New insulin glargine 300 U/ml compared with glargine 100 U/ml in insulin-naïve people with type 2 diabetes on oral glucose-lowering drugs

a randomized controlled trial (EDITION 3)

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ORIGINAL ARTICLE

New insulin glargine 300 U/ml compared with glargine 100 U/ml in insulin-naïve people with type 2 diabetes on oral glucose-lowering drugs: a randomized controlled trial (EDITION 3)

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Aims: To compare the efficacy and safety of new insulin glargine 300 U/ml (Gla-300) with that of glargine 100 U/ml (Gla-100) in insulin-naïve people with type 2 diabetes using oral glucose-lowering drugs.

Methods: The EDITION 3 study was a multicentre, open-label, parallel-group study. Participants were randomized to Gla-300 or Gla-100 once daily for 6 months, discontinuing sulphonylureas and glinides, with a dose titration aimed at achieving pre-breakfast plasma glucose concentrations of 4.4–5.6 mmol/l (80–100 mg/dl). The primary endpoint was change in glycated haemoglobin (HbA1c) from baseline to month 6. The main secondary endpoint was percentage of participants with ≥1 nocturnal confirmed [≤3.9 mmol/l (≤70 mg/dl)] or severe hypoglycaemia from week 9 to month 6. Other measures of glycaemia and hypoglycaemia, weight change and insulin dose were assessed.

Results: Randomized participants (n = 878) had a mean (standard deviation) age of 57.7 (10.1) years, diabetes duration 9.8 (6.4) years, body mass index 33.0 (6.7) kg/m^2 and HbA1c 8.54 (1.06) % [69.8 (11.6) mmol/mol]. HbA1c levels decreased by equivalent amounts with the two treatments; the least squares mean difference in change from baseline was 0.04 [95% confidence interval (CI) −0.09 to 0.17] % or 0.4 (−1.0 to 1.9) mmol/mol. Numerically fewer participants reported ≥1 nocturnal confirmed (≤3.9 mmol/l) or severe hypoglycaemia from week 9 to month 6 [relative risk (RR) 0.89 (95% CI 0.66 to 1.20)] with Gla-300 versus Gla-100; a significantly lower risk of hypoglycaemia with this definition was found over the 6-month treatment period [RR 0.76 (95% CI 0.59 to 0.99)]. No between-treatment differences in adverse events were identified.

Conclusions: Gla-300 is as effective as Gla-100 in reducing HbA1c in insulin-naïve people with type 2 diabetes, with lower hypoglycaemia risk.

Keywords: basal insulin analogues, basal insulin initiation, type 2 diabetes

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Introduction

Many people who initially achieve glycaemic control with oral glucose-lowering drugs will eventually require insulin, either alone or in combination with other agents [1]; however, hypoglycaemia, weight gain and the limited flexibility of some insulin regimens [2–5] may contribute to omission of injections or failure to make appropriate adjustments of insulin dose(s) [4,6], negatively affecting glycaemic control.

At present, the most widely used basal insulin is insulin glargine 100 U/ml (Gla-100), which has a well-established mode of action, and efficacy and safety profile [7–11]. However, to improve current treatment options, a basal insulin conferring an even lower risk of hypoglycaemia would be desirable. New insulin glargine 300 U/ml (Gla-300) has been developed to optimize glycaemic control, while minimizing the risk of hypoglycaemia. After subcutaneous (s.c.) injection, the pharmacokinetic and pharmacodynamic action profiles of Gla-300 were more constant and prolonged compared with those of Gla-100 [12], as a result of a more gradual and extended release of glargine from the s.c. depot. This translates into continued blood glucose control beyond 24 h [12].

To determine whether these pharmacokinetic and pharmacodynamic properties will confer clinical benefits, Gla-300 is being investigated in comparison with Gla-100 in the phase IIIa EDITION programme. The first two studies in this programme, in people with type 2 diabetes receiving either a high dose of basal insulin in combination with mealtime insulin (EDITION 1) or basal insulin in combination with oral therapy (EDITION 2), showed that Gla-300 is as effective as Gla-100 in terms of glycaemic control, with significantly lower risk of nocturnal confirmed or severe hypoglycaemia and similar or

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significantly less hypoglycaemia at any time of day [13,14]. The EDITION 3 study investigated the safety and efficacy of Gla-300 in comparison with Gla-100, in insulin-naïve people with type 2 diabetes.

