37 (0.15)	0.40 (0.18)
HbA_{1c} (%)	8.13 (0.77)	7.70 (0.99)	8.12 (0.79)	7.68 (0.80)
Change		−0.42 (0.98)		−0.44 (0.72)
LS change difference		0.04 (−0.10 to 0.19)		
HbA_{1c} (mmol/mol)	65.3 (8.4)	60.6 (10.8)	65.2 (8.6)	60.4 (8.7)
Change		−4.6 (10.7)		−4.8 (7.9)
LS change difference		0.4 (−1.1 to 2.1)		
Prebreakfast SMPG (mg/dL)	160.5 (46.1)	152.7 (38.7)	167.1 (45.2)	152.5 (36.3)
Change		−6.2 (51.0)		−13.2 (49.0)
Mean daily SMPG (mg/dL)	169.3 (45.8)	158.8 (38.0)	173.2 (42.1)	152.1 (32.8)
Change		−11.2 (51.9)		−20.1 (50.6)
LS change (SE)		−11.7 (2.6)		−18.3 (2.6)
Preinjection SMPG (mg/dL)	177.6 (50.6)	163.4 (47.4)	186.3 (47.4)	167.4 (42.8)
Change		−14.6 (66.4)		−19.9 (57.0)
LS change (SE)		−21.0 (4.0)		−14.7 (4.2)
Variability of preinjection SMPG (CV)	34.4 (15.8)	30.7 (13.3)	32.9 (15.4)	30.6 (14.0)
Change		−3.5 (17.8)		−1.4 (17.3)
LS change (SE)		−3.0 (1.6)		−1.8 (1.7)
Clinic FPG (mg/dL)	185.9 (76.2)	175.5 (71.4)	199.3 (79.6)	173.5 (69.4)
Change		−7.6 (94.6)		−26.1 (95.1)
LS change (SE)		−17.1 (4.7)		−20.5 (4.7)

