



# New Insulin Glargine 300 Units/mL Versus Glargine 100 Units/mL in People With Type 2 Diabetes Using Basal and Mealtime Insulin: Glucose Control and Hypoglycemia in a 6-Month Randomized Controlled Trial (EDITION 1)

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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 on basal insulin ( $\geq 42$  units/day) plus mealtime insulin.

## RESEARCH DESIGN AND METHODS

EDITION 1 (NCT01499082) was a 6-month, multinational, open-label, parallel-group study. Adults with glycated hemoglobin A<sub>1c</sub> (HbA<sub>1c</sub>) 7.0–10.0% (53–86 mmol/mol) were randomized to Gla-300 or Gla-100 once daily with dose titration seeking fasting plasma glucose 4.4–5.6 mmol/L. Primary end point was HbA<sub>1c</sub> change from baseline; main secondary end point was percentage of participants with one or more confirmed ( $\leq 3.9$  mmol/L) or severe nocturnal hypoglycemia from week 9 to month 6.

## RESULTS

Participants ( $n = 807$ ) had mean age 60 years, diabetes duration 16 years, BMI 36.6 kg/m<sup>2</sup>, and HbA<sub>1c</sub> 8.15% (65.6 mmol/mol). HbA<sub>1c</sub> reduction was equivalent between regimens; least squares mean difference  $-0.00\%$  (95% CI  $-0.11$  to  $0.11$ ) ( $-0.00$  mmol/mol [ $-1.2$  to  $1.2$ ]). Fewer participants reported one or more confirmed ( $\leq 3.9$  mmol/L) or severe nocturnal hypoglycemic events between week 9 and month 6 with Gla-300 (36 vs. 46% with Gla-100; relative risk 0.79 [95% CI 0.67–0.93];  $P < 0.005$ ); nocturnal hypoglycemia incidence and event rates were also lower with Gla-300 in the first 8 weeks of treatment. No between-treatment differences in tolerability or safety were identified.

## CONCLUSIONS

Gla-300 controls HbA<sub>1c</sub> as well as Gla-100 for people with type 2 diabetes treated with basal and mealtime insulin but with consistently less risk of nocturnal hypoglycemia.

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Long-acting (basal) insulin analogs have contributed significantly to the management of diabetes over the last decade. The first and most commonly used analog is insulin glargine 100 units/mL (Gla-100) (1,2), which has a well-established mode of action and profile of efficacy and safety (3–6). It has advantages compared with human NPH insulin, notably reduction of nocturnal and overall hypoglycemia (2,7,8). This benefit is clinically relevant because, in addition to concern about medical risks associated with hypoglycemia, fear of hypoglycemia is a leading barrier to starting insulin therapy (9–11). However, hypoglycemia continues to be observed during Gla-100 treatment, suggesting that a basal insulin with an even flatter and longer profile of action might further improve safety and tolerability.

The new insulin glargine 300 units/mL (Gla-300) has a reduced redissolution rate following subcutaneous injection as compared with Gla-100 and thereby the potential for meeting this need (12,13). Glucose clamp studies confirm that Gla-300 provides flatter and more prolonged pharmacokinetic and pharmacodynamic profiles than Gla-100 (12,13). To determine whether these properties will translate to clinical benefits, the phase 3a EDITION program is assessing the efficacy and safety of Gla-300 compared with Gla-100 in different patient populations. EDITION 1, the first of these studies to be completed, enrolled people with type 2 diabetes not adequately controlled despite previously using  $\geq 42$  units/day of basal insulin together with mealtime insulin. This represents a potentially challenging and growing population of people with long-duration type 2 diabetes, who require high-dose basal insulin and mealtime insulin therapy.

## RESEARCH DESIGN AND METHODS

### Study Design and Participants

EDITION 1 was a multicenter, open-label, parallel-group study conducted in 13 countries (three in North America, nine in Europe, and in South Africa) between 15 December 2011 and 30 January 2013. Appropriate ethics committees approved the protocol, which was conducted according to Good Clinical Practice and the Declaration of Helsinki. All participants provided written, informed consent. Entry criteria included age  $\geq 18$  years with type 2 diabetes

(World Health Organization definition) (14); use of basal and mealtime insulin therapy, including current basal therapy with  $\geq 42$  units/day of either Gla-100 or NPH, together with mealtime therapy with insulin lispro, aspart, or glulisine with or without metformin for at least 1 year; and glycated hemoglobin A<sub>1c</sub> (HbA<sub>1c</sub>) 7.0–10.0% ( $\geq 53$  to  $\leq 86$  mmol/mol). Exclusion criteria included use of human mealtime insulin or any premixed or basal insulin other than insulin glargine or NPH; oral glucose-lowering drugs other than metformin in the last 3 months or injected glucose-lowering agents other than insulin; and any history of proliferative diabetic or other unstable retinopathy or clinically important cardiac, renal, hepatic, or other systemic disease.

### Randomization and Masking

Participants were randomized (1:1) to receive once-daily injections of either Gla-300 (Sanofi, using a modified SoloSTAR pen injector) or Gla-100 (Lantus [Sanofi], using a SoloSTAR pen). The SoloSTAR pen injectors both delivered the same volume (0.01 mL) per “click.” The precision of the modified version of the SoloSTAR device was adequate for use with Gla-300 at starting doses at or above 39 units, so that a single downward titration of 3 units from 42 to 39 units daily could be done with acceptable accuracy. Randomization used a centralized interactive voice or internet response system (block size 4) and was stratified by HbA<sub>1c</sub>  $< 8.0$  and  $\geq 8.0\%$  ( $< 64$  and  $\geq 64$  mmol/mol) at screening. Due to differences in the injection devices, this was an open-label study. A 6-month open-label extension followed the main treatment period; here we report only the main treatment period.