Research Design and Methods

Study Design and Participants

The EDITION 3 study was a multicentre, randomized, open-label, two-arm, parallel-group, phase IIIa study conducted from August 2012 to September 2013, involving 878 participants with type 2 diabetes. The study comprised a 2-week screening phase and a 6-month treatment period, followed by a 6-month safety extension period. Results from the main 6-month treatment period are reported in the present paper.

Participants were recruited as outpatients in 197 centres across 15 countries (2 in North America, 12 in Europe, and Japan). Appropriate 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 (WHO definition [15]) for at least 1 year before screening, having used oral glucose-lowering drugs for at least 6 months before screening and being insulin-naïve. Exclusion criteria included glycated haemoglobin (HbA1c) <7.0 % (53 mmol/mol) or >11.0 % (97 mmol/mol) at screening. If participants were receiving oral glucose-lowering drugs not approved for combination with insulin, and/or sulphonylureas or glinides, these medications were discontinued at baseline.

The study was registered with ClinicalTrials.gov under the registration no: NCT01676220.

Randomization and Study Treatments

Participants were randomized (1 : 1) to receive once-daily injections of either Gla-300, using a modified TactiPen® injector (Sanofi, Paris, France), or Gla-100 (Lantus®; Sanofi), using a SoloSTAR® pen injector (Sanofi). Randomization was performed using a centralized interactive voice or internet response system and was stratified by HbA1c at the screening visit [<8.0 or ≥8.0 % (<64 or ≥64 mmol/mol)] and geographical region (non-Japan/Japan). Because of differences in the injection devices, this was an open-label study.

Study Procedures

Participants were given a glucose meter and test strips (Accu-Chek; Roche Diagnostics, Mannheim, Germany), and training in recording self-monitored plasma glucose (SMPG) results in a diary. Injections were to be administered from before the evening meal until bedtime, but at the same time of day throughout the 6-month treatment period. Starting dose was 0.2 U/kg body weight for both insulins, rounded down to the closest whole number divisible by three. When more than one injection was needed (>80 U with Gla-100, >90 U with Gla-300), injection doses were given at the same time.

Insulin dose was adjusted once weekly (and not more than every 3 days), aiming for a fasting SMPG of 4.4–5.6 mmol/l (80–100 mg/dl) in the absence of hypoglycaemia. Adjustments were restricted by protocol to changes in multiples of 3 U, the smallest equal adjustment possible for both pen injectors. Dosage was to increase by 3 U for SMPG >5.6 and <7.8 mmol/l, and by 6 U if ≥7.8 mmol/l and to decrease by 3 U if SMPG was ≥3.3 and <4.4 mmol/l, and by ≥3 U (with investigator discretion) for SMPG <3.3 mmol/l or if severe or multiple symptomatic hypoglycaemic events occurred. Participants stopped some background therapies as described above, but otherwise continued previous therapies at unchanged doses. Rescue treatment was allowed at the investigators' discretion.

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, 9–11 and 22. Samples for central laboratory measurement of both HbA1c and fasting plasma glucose (FPG) concentration were collected during clinic visits at baseline, week 12 and month 6. Eight-point SMPG profiles (at 03:00 hours, before and 2 h after breakfast, lunch and dinner, and at bedtime) were performed at baseline and before each study visit.