Mean (SD) or mean (95% CI), unless otherwise stated. CV, coefficient of variation. *For insulin doses, average of prior 7 days.
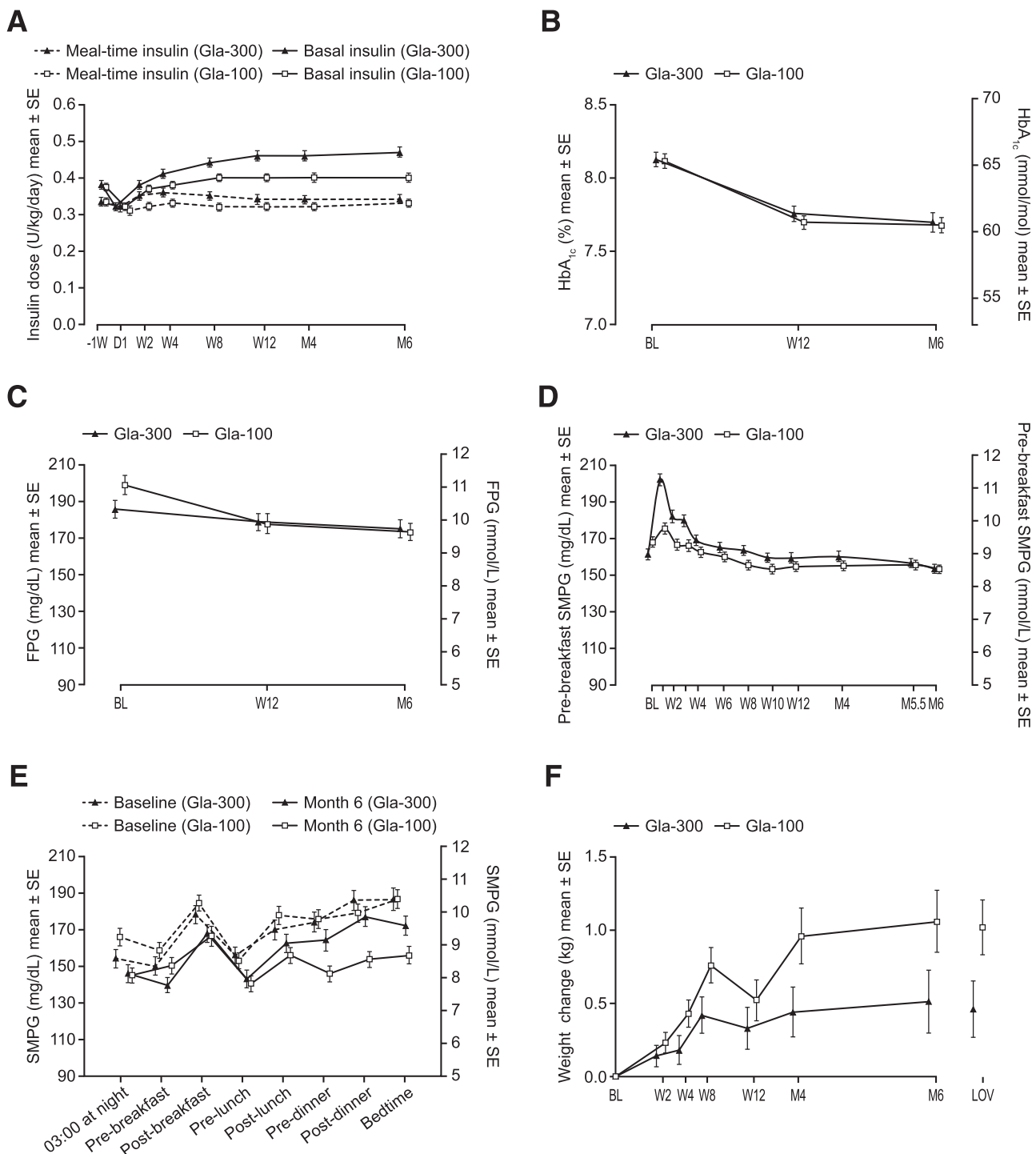
Figure 1—Time course of daily basal and mealtime insulin dose (A), glycated hemoglobin (B), laboratory-measured clinic FPG (C), prebreakfast SMPG (D), SMPG profiles (E), and time course of body weight change (F) in the mITT population. BL, baseline; LOV, last on treatment value.

confirmed (≤70 mg/dL) or severe hypoglycemic events compared with 257 (94%) in the Gla-100 group. For nocturnal hypoglycemia, this was 188 (69%) and 193 (70%) of study participants. The corresponding incidence rates were 78.4 and 72.5 events/person-year for any time of day, and 8.0 and 9.0 events/person-year for

nocturnal hypoglycemia. Where only documented symptomatic hypoglycemia was considered (excluding asymptomatic hypoglycemia) or if the criterion for confirmation was taken as <54 mg/dL, or both, then the number of events was lower but the patterns were unchanged (Supplementary Table 2).

The cumulative mean numbers of confirmed or severe hypoglycemic events per participant for both the SMPG thresholds are given in Supplementary Fig. 3. Inspection suggests the curves for any time of day are similar, as are the slopes of the nocturnal curves from ~8 weeks. However, there is suggestion of divergence in the first 8 weeks

for both glucose thresholds for nocturnal events, with lower slopes (rates) for Gla-300. In the preplanned analysis by study period, the rate ratio (RR) for Gla-300 versus Gla-100 is indeed lower in the first 8 weeks using the ≤70 mg/dL threshold (RR 0.69 [95% CI 0.53–0.91]), for documented symptomatic hypoglycemia for both thresholds, and with a similar central estimate but wider CIs for confirmed or severe hypoglycemia at the <54 mg/dL confirmation threshold (Fig. 2). Data analyzed the same way for the period after 8 weeks, or for any time of day (24 h), suggested no differences (Fig. 2).

Severe hypoglycemia was reported by 18 people (6.6%) in the Gla-300 group and by 26 (9.5%) in the Gla-100 group; of these, 6 (2.2%) and 7 people (2.5%) had nocturnal events. Annualized rates were comparable between the Gla-300 and Gla-100 groups (0.24 vs. 0.34 events/person-year at any time of day [24 h]; 0.08 vs. 0.06 events/person-year during the night).