### Interventions

Participants were given a glucose meter and test strips and educated in their use, including recording self-measured plasma glucose (SMPG) results in a diary. For participants previously using Gla-100 or once-daily NPH, the starting dose of Gla-300 or Gla-100 was the basal insulin dose used the 3 days prior to randomization; for those previously taking NPH more than once daily, the new daily basal dose was reduced by  $\sim 20\%$ . Injections were to be given in the evening from before dinner to bedtime but at the same time for each individual during 6 months of randomized treatment. Starting basal doses at randomization

were divisible by 3, rounding down if necessary. When more than one basal insulin injection was needed to deliver the required dosage ( $> 80$  units with Gla-100;  $> 180$  units with Gla-300), split injections were given at the same time. Basal insulin dosage was generally adjusted weekly, and no more often than every 3 days, aiming for a prebreakfast SMPG of 4.4–5.6 mmol/L based on the median of the previous 3 days. 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. Dosage was to increase by 3 units for  $> 5.6$  and  $< 7.8$  mmol/L and by 6 units if  $\geq 7.8$  mmol/L, and it was to decrease by 3 units if SMPG readings were  $< 4.4$  mmol/L or at the discretion of the investigator. Mealtime insulin doses were adjusted at the discretion of the investigator after basal insulin had been optimized but could be reduced earlier if needed when basal dosage was increased. Mealtime dose titration could be based on either postmeal SMPG (target range 6.7–8.9 mmol/L) or on values before the following meal or at bedtime (5.0–7.2 mmol/L). Metformin was to continue at prior dosage throughout the study. Beyond this guidance, investigators and participants were expected to use individual judgment in cessation of titration or other adjustments for reasons of safety.

Assessment 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<sub>1c</sub> and fasting plasma glucose (FPG) concentration 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 before baseline and at all later study visits.

### Outcomes

The primary end point was HbA<sub>1c</sub> change from baseline to month 6 or the last visit on treatment. The main secondary efficacy end point was the percentage of participants with one or more confirmed ( $\leq 3.9$  mmol/L) or severe nocturnal (0000–0559 h) hypoglycemic events, reported between the start of week 9 and month 6. Other

secondary end points included change from baseline in FPG; percentage of participants attaining HbA<sub>1c</sub> <7.0% (53 mmol/mol) and ≤6.5% (48 mmol/mol) or FPG ≤6.7 and <5.6 mmol/L; changes of mean and variability of 24-h plasma glucose based on 8-point SMPG profiles; change in preinjection SMPG and change in variability of preinjection SMPG; and changes of basal and total daily insulin doses and of body weight. Percentages of participants with hypoglycemic events and annualized event rates were calculated as categorized by the American Diabetes Association and were analyzed during the day (daytime; 0600–2359 h), during the night (nocturnal; 0000–0559 h), and any time of day or night (24 h) (15). Specifically, hypoglycemic categories included the following: 1) any hypoglycemia (events whether confirmed by SMPG or not and whether symptomatic or asymptomatic); 2) documented symptomatic hypoglycemia (symptomatic events with SMPG ≤3.9 mmol/L); 3) asymptomatic hypoglycemia (events confirmed by SMPG ≤3.9 mmol/L but without symptoms); and 4) severe hypoglycemia (events requiring assistance by another person to administer carbohydrate, glucagon, or other therapy). In addition to the threshold of ≤3.9 mmol/L, hypoglycemic events with a plasma glucose of <3.0 mmol/L were analyzed separately. Confirmed or severe hypoglycemia included documented symptomatic or asymptomatic events together with severe events.

Other adverse events (AEs), including injection-site reactions, were systematically recorded at each contact with investigators. Treatment satisfaction was assessed using the validated Diabetes Treatment Satisfaction Questionnaire (DTSQ), completed at baseline, week 12, and month 6 (16,17).

#### Data Analysis and Statistics

Analyses were performed using SAS version 9.2 (Cary, NC). A sample size of 800 evaluable participants was estimated to give 99% power for the upper confidence limit of the mean difference in change of HbA<sub>1c</sub> between insulin formulations not to exceed 0.4% (4.4 mmol/mol), assuming that the SD of change is 1.3% (14.2 mmol/mol), for a true difference of 0.0%. Primary efficacy and secondary end points used the modified intent to treat (mITT) population, defined as all

randomized participants who received at least one dose of study insulin and had both a baseline and one or more postbaseline assessment. If a participant discontinued treatment prematurely or did not have an efficacy measurement at month 6, the last postbaseline efficacy measurement was used (last observation carried forward procedure). Safety analyses included all participants randomized and exposed to one or more doses of study insulin.

To assess noninferiority for the primary end point, the upper bound of the two-sided 95% CI, estimated by a covariance (ANCOVA) model, was compared with the predefined noninferiority margin (HbA<sub>1c</sub> <0.4%; <4.4 mmol/mol). If noninferiority was demonstrated for HbA<sub>1c</sub>, superiority was to be tested for HbA<sub>1c</sub> (one-sided  $\alpha = 0.025$ ) and the main secondary efficacy end points according to a hierarchical testing procedure. All continuous secondary efficacy variables were analyzed using either ANCOVA (all except for change in variability of plasma glucose) or ANOVA

(change in variability) models. Categorical secondary efficacy variables (responder rates) were analyzed using a Cochran-Mantel-Haenszel method stratified according to screening HbA<sub>1c</sub> (<8.0 and ≥8.0% [ $<64$  and  $\geq 64$  mmol/mol]). AEs were coded using the MedDRA system.