Outcomes

The primary endpoint was change in HbA1c from baseline to month 6. The main secondary efficacy endpoint was the percentage of participants experiencing one or more nocturnal (00:00–05:59 hours) confirmed [≤3.9 mmol/l (≤70 mg/dl)] or severe hypoglycaemic event, reported between the start of week 9 and the end of month 6. Other secondary endpoints included the change in pre-injection SMPG from baseline to month 6; between-day variability of pre-injection SMPG at month 6; change in laboratory-measured FPG; percentage of participants achieving HbA1c <7.0 % (<53 mmol/mol) and ≤6.5 % (≤48 mmol/mol) or laboratory-measured FPG ≤6.7 mmol/l (≤120 mg/dl) and <5.6 mmol/l (<100 mg/dl) at month 6; change in mean 24-h SMPG based on eight-point SMPG profiles; and change in basal daily insulin dose and body weight. The percentage of participants experiencing hypoglycaemic events, as defined by the American Diabetes Association [16], and annualized event rates were analysed as safety endpoints occurring at any time of day (24 h), during the night (nocturnal; 00:00–05:59 hours) or during the day (daytime; 06:00–23:59 hours). All possible hypoglycaemic events were recorded (whether symptomatic or asymptomatic, and confirmed by SMPG or not). 'Documented symptomatic hypoglycaemia' was defined as symptomatic events with SMPG ≤3.9 mmol/l, and 'severe hypoglycaemia' as events requiring assistance by another person to administer carbohydrate, glucagon or other therapy. 'Confirmed or severe hypoglycaemia' included documented symptomatic or asymptomatic (SMPG ≤3.9 mmol/l) hypoglycaemia and severe events. Hypoglycaemic events with a plasma glucose measurement of <3.0 mmol/l (<54 mg/dl) were also analysed. Adverse events (AEs), including injection-site reactions, were recorded throughout the study.

Participant-reported outcomes recorded included treatment satisfaction, assessed using the Diabetes Treatment Satisfaction Questionnaire, status version (DTSQs) [17–19], health-related quality of life, assessed using the EuroQol 5

Dimensions (EQ-5D) questionnaire [20], and behaviours and worries related to fear of hypoglycaemia, assessed using the hypoglycaemia fear scale (HFS-II) [21]. These were all completed at baseline, week 12 and month 6.

Data Analysis and Statistics

Analyses were performed using SAS version 9.2 (Cary, NC, USA). A sample size of 800 was chosen to provide 99% power for the upper confidence interval (CI) limit of the mean difference in change in HbA1c between Gla-300 and Gla-100 not to exceed 0.40 % (4.4 mmol/mol), assuming a standard deviation (s.d.) of 1.3 % (14.2 mmol/mol) for a true difference of 0.0%. A sample size of 800 also provided >80% power to detect a treatment difference of 12.5% versus 20% for the main secondary endpoint (one-sided $\alpha = 0.025$). All efficacy endpoints used the modified intention-to-treat (mITT) population, defined as all randomized participants who received at least one dose of study insulin and had both a baseline and ≥1 post-baseline assessment of main efficacy endpoints. The safety population comprised all participants randomized and exposed to ≥1 dose of study insulin.

To assess non-inferiority for the primary endpoint, the upper bound of the two-sided 95% CI of the least squares (LS) mean difference, estimated using a mixed-effect model with repeated measures approach, was compared with a pre-defined non-inferiority margin (<0.40 % HbA1c; <4.4 mmol/mol). If non-inferiority was observed for HbA1c, superiority was to be tested (one-sided $\alpha = 0.025$) for the main secondary efficacy endpoints according to a hierarchical testing procedure.

All continuous efficacy variables except change in basal daily insulin dose were analysed using a mixed-effect model with repeated measures approach, and categorical secondary efficacy variables were analysed using a Cochran–Mantel–Haenszel method. Further details on statistical analyses are provided in Appendix S1.

Results

Study Population

Of 878 participants with type 2 diabetes randomized to Gla-300 (n = 439) or Gla-100 (n = 439), 435 and 438, respectively, received treatment, and comprised the safety population (Figure S1). The mITT population comprised 432 and 430 participants, respectively. Treatment was discontinued by 62 (14%) and 75 (17%) participants in the Gla-300 and Gla-100 groups, respectively, mostly at their own request. Rescue medication was required by 15 participants (3%) in the Gla-300 group and 7 (2%) in the Gla-100 group. Baseline characteristics were similar in the two treatment groups (Table 1). Before the start of treatment, 59% of participants were taking sulphonylureas and <1% were taking glinides (both discontinued), while 91% were taking metformin and 22% were taking dipeptidyl peptidase-4 inhibitors (both continued).