When analyzed by morning or evening injection time, hypoglycemia on Gla-300 did not differ. Thus one or more nocturnal confirmed (≤70 mg/dL) or severe hypoglycemic events was experienced by 68% of participants for morning injection and 69% for evening injection (Gla-100: 69% and 71%), and for events at any time (24 h), 94% for

morning injection and 92% for evening injection (Gla-100: 93% and 94%). Severe events were few although numerically lower for morning injection than for evening injection with Gla-300 (n = 9 vs. 21, 0.15 vs. 0.33 events/person-year) and for Gla-100 (11 vs. 32, 0.18 vs. 0.50 events/person-year).

Body Weight
Body weight increased more slowly with Gla-300 than with Gla-100 (Fig. 1). At 6 months the increase was smaller with Gla-300 (0.5 [SE 3.3] kg) than with Gla-100 (1.0 [3.2] kg), with a difference of −0.6 kg (95% CI −1.1 to −0.03, P = 0.037).

Participant-Reported Outcomes
The LS mean change in total treatment satisfaction score to month 6 was similar in the two groups (Supplementary Table 3). No notable differences were seen for morning versus evening injection in either treatment group (data not shown). The EQ-5D single utility index was unchanged in the Gla-300 and Gla-100 groups (Supplementary Table 3). On the EQ-5D visual analog scale, the changes were Gla-300 2.88 (95% CI 1.31–4.45) and Gla-100 1.70 (0.14–3.27). No meaningful differences were seen between morning and evening injection groups.

The total HFS score did not change with either insulin group during the

study period (data not shown), despite being low at baseline (Gla-300 0.95 [SD 0.56], Gla-100 0.99 [0.58]); this was also true when analyzed by morning or evening injection.

Adverse Events and Insulin Antibodies
The number of participants with any treatment-emergent AE (TEAE) was similar in the Gla-300 and Gla-100 groups (167 [61%] vs. 160 [58%]) (Supplementary Table 4). A comparable number of participants experienced injection site reactions in the Gla-300 group (6 [2.2%]) and in the Gla-100 group (4 [1.5%]). Three participants in each treatment group withdrew from the study due to TEAEs. The number of participants with serious TEAEs was also similar between groups (Gla-300: 17 [6.2%]; Gla-100: 22 [8.0%]), with no signal for any type of event being different (Supplementary Table 4). One participant in the Gla-300 group, with preexisting cardiovascular disease, died of a cardiac event during the 6-month treatment period.