#### Role of Funding Source

Sanofi was the sponsor and designed and coordinated the study, monitored clinical sites, collected and managed the data, and performed statistical analyses. M.C.R., G.B.B., and P.D.H. took part in 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

Of 807 participants randomized to Gla-300 ( $n = 404$ ) or Gla-100 ( $n = 403$ ), 404 and 402, respectively, received study insulin (safety population), and 404

**Table 1—Baseline characteristics of all randomized participants**

	Gla-300 ( $n = 404$ )	Gla-100 ( $n = 403$ )
Age (years)	60.1 (8.5)	59.8 (8.7)
Sex (male), $n$ (%)	217 (53.7)	210 (52.1)
Ethnic group, $n$ (%)		
Caucasian	371 (91.8)	374 (92.8)
Black	26 (6.4)	21 (5.2)
Asian/Oriental	6 (1.5)	5 (1.2)
Other	1 (0.2)	3 (0.7)
Body weight (kg)	106.2 (21.5)	106.4 (20.0)
BMI (kg/m <sup>2</sup> )	36.6 (6.8)	36.6 (6.1)
Duration of diabetes (years)	15.6 (7.2)	16.1 (7.8)
Duration of basal insulin treatment (years)	6.7 (4.7)	6.5 (4.8)
Basal insulin dose		
(units/kg/day)	0.67 (0.26)	0.67 (0.24)
(units/day)	70.0 (30.4)	70.3 (28.5)
Mealtime insulin dose		
(units/kg/day)	0.54 (0.34)	0.54 (0.32)
(units/day)	57.1 (36.5)	58.4 (37.9)
Total insulin dose		
(units/kg/day)	1.19 (0.48)	1.20 (0.45)
(units/day)	126.3 (56.7)	128.0 (56.1)
Prior use of insulin glargine, $n$ (%)	373 (92.3)	369 (91.6)
Prior use of metformin, $n$ (%)	227 (56.2)	236 (58.6)
FPG		
(mmol/L)	8.8 (2.9)	8.9 (2.9)
(mg/dL)	158.3 (51.8)	160.7 (52.8)
HbA <sub>1c</sub>		
(%)	8.15 (0.78)	8.16 (0.77)
(mmol/mol)	65.6 (8.5)	65.7 (8.4)

Data are presented as mean (SD), unless otherwise indicated.

and 400 formed the mITT population (Supplementary Fig. 1). Treatment was discontinued before 6 months by 30 (7.4%) of 404 participants on Gla-300 and 31 (7.7%) of 403 on Gla-100. The two groups had similar characteristics at baseline (Table 1). Participants had a mean age of 60 years, duration of diabetes of 16 years, BMI of 36.6 kg/m<sup>2</sup>, HbA<sub>1c</sub> of 8.15% (65.6 mmol/mol), FPG of 8.9 mmol/L (160 mg/dL), and basal and total insulin doses of 0.67 and 1.20 units/kg/day.

### Glycemic Responses and Insulin

#### Dosage

Mean HbA<sub>1c</sub> decreased similarly in the two treatment groups (Fig. 1A). At the end of treatment, HbA<sub>1c</sub> was 7.25% (SD 0.85) (55.7 mmol/mol [9.3]) with Gla-300 and 7.28% (0.92) (56.1 mmol/mol [10.1]) with Gla-100. The least squares (LS) mean change was  $-0.83\%$  (SE 0.06) ( $-9.1$  mmol/mol [0.7]) for both groups; difference  $-0.00\%$  (95% CI  $-0.11$  to  $0.11$ ) ( $-0.00$  mmol/mol [ $-1.2$  to  $1.2$ ]), thus

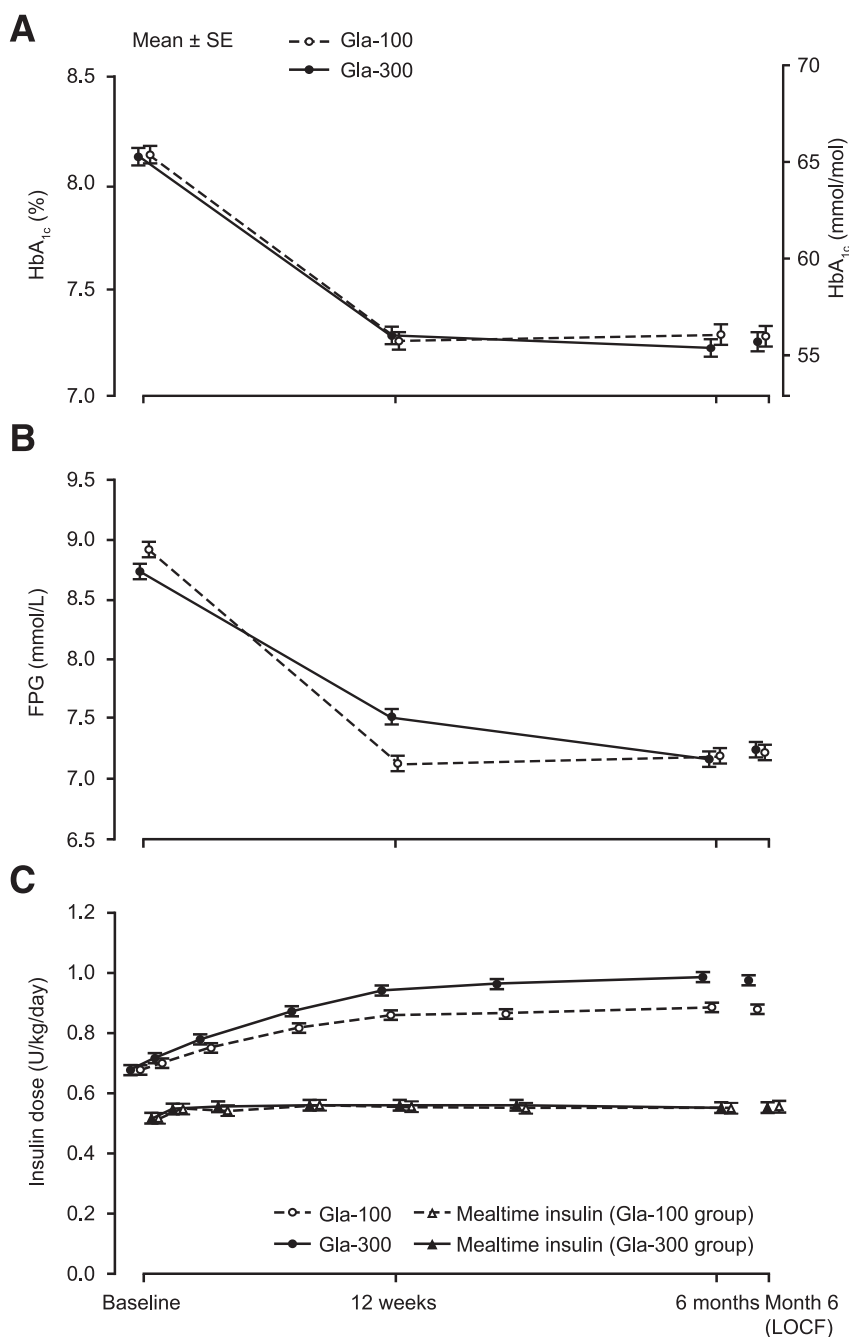
meeting the noninferiority criterion. Similar reductions in laboratory-measured FPG from baseline were observed in both treatment groups (from 8.72 mmol/L [SD 2.83] to 7.24 mmol/L [2.57] with Gla-300 and 8.90 mmol/L [2.94] to 7.21 mmol/L [2.40] with Gla-100) (Fig. 1B). The percentages of participants attaining target HbA<sub>1c</sub> levels were similar with Gla-300 and Gla-100 (39.6 and 40.9% for HbA<sub>1c</sub> <7.0% [53 mmol/mol] and 26.5 and 23.2% for FPG <5.6 mmol/L, respectively) (Supplementary Table 1).