Glycaemic Responses and Insulin Dose

The mean decrease in HbA1c (primary endpoint) was equivalent in the two treatment groups (Table 1, Figure 1A). At month 6 the LS mean difference in change of HbA1c was 0.04 (95% CI −0.09 to 0.17) % [0.4 (95% CI −1.0 to 1.9) mmol/mol], meeting the non-inferiority criterion.

The proportion of participants reaching target HbA1c or laboratory-measured FPG at month 6 was much the same in the two treatment groups (Table 1).

Similar results in both the Gla-300 and Gla-100 groups were observed for change in pre-injection SMPG (sometimes a pre- and sometimes a post-dinner measurement) and variability in pre-injection SMPG (Table 1). The mean change in laboratory-measured FPG from baseline to month 6 was somewhat greater in the Gla-100 group than in the Gla-300 group [LS mean difference 0.39 (95% CI 0.10 to 0.68) mmol/l; Table 1, Figure 1B]. Over the 24-h period, the eight-point SMPG profiles showed a similar decrease from baseline to month 6 with both Gla-300 and Gla-100 [LS mean difference 0.18 (95% CI −0.07 to 0.42); Table 1, Figure S2]. The pre-breakfast SMPG decreased more gradually with Gla-300 than with Gla-100 (Figure 1C).

The basal insulin dose increased throughout the 6-month treatment period in both treatment groups, but more so with Gla-300 (Figure 1D); to a mean (s.d.) of 0.62 (0.29) U/kg/day [59.4 (32.3) U/day] at month 6 with Gla-300, and to 0.53 (0.24) U/kg/day [52.0 (27.8) U/day] with Gla-100.

Hypoglycaemia

Nocturnal (00:00–05:59 hours) Hypoglycaemia. Between the start of week 9 and month 6, the percentage of participants experiencing at least one nocturnal (00:00–05:59 hours) confirmed (≤3.9 mmol/l) or severe hypoglycaemic event was 16% with Gla-300 and 17% with Gla-100 [relative risk (RR) 0.89 (95% CI 0.66 to 1.20); main secondary efficacy endpoint (mITT population)]. Over 6 months of treatment, 78 participants (18%) in the Gla-300 group experienced such events, compared with 103 participants (24%) in the Gla-100 group, a relative risk reduction of 24% [RR 0.76 (95% CI 0.59 to 0.99); Figure 2A, Table S1]. The annualized event rates of nocturnal confirmed or severe hypoglycaemia were similar in the two treatment groups during the 6-month study period (Figure 2B, Table S2). Curves showing the cumulative mean number of nocturnal confirmed or severe hypoglycaemic events per participant over 6 months are shown in Figure S3.

There was a trend towards a lower percentage of participants experiencing nocturnal documented symptomatic hypoglycaemia (≤3.9 mmol/l) with Gla-300 versus Gla-100, both over the full study period and during the first 8 weeks (Figure 2A). This trend was also apparent for hypoglycaemia rates in the first 8 weeks (Figure 2B). Using a more stringent threshold (<3.0 mmol/l) for confirmation of hypoglycaemia, a numerically greater reduction in the percentage of participants with, and event rate of, nocturnal hypoglycaemia with Gla-300 versus Gla-100 over 6 months was apparent (Figure 2).

Hypoglycaemia at Any Time of Day (24 h). The percentage of participants who experienced ≥1 confirmed (≤3.9 mmol/l) or severe hypoglycaemic event was lower with Gla-300 (201/435, 46%) than with Gla-100 (230/438, 53%) over the 6-month study period [RR 0.88 (95% CI 0.77 to 1.01); Figure 2A, Table S1].

Table 1. Baseline characteristics of all randomized participants (randomized population), and glycaemic control measures at baseline and month 6 (modified intention-to-treat population).