When analyzed by number of participants, those insulin antibody positive, number with cross-reacting insulin antibodies, median antibody titer, upper quartile, maximum level, and at baseline, week 4, week 12, month 6 and for the entire study period, no signal of
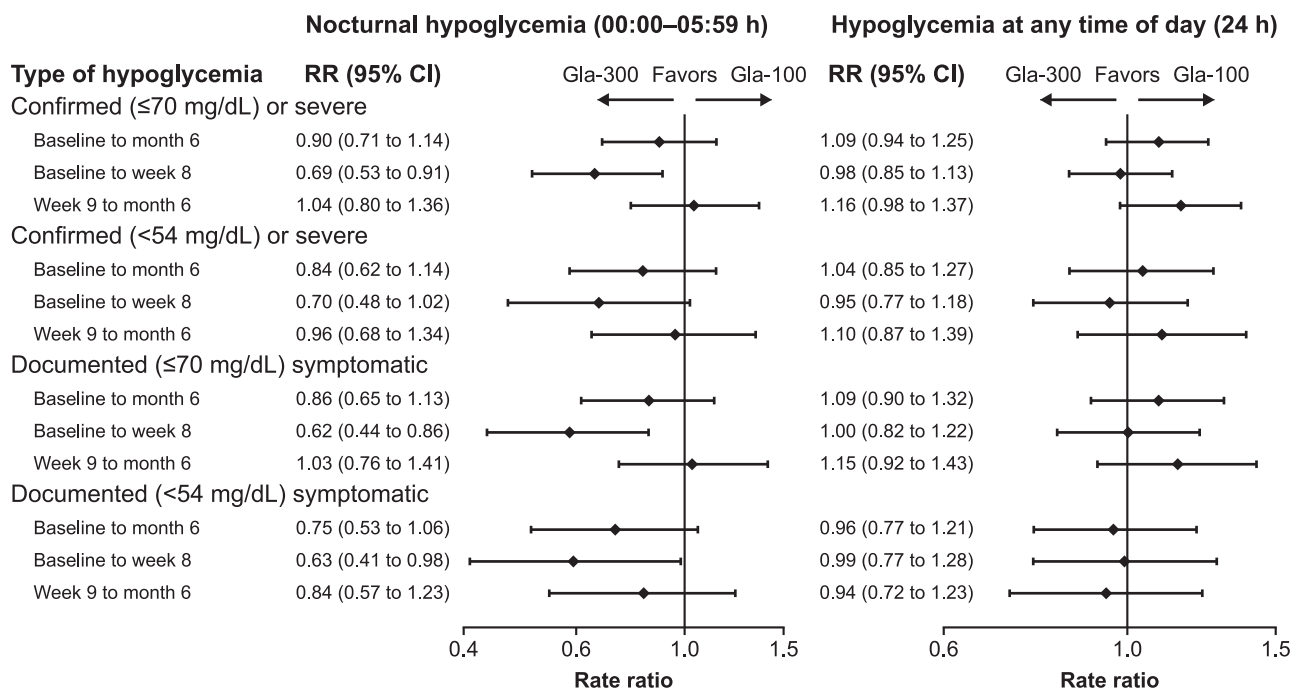

Type of hypoglycemia	Nocturnal hypoglycemia (00:00–05:59 h) RR (95% CI)		Hypoglycemia at any time of day (24 h) RR (95% CI)	
Confirmed (≤70 mg/dL) or severe				
Baseline to month 6	0.90 (0.71 to 1.14)		1.09 (0.94 to 1.25)	
Baseline to week 8	0.69 (0.53 to 0.91)		0.98 (0.85 to 1.13)	
Week 9 to month 6	1.04 (0.80 to 1.36)		1.16 (0.98 to 1.37)	
Confirmed (<54 mg/dL) or severe				
Baseline to month 6	0.84 (0.62 to 1.14)		1.04 (0.85 to 1.27)	
Baseline to week 8	0.70 (0.48 to 1.02)		0.95 (0.77 to 1.18)	
Week 9 to month 6	0.96 (0.68 to 1.34)		1.10 (0.87 to 1.39)	
Documented (≤70 mg/dL) symptomatic				
Baseline to month 6	0.86 (0.65 to 1.13)		1.09 (0.90 to 1.32)	
Baseline to week 8	0.62 (0.44 to 0.86)		1.00 (0.82 to 1.22)	
Week 9 to month 6	1.03 (0.76 to 1.41)		1.15 (0.92 to 1.43)	
Documented (<54 mg/dL) symptomatic				
Baseline to month 6	0.75 (0.53 to 1.06)		0.96 (0.77 to 1.21)	
Baseline to week 8	0.63 (0.41 to 0.98)		0.99 (0.77 to 1.28)	
Week 9 to month 6	0.84 (0.57 to 1.23)		0.94 (0.72 to 1.23)	

Figure 2—RRs of hypoglycemic events (events/person-year) for the defined nocturnal period and for any time of day (24 h) with Gla-300 vs. Gla-100 during 6 months of treatment (safety population).

differences between Gla-300 and Gla-100 groups was detectable (data not shown).