Daily basal insulin dosage increased from 0.67 units/kg/day (SD 0.29) to 0.97 units/kg/day (0.37) (70 units/day [32] to 103 units/day [42]) at the end of the 6-month treatment period with Gla-300 and from 0.67 units/kg/day (0.28) to 0.88 units/kg/day (0.32) (71 units/day [33] to 94 units/day [38]) with Gla-100; LS mean difference 0.09 units/kg/day (SE 0.02) (95% CI 0.062–0.124) (Fig. 1C). Mealtime insulin doses increased slightly in the first 2 weeks but were unchanged from baseline and alike in the two groups thereafter (final 0.55 units/kg/day [SD 0.35]). Final total daily dosage was 1.53 units/kg/day (0.61) with Gla-300 and 1.43 units/kg/day (0.60) with Gla-100. Body weight increased by 0.9 kg in both treatment groups.

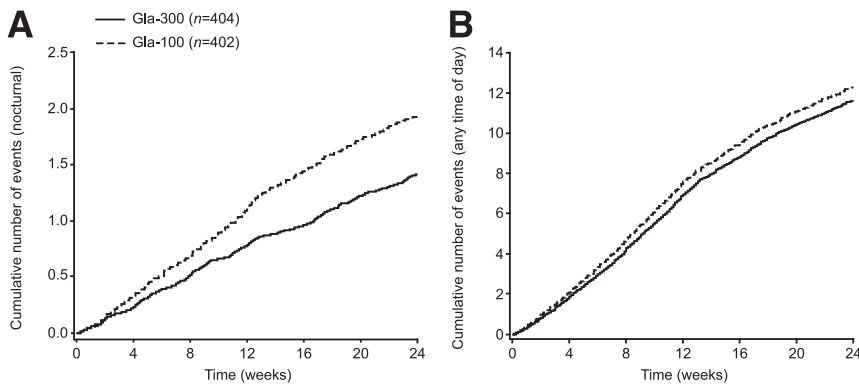
The SMPG profiles declined in both treatment groups (Supplementary Fig. 2 and Supplementary Table 1). The mean of all daily measurements declined to the same degree with each treatment, and no significant differences between changes in means at individual time points were demonstrated, including comparisons of fasting, 0300 h, and preinjection measurements. The reduction of preinjection SMPG (combination of pre- and postdinner measurements) from baseline to month 6 was similar between treatments (LS mean change  $-0.90$  mmol/L [SE 0.18] and  $-0.84$  mmol/L [0.18]). There was also no between-treatment difference in the change of day-to-day variability of preinjection SMPG during treatment.

#### Hypoglycemia

Curves displaying the cumulative mean number of nocturnal (Fig. 2A) and any time (Fig. 2B) confirmed or severe hypoglycemic events during the course of treatment are shown in Fig. 2.



**Figure 1**—Clinical measures during treatment in the mITT population by visit and with last observation carried forward (LOCF). A: HbA<sub>1c</sub>. B: FPG. C: Daily basal insulin and mealtime insulin dosage.



**Figure 2**—Cumulative mean numbers of confirmed (plasma glucose  $\leq 3.9$  mmol/L [70 mg/dL]) or severe hypoglycemic events per participant during the main 6-month treatment period in the safety population. A: Nocturnal events. B: Events at any time of day or night (24 h).