Baseline characteristics	Gla-300 (n = 439)	Gla-100 (n = 439)	All (n = 878)
Mean (s.d.) age, years	58.2 (9.9)	57.2 (10.3)	57.7 (10.1)
Gender: male, n (%)	253 (57.6)	254 (57.9)	507 (57.7)
Ethnic group, n (%)			
Caucasian	347 (79.0)	338 (77.0)	685 (78.0)
Black	44 (10.0)	57 (13.0)	101 (11.5)
Asian/Oriental	39 (8.9)	37 (8.4)	76 (8.7)
Other	9 (2.1)	7 (1.6)	16 (1.8)
Mean (s.d.) body weight, kg	95.1 (23.3)	95.6 (22.6)	95.3 (22.9)
Mean (s.d.) body mass index, kg/m^2	32.8 (6.9)	33.2 (6.6)	33.0 (6.7)
Mean (s.d.) eGFR, ml/min/1.73 m^2	81.3 (19.6)	80.7 (19.9)	81.0 (19.7)
Mean (s.d.) duration of diabetes, years*	10.1 (6.5)	9.6 (6.2)	9.8 (6.4)
HbA1c			
%	8.51 (1.04)	8.57 (1.07)	8.54 (1.06)
mmol/mol	69.5 (11.4)	70.1 (11.7)	69.8 (11.6)
Previous use of metformin, n (%)†	394 (90.6)	402 (92.0)	796 (91.3)
Previous use of sulphonylureas, n (%)†	257 (59.1)	256 (58.6)	513 (58.8)
Previous use of DPP-4 inhibitors, n (%)†	90 (20.7)	98 (22.4)	188 (21.6)

Glycaemic control measure	Gla-300 (n = 432)		Gla-100 (n = 430)
HbA1c, mean			
Baseline (s.d.)			
mmol/mol	69.3 (11.4)		70.3 (11.7)
%	8.49 (1.04)		8.58 (1.07)
Month 6 (s.d.)			
mmol/mol	53.9 (10.5)		53.5 (10.4)
%	7.08 (0.96)		7.05 (0.95)
LS mean change (s.e.)			
mmol/mol	−15.5 (0.5)		−16.0 (0.5)
%	−1.42 (0.05)		−1.46 (0.05)
LS mean difference (95% CI),			
mmol/mol		0.4 (−1.0 to 1.9)	
%		0.04 (−0.09 to 0.17)	
Participants attaining HbA1c targets, n (%)			
<7.0 % or 53 mmol/mol	186 (43.1)		181 (42.1)
≤6.5 % or 48 mmol/mol	108 (25.0)		118 (27.4)
Mean FPG, mmol/l			
Baseline (s.d.)	9.93 (2.86)		10.21 (2.90)
Month 6 (s.d.)	6.67 (2.16)		6.30 (1.82)
LS mean change (s.e.)	−3.41 (0.10)		−3.80 (0.11)
LS mean difference (95% CI)		0.39 (0.10 to 0.68)	
Participants attaining FPG targets, n (%)			
≤6.7 mmol/l	217 (50.2)		231 (53.7)
<5.6 mmol/l	113 (26.2)		127 (29.5)
SMPG profiles, mmol/l			
All eight measurements, mean			
Baseline (s.d.)	10.70 (2.79)		10.89 (2.86)
Month 6 (s.d.)	7.96 (1.62)		7.79 (1.65)
LS mean change (s.e.)	−2.72 (0.09)		−2.90 (0.09)
LS mean difference (95% CI)		0.18 (−0.07 to 0.42)	
Pre-breakfast, mean			
Baseline (s.d.)	9.75 (2.37)		9.97 (2.55)
Month 6 (s.d.)	6.40 (1.25)		6.17 (1.11)
Mean change (s.d.)	−3.35 (2.37)		−3.69 (2.37)
Pre-injection, mean			
Baseline (s.d.)	10.93 (3.71)		11.23 (3.52)
Month 6 (s.d.)	8.90 (2.24)		8.68 (2.31)
LS mean change (s.e.)	−2.16 (0.16)		−2.33 (0.16)
LS mean difference (95% CI)		0.17 (−0.28 to 0.61)	
Pre-injection, mean variability (coefficient of variation, %)			
Month 6 (s.d.)	18.8 (9.8)		18.4 (9.4)
LS mean (s.e.)	18.7 (0.5)		18.3 (0.5)
LS mean difference (95% CI)		0.4 (−1.0 to 1.8)	

CI, confidence interval; DPP-4, dipeptidyl peptidase 4; eGFR, estimated glomerular filtration rate; FPG, fasting plasma glucose; Gla-100, glargine 100 U/ml; Gla-300, glargine 300 U/ml; HbA1c, glycated haemoglobin; LS, least squares; s.d., standard deviation; s.e., standard error; SMPG, self-monitored plasma glucose.