CONCLUSIONS

The EDITION 4 study is the international comparison of Gla-300 versus Gla-100 in long duration type 1 diabetes. As such, the investigators and participants had no prior experience of how best to use the new insulin, while >80% (Table 1) were already using Gla-100. Nevertheless, Gla-300 easily met the primary end point of noninferiority for HbA$_{1c}$, with a central estimate of zero. When analyzed by morning or evening injection, the populations studied are smaller and CIs are wider, but Gla-300 would be judged noninferior for both injection times compared with Gla-100 if the same criterion was used.

Glucose control improved in both groups by HbA$_{1c}$ and related measures, suggesting a significant study effect. Nevertheless, when judged independent of injection time, prebreakfast SMPG was also the same for the two insulins by 6 months (Fig. 1), as might be expected for the dose titration target. Some disturbance of this measure can be seen in both groups in the first 4 weeks (Fig. 1), perhaps because of the reduction in the basal insulin dose from before the study to the first injection on randomized treatment. Investigator/participant caution may be the cause of dose reductions greater than mandated by the protocol, with a large number of participants switching from evening to morning injection. If the difference in prebreakfast SMPG between Gla-100 and Gla-300 at 2 weeks is real, then it might be anticipated that people coming from prior Gla-100 and open-label randomized to it would rapidly return to prior doses if prebreakfast SMPG deteriorated, whereas some caution continued for those randomized to the new insulin.

Inspection of the 8-point SMPG profiles is perhaps most revealing when morning and evening injections are shown separately (Supplementary Fig. 2), with evidence of a difference near breakfast time for the comparator insulin, Gla-100. In contrast, the profiles for Gla-300 are indistinguishable when it is given morning or evening, as might be expected for a basal insulin with a flat profile and duration of action in excess of 24 h (8). The afternoon profile for evening Gla-100 is perhaps better than expected for this regimen when an afternoon rise might be anticipated (16). However, adjustments of mealtime insulin would confound glucose profile findings.

Interpretation of the finding that the basal insulin dose was higher with Gla-300 is complicated by the additional randomization between morning and evening injection. The dose trajectory for Gla-100 was very different for evening (unchanged from prior) and morning (increase by nearly 20%), presumably reflecting uptitration of the latter to attempt to maintain prebreakfast glucose control. Insulin doses for Gla-300 with equivalent control were higher than for Gla-100 in studies in type 2 diabetes (9,10). This increase is likely to reflect the more prolonged absorption of Gla-300 from the more compact subcutaneous depot, as seen in the pharmacokinetic studies (12), which might result in lower bioavailability secondary to longer exposure to tissue peptidases. The circulating molecule after subcutaneous Gla-300 and Gla-100 injection is the same, A21-Gly-human insulin, so receptor potency cannot explain differences in dose requirement (17). Accordingly, the circulating (effector) insulin concentration should be the same.

Because of age and long duration of diabetes, some of the participants would be expected to have reduced awareness of hypoglycemia, contributing to the rate of hypoglycemia requiring assistance ("severe"). Nevertheless, less than 10% of people had such an event over 6 months, with no statistical power for discrimination between the insulins. However, there is no signal for any worse problem with Gla-300, the central estimates of relative risk being on the side of benefit (Supplementary Table 2). For severe hypoglycemia at night, numbers are too small to make meaningful comparisons (Supplementary Table 2).

The predefined hypoglycemia category was all confirmed (≤70 mg/dL [≤3.9 mmol/L]) or severe episodes, but the study was not powered for this. No between-group differences were noted with this category at the threshold of 70 mg/dL (≤3.9 mmol/L) for hypoglycemia at any time of day (Fig. 2). Assessment of documented symptomatic hypoglycemia or a lower confirmation threshold was consistent with the predefined measure (Fig. 2). Rates of nocturnal confirmed or severe hypoglycemia were lower on the cumulative event curves for approximately the first 8 weeks (Supplementary Fig. 3), consistent with the studies from type 2 diabetes (9,10). This was statistically significant by RRs (Fig. 2). After 8 weeks, the curves are parallel, indicating similar rates from 8 weeks to 6 months. The lines for Gla-300 and Gla-100 are superimposable for hypoglycemia at any time of day, but much of this will be determined by mealtime not basal insulin. In addition, when analyzed by morning or evening injection times, the cumulative curves remain superimposable (Supplementary Fig 3). This lower rate of hypoglycemia in the early phase of study includes the period when prebreakfast glucose control was higher on Gla-300, as discussed above, and when basal insulin doses had increased to a similar extent for both insulins. However, as also noted above, the morning injection of Gla-100 continued to be associated with prebreakfast hyperglycemia to the end of the study, so it is possible that any advantage of the Gla-300 profile is lost because of underinsulinization of the comparator. Either way, it seems clear that transfer of people to Gla-300 is not associated with a postchange risk of an increase in hypoglycemia.