The proportion of participants with one or more confirmed ( $\leq 3.9$  mmol/L) or severe nocturnal hypoglycemic events between the start of week 9 and month 6 was 36% (146 of 404) on Gla-300, compared with 46% (184 of 400) on Gla-100. Analysis of this prespecified main measure of hypoglycemia demonstrated superiority of Gla-300 over Gla-100 with a significantly lower relative risk (RR 0.79 [95% CI 0.67–0.93],  $P = 0.0045$ ). The percentages of participants affected and rates of events per participant-year of exposure for other intervals of time and categories of hypoglycemia are shown in Supplementary Tables 2 and 3; RRs are shown in Fig. 3. With the exception of severe nocturnal hypoglycemic events, which were too few for meaningful analysis, the percentage of participants within each category of nocturnal events (any hypoglycemia; documented [ $\leq 3.9$  and  $< 3.0$  mmol/L] symptomatic hypoglycemia; and confirmed [ $\leq 3.9$  and  $< 3.0$  mmol/L] or severe hypoglycemia) was lower with Gla-300 than with Gla-100 (RR 0.72–0.78) throughout the course of treatment. Likewise, annualized rates for nocturnal events were lower with Gla-300 (RR 0.60–0.78) across all categories of hypoglycemia other than severe events.

No significant increase in either the numbers of participants affected or annualized rates for daytime hypoglycemia was apparent in any category. Risks of any time events, nocturnal and daytime together, were equivalent or lower with Gla-300. The percentage of participants reporting severe hypoglycemia at any time of day or night (24 h) was similar for the two groups: 5.0% for

Gla-300 vs. 5.7% for Gla-100 (RR 0.87 [95% CI 0.48–1.55]).

#### Treatment Satisfaction

Treatment satisfaction scores, as measured by the DTSQ, were similar between treatment groups and generally increased from baseline to month 6, with a small between-treatment difference in favor of Gla-300 versus Gla-100 (treatment satisfaction scores increased in 63 and 58% of participants, respectively) (Supplementary Table 4). The perceived frequency of hypoglycemia, as captured by Item 3 of the DTSQ, was similar between groups. The cumulative distribution functions of Item 3 show that at month 6, more than half of the participants experienced a decrease from baseline in the perception of hypoglycemia, with a small between-treatment difference in favor of Gla-300 (change from baseline to month 6:  $\leq 0$  in 59 and 54% of participants in the Gla-300 and Gla-100 groups, respectively).

#### AEs

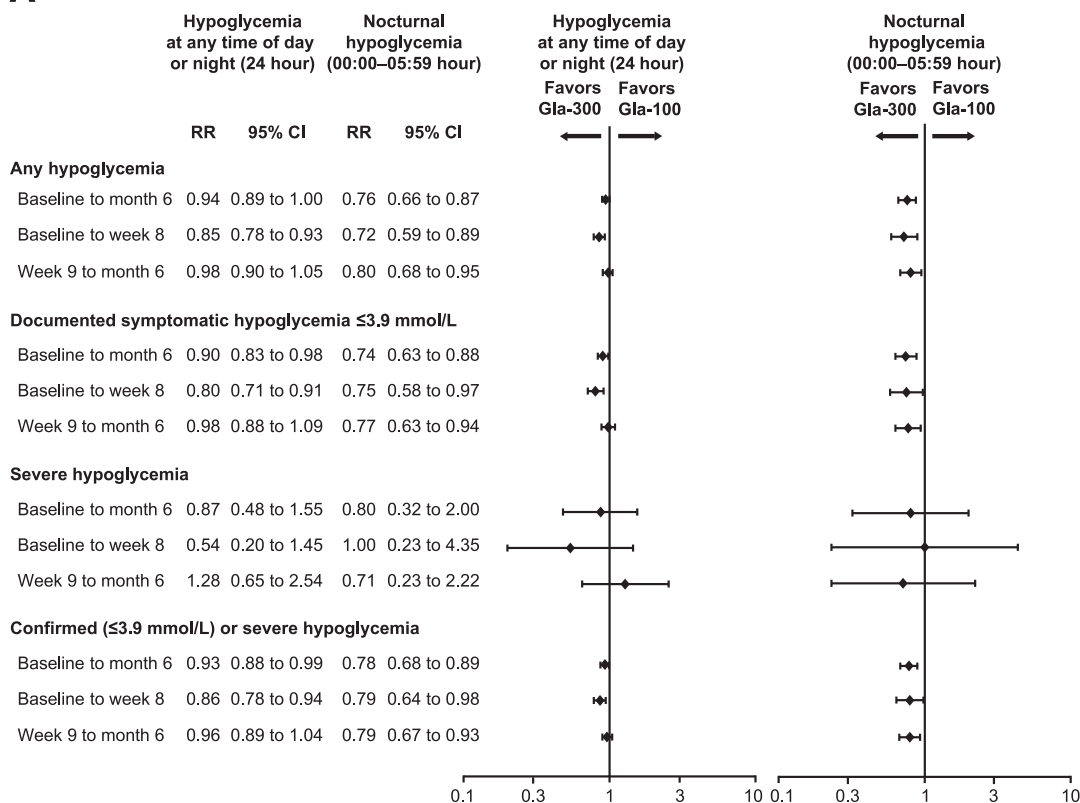
The most common AEs were infections, gastrointestinal events, or musculoskeletal complaints; these were equally distributed between the groups. Injection-site reactions were reported by nine (2.2%) and six (1.5%) people treated with Gla-300 and Gla-100, respectively. Serious treatment-emergent AEs (Supplementary Table 5) were reported by 26 people (6.4%) on Gla-300 and 21 (5.2%) on Gla-100, with a maximum of two events of any one type of event for both insulins, including two of hypoglycemic coma on Gla-300. Treatment-emergent AEs led to withdrawal from the study in six (1.5%) people in the Gla-300 group and seven (1.7%) in the

Gla-100 group. Three participants experienced a serious treatment-emergent AE with fatal outcome during the study, one in the Gla-300 group (bronchogenic carcinoma) and two in the Gla-100 group (one with multidrug intoxication associated with recurrent depression and one with chronic heart and kidney failure). Two additional participants in the Gla-300 group had an AE with fatal outcome 4 and 12 days after treatment discontinuation (due to pulmonary embolism and infected thrombosis and heart embolism, respectively). No deaths were considered related to study medication.