The findings differ from the type 2 diabetes studies of prior insulin users, where reductions in nocturnal (and for some definitions, any-time) hypoglycemia were found in the first 8 weeks as here, but also over 6 months (9,10). The findings also differ from the type 1 diabetes study in Japan, where, in a more culturally homogeneous population, Gla-300 did show an advantage for nocturnal hypoglycemia (11). A possible explanation is that in type 1 diabetes, hypoglycemia, occurring much more frequently, is more sensitive to erratic insulin absorption and lifestyle changes because delivery is not buffered by endogenous insulin secretion. A small study using continuous glucose monitoring in type 1 diabetes did show glucose profile differences between the insulins (18).

The study of continuous glucose monitoring also showed a very flat 24-h

glucose profile for Gla-300 and very similar for morning or evening injection time (18). This would be consistent with the time of injection during the day being of little relevance with this longer-acting insulin. Our data show no difference in HbA$_{1c}$, 8-point SMPG profiles, or hypoglycemia for morning compared with evening Gla-300 at insulin doses much more similar for the two injection times than for Gla-100 (Supplementary Table 1 and Supplementary Figs. 2 and 3). This freedom to choose a morning or evening injection schedule with Gla-300 may reduce the treatment burden for some people with type 1 diabetes by allowing injection time preference to be a matter of personal choice.

In the EDITION type 2 diabetes studies there has been advantage for Gla-300 in change in body weight (10,19). That is now found in people with type 1 diabetes. The effect was seen throughout the 6 months of study (Fig. 1). Glucose control and insulin dose data would not seem to offer an explanation, but perhaps the lower peak to trough insulin concentration of Gla-300 is in some way relevant.

AEs were similar in the two groups; however, most AEs recorded in this kind of study are background noise, which should be equal between randomized arms (20). Detailed breakdown of AEs, including serious AEs, by organ and term did not reveal any signal of concern. Injection site reactions did not differ, and discontinuation did not appear to be study-treatment related. The lack of new safety signals is consistent with the circulating active metabolite of glargine being the same with Gla-300 as Gla-100 (17). The major tolerability issue remains hypoglycemia.

There are several limitations in studies of this kind in type 1 diabetes. These include the open-label design due to different pen injectors, leading to possible technology bias in favor of the new insulin, and familiarity bias in favor of the comparator. Possible confounding by adjustment of the prandial insulin dose is of concern, but with no evidence of this in our data. However, most of the hypoglycemia occurred during the day and was likely related to the prandial insulin. Hypoglycemia end points are a problem in type 1 diabetes because study prevalence (number with ≥1

event) lacks power through affecting nearly everyone over 6 months, whereas the incident event rates suffer a very skewed distribution, with a small number of individuals experiencing most of the episodes. Lastly, the discontinuation rate in this study was higher than is desirable.

In conclusion, EDITION 4 establishes that in an international population of people with type 1 diabetes Gla-300 has similar glucose control properties to Gla-100, although with a somewhat higher dose requirement and less weight gain. A comparison between morning and evening injection times suggests no difference in glucose profiles, hypoglycemia, or AEs for Gla-300, consistent with the PK/PD data and implying that the injection can be any time of day. No evidence of any new tolerability or safety problem was apparent, and transfer from other insulin regimens seems to be safe, indeed, with a reduced rate of nocturnal hypoglycemia in the first 8 weeks.

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