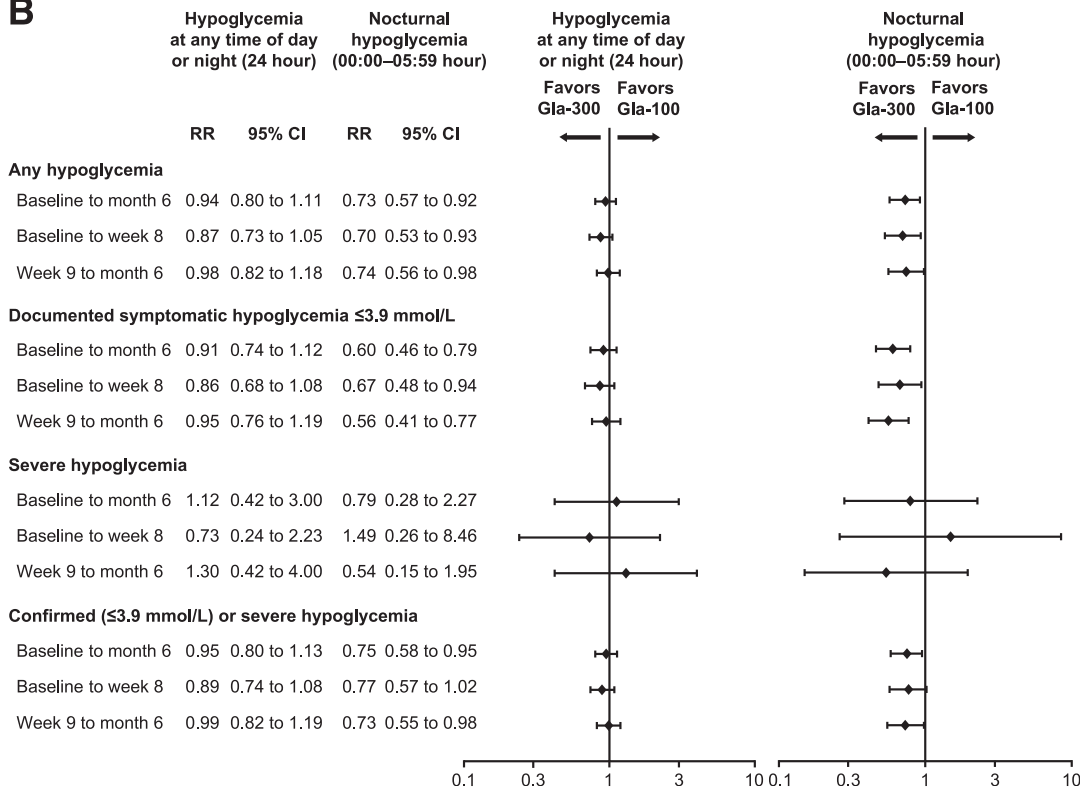
#### CONCLUSIONS

This large, randomized, 6-month efficacy and safety study of Gla-300 enrolled a population of people with type 2 diabetes using mealtime insulin with basal insulin at a dosage of at least 42 units/day. This dosage requirement was selected to ensure adequate dose precision with the pen injector used for Gla-300. Improvements of HbA<sub>1c</sub>, FPG, and profiles of SMPG were essentially the same with Gla-300 as with Gla-100. Attainment of mean HbA<sub>1c</sub> 7.3% (56 mmol/mol) by each group suggests good adherence to basal insulin titration by the site investigators and study participants. Similar levels of glycemic control have been reported in other studies of type 2 diabetes requiring regimens including both basal and mealtime insulin (18–20). Despite equivalent efficacy in terms of glycemic control, use of Gla-300 resulted in a 10% absolute and 21% relative decrease in risk of experiencing at least one confirmed or severe nocturnal hypoglycemic event from week 9 to month 6. This time period was chosen to avoid any possibility of temporary alteration of the risk of hypoglycemia following a switch from a known therapy (in most cases Gla-100) to an unfamiliar new insulin. However, the between-treatment differences observed in both incidence and event rate of nocturnal hypoglycemia, favoring Gla-300, were apparent both in the first 8 weeks and later in the course of treatment, as is visually evident in Fig. 2. This appears different from the experience with insulin degludec, another new long-acting analog, where differences in nocturnal hypoglycemia seem to emerge later, for reasons that are unclear (21).

**A**



**B**



**Figure 3**—RRs of hypoglycemic events at any time of day or night (24 h) or during the night alone (nocturnal) with Gla-300 vs. Gla-100 during 6 months of treatment in the safety population. *A*: Risk of at least one hypoglycemic event per participant. *B*: Risk of events per participant-year of exposure. Total participant-year: baseline to month 6: Gla-300, 195 and Gla-100, 193; baseline to week 8: Gla-300, 63 and Gla-100, 62; week 9 to month 6: Gla-300, 132 and Gla-100, 131. 95% CIs are shown.

Insulin glargine (Gla-100) is already known to give lower rates of nocturnal hypoglycemia than NPH insulin (2,7,8), so the current results are doubly encouraging.

This observation was further supported by the consistency of patterns of events regardless of the category of hypoglycemia, which were all equivalent between the two insulins or favored Gla-300. Notably, the RR of confirmed ( $\leq 3.9$  mmol/L) or severe nocturnal hypoglycemia was 21% lower with Gla-300 during the first 8 weeks of the study, 21% lower from week 9 to the end of treatment, and 22% lower for the whole treatment period. Similarly, the rate of nocturnal confirmed or severe events (including multiple events for an individual over the course of the study) was 25% lower with Gla-300. None of the categories of hypoglycemia showed an increase of events with Gla-300 during the daytime (0600–2359 h), and severe hypoglycemia was uncommon with both treatments.

Differences of study design and populations limit comparison of the present findings with other studies of longer-acting insulin using treat-to-target protocols, but the published experience nevertheless is of interest. In the original Treat-to-Target study, which enrolled insulin-naïve participants, initiation and titration of Gla-100 resulted in an annualized rate of confirmed hypoglycemic events ( $\leq 4.0$  mmol/L) that was 29% lower than observed with NPH insulin, and the rate of confirmed nocturnal events was 44% lower (2). Subsequent studies in previously insulin-naïve people have shown reductions in hypoglycemia with Gla-100 or insulin detemir relative to NPH insulin that are of about the same magnitude (22). Two similarly designed studies have evaluated beginning treatment with insulin degludec compared with Gla-100 (21,23). These are of interest because degludec, like Gla-300, is reported to have an action profile extending beyond 24 h. In one of these studies, the annualized rate of nocturnal hypoglycemia confirmed  $< 3.1$  mmol/L was 36% lower ( $P = 0.038$ ) with insulin degludec U100 versus Gla-100 (21). In the other, a U200 formulation of insulin degludec was associated with a nominally but nonsignificantly lower rate of confirmed ( $< 3.1$  mmol/L) nocturnal hypoglycemia compared with Gla-100 (RR 0.86,  $P = 0.46$ )

(23). Collectively, these studies of insulin-naïve populations suggest that Gla-100 and insulin detemir confer lower risks of hypoglycemia than NPH insulin, whereas the longer-acting insulin degludec may have even less tendency to cause nocturnal hypoglycemia than Gla-100.

A recent comparison of insulin degludec U100 with Gla-100 in a population with type 2 diabetes that included people who were previously treated with basal and mealtime insulin more closely resembles the current study (24). Equivalent glycemic control was attained with degludec and Gla-100. The annualized rate of confirmed nocturnal hypoglycemic events was 25% ( $P = 0.040$ ) lower with insulin degludec than with Gla-100. These findings are similar to those of the current study, but again the comparison is limited by differences in the populations examined. The current study has a different definition of confirmed hypoglycemia ( $\leq 3.9$  vs.  $< 3.1$  mmol/L) and enrolled participants with higher BMI (36.6 vs.  $\sim 32$  kg/m<sup>2</sup>), longer duration of diabetes ( $\sim 16$  vs.  $\sim 13.5$  year), more frequent prior use of mealtime as well as basal insulin therapy (100 vs.  $\sim 50\%$ ), and higher basal insulin doses (0.7 vs.  $\sim 0.4$  units/kg).

Some additional questions remain. The 10% higher dosage of Gla-300 at the end of treatment might be due to a slight decrease in bioavailability related to a longer subcutaneous residence time with exposure to tissue peptidases. The glargine molecule is unchanged in Gla-300, therefore new safety concerns appear unlikely; the main circulating molecule is 21<sup>A</sup>-Gly-human insulin (metabolite M1) after injection with each formulation (25). No evidence of increased injection-site problems or other AEs appeared in this study, but more participant-years of observation will be needed to confirm long-term safety. Finally, it remains to be shown whether other populations of people with diabetes will experience similar, or perhaps greater, reductions in risk of hypoglycemia with Gla-300. Strengths of this study include enrollment of a relatively large number of people representing a growing population with long-duration type 2 diabetes requiring high-dose basal insulin and mealtime insulin therapy; a closely supervised titration scheme to optimize basal

insulin delivery leading to good and equivalent glycemic control in each treatment group; and the consistency of the findings with different categories of hypoglycemia and different intervals of time in the study. Limitations include the unavoidable open-label nature of the protocol, relatively short duration of study, and limited titration of mealtime insulin doses. Although the obesity and high insulin requirement of the EDITION 1 population are now common in type 2 diabetes, the results of this study cannot be generalized to the whole population of people with insulin-requiring diabetes, which includes many taking  $< 42$  units of basal insulin daily. Completion of later EDITION studies will address the last concern. Further details regarding the rationale for use of Gla-300 in both EDITION 1 and the rest of the EDITION studies are available in a video presentation (Video 1, available at <http://bcove.me/psne9yp6>).

In conclusion, EDITION 1 showed the new insulin Gla-300, administered for 6 months, improved glycemic control for obese people with long-duration type 2 diabetes as well as Gla-100 but with less nocturnal hypoglycemia and no increase of daytime hypoglycemia. No between-treatment differences in the safety profile were identified. Gla-300 is being further investigated in studies of other populations in the EDITION program.

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## References

- Owens DR. Insulin preparations with prolonged effect. *Diabetes Technol Ther* 2011;13 (Suppl. 1):S5–S14
- Riddle MC, Rosenstock J, Gerich J; Insulin Glargine 4002 Study Investigators. The treat-to-target trial: randomized addition of glargine or human NPH insulin to oral therapy of type 2 diabetic patients. *Diabetes Care* 2003;26:3080–3086
- Bolli GB, Andreoli AM, Lucidi P. Optimizing the replacement of basal insulin in type 1 diabetes mellitus: no longer an elusive goal in the post-NPH era. *Diabetes Technol Ther* 2011;13 (Suppl. 1):S43–S52
- ORIGIN Trial Investigators. Characteristics associated with maintenance of mean A1C < 6.5% in people with dysglycemia in the ORIGIN trial. *Diabetes Care* 2013;36:2915–2922
- Gerstein HC, Bosch J, Dagenais GR, et al.; ORIGIN Trial Investigators. Basal insulin and cardiovascular and other outcomes in dysglycemia. *N Engl J Med* 2012;367:319–328
- Inzucchi SE, Bergenstal RM, Buse JB, et al.; American Diabetes Association (ADA); European Association for the Study of Diabetes (EASD). Management of hyperglycemia in type 2 diabetes: a patient-centered approach: position statement of the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD). *Diabetes Care* 2012;35:1364–1379
- Janka HU, Plewe G, Riddle MC, Kliebe-Frisch C, Schweitzer MA, Yki-Järvinen H. Comparison of basal insulin added to oral agents versus twice-daily premixed insulin as initial insulin therapy for type 2 diabetes. *Diabetes Care* 2005;28:254–259
- Gerstein HC, Yale JF, Harris SB, Issa M, Stewart JA, Dempsey E. A randomized trial of adding insulin glargine vs. avoidance of insulin in people with type 2 diabetes on either no oral glucose-lowering agents or submaximal doses of metformin and/or sulphonylureas. The Canadian INSIGHT (Implementing New Strategies with Insulin Glargine for Hyperglycaemia Treatment) Study. *Diabet Med* 2006;23:736–742
- Davies M. The reality of glycaemic control in insulin treated diabetes: defining the clinical challenges. *Int J Obes Relat Metab Disord* 2004;28(Suppl. 2):S14–S22
- Cryer PE. Hypoglycaemia: the limiting factor in the glycaemic management of type I and type II diabetes. *Diabetologia* 2002;45:937–948
- Korytkowski M. When oral agents fail: practical barriers to starting insulin. *Int J Obes Relat Metab Disord* 2002;26(Suppl. 3):S18–S24
- Tillner J, Bergmann K, Teichert L, et al. Euglycemic clamp profile of new insulin glargine U300 formulation in patients with type 1 diabetes (T1DM) is different from glargine U100 (Abstract). *Diabetes* 2013;62:A920-P
- Dahmen R, Bergmann K, Lehman A, et al. New insulin glargine U300 formulation evens and prolongs steady state PK and PD profiles during euglycemic clamp in patients with type 1 diabetes (T1DM) (Abstract). *Diabetes* 2013;62:A113
- World Health Organization. *Definition, Diagnosis, and Classification of Diabetes Mellitus and its Complications: Report of a WHO Consultation. Part 1: Diagnosis and Classification of Diabetes Mellitus*. Geneva, World Health Organization, 1999. Available from [http://whqlibdoc.who.int/hq/1999/who\\_ncd\\_ncs\\_99.2.pdf](http://whqlibdoc.who.int/hq/1999/who_ncd_ncs_99.2.pdf). Accessed 6 November 2013
- American Diabetes Association Workgroup on Hypoglycemia. Defining and reporting hypoglycemia in diabetes: a report from the American Diabetes Association Workgroup on Hypoglycemia. *Diabetes Care* 2005;28:1245–1249
- Bradley C, Lewis KS. Measures of psychological well-being and treatment satisfaction developed from the responses of people with tablet-treated diabetes. *Diabet Med* 1990;7:445–451
- Lewis KS, Bradley C, Knight G, Boulton AJ, Ward JD. A measure of treatment satisfaction designed specifically for people with insulin-dependent diabetes. *Diabet Med* 1988;5:235–242
- Fritsche A, Larbig M, Owens D, Häring HU; GINGER study group. Comparison between a basal-bolus and a premixed insulin regimen in individuals with type 2 diabetes—results of the GINGER study. *Diabetes Obes Metab* 2010;12:115–123
- Meneghini L, Mersebach H, Kumar S, Svendsen AL, Hermansen K. Comparison of 2 intensification regimens with rapid-acting insulin aspart in type 2 diabetes mellitus inadequately controlled by once-daily insulin detemir and oral antidiabetic drugs: the step-wise randomized study. *Endocr Pract* 2011;17:727–736
- Riddle MC, Rosenstock J, Vlainic A, et al. Randomized, 1-year comparison of three ways to initiate and advance insulin for type 2 diabetes: twice-daily premixed insulin versus basal insulin with either basal-plus one prandial insulin or basal-bolus up to three prandial injections. *Diabetes Obes Metab* 2014;16:396–402
- Zinman B, Philis-Tsimikas A, Cariou B, et al.; NN1250-3579 (BEGIN Once Long) Trial Investigators. Insulin degludec versus insulin glargine in insulin-naïve patients with type 2 diabetes: a 1-year, randomized, treat-to-target trial (BEGIN Once Long). *Diabetes Care* 2012;35:2464–2471
- Hermansen K, Davies M, Dereziński T, Martínez Ravn G, Clauson P, Home P. A 26-week, randomized, parallel, treat-to-target trial comparing insulin detemir with NPH insulin as add-on therapy to oral glucose-lowering drugs in insulin-naïve people with type 2 diabetes. *Diabetes Care* 2006;29:1269–1274
- Gough SC, Bhargava A, Jain R, Mersebach H, Rasmussen S, Bergenstal RM. Low-volume insulin degludec 200 units/ml once daily improves glycemic control similarly to insulin glargine with a low risk of hypoglycemia in insulin-naïve patients with type 2 diabetes: a 26-week, randomized, controlled, multinational, treat-to-target trial: the BEGIN LOW VOLUME trial. *Diabetes Care* 2013;36:2536–2542
- Garber AJ, King AB, Del Prato S, et al.; NN1250-3582 (BEGIN BB T2D) Trial Investigators. Insulin degludec, an ultra-longacting basal insulin, versus insulin glargine in basal-bolus treatment with mealtime insulin aspart in type 2 diabetes (BEGIN Basal-Bolus Type 2): a phase 3, randomised, open-label, treat-to-target non-inferiority trial. *Lancet* 2012;379:1498–1507
- Steintraesser A, Schmidt R, Bergmann K, Dahmen R, Becker RH. Investigational new insulin glargine 300 U/ml has the same metabolism as insulin glargine 100 U/ml. *Diabetes Obes Metab*. 26 February 2014 [Epub ahead of print]