*Gla-300, n = 435, Gla-100, n = 436.

†Taken within the 3 months before randomization (Gla-300, n = 435, Gla-100, n = 437).

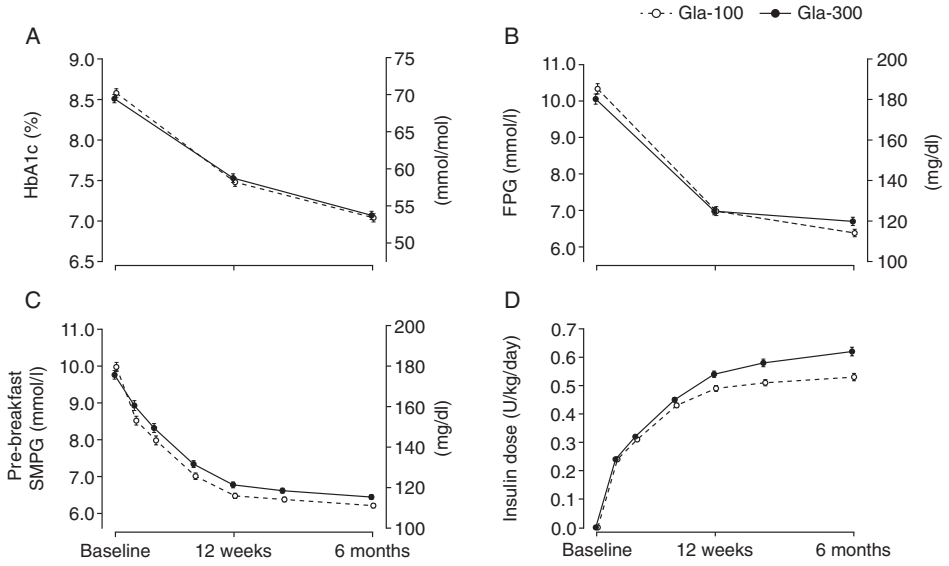


Figure 1. Clinical measures (mean ± standard error) during treatment by visit (modified intention-to-treat population): (A) glycated haemoglobin (HbA1c). (B) Laboratory-measured fasting plasma glucose (FPG). (C) Pre-breakfast self-monitored plasma glucose (SMPG). (D) Daily basal insulin dose. For data values, please refer to Table 1 (HbA1c, laboratory-measured FPG and pre-breakfast SMPG) and Results (insulin dose). Gla-100, glargine 100 U/ml; Gla-300, glargine 300 U/ml.

Likewise, a lower percentage for Gla-300 was reported in the first 8 weeks [24 vs 29%; RR 0.83 (95% CI 0.67 to 1.03)] and from week 9 to month 6 [40 vs 46%; RR 0.86 (95% CI 0.74 to 1.00); Figure 2A and Table S1]. The annualized event rate of this definition of hypoglycaemia was significantly lower with Gla-300 versus Gla-100 over 6 months [6.4 vs 8.5 events per participant-year; RR 0.75 (95% CI 0.57 to 0.99); p = 0.042] and showed a more pronounced reduction during the first 8 weeks [4.5 vs 8.5 events per participant-year; RR 0.61 (95% CI 0.43 to 0.86); Figure 2B]. Cumulative curves show divergence that is maintained over the 6 months (Figure S3).

When considering both the percentage of participants experiencing, and annualized rates of, documented symptomatic (≤3.9 mmol/l) hypoglycaemia at any time of day (24 h), results favoured Gla-300 during all predefined study periods (RR 0.42–0.85; Figure 2A, B) with significant relative reductions in the annualized rate reported from baseline to month 6 [RR 0.62 (95% CI 0.44 to 0.87)], and during the first 8 weeks [RR 0.42 (95% CI 0.26 to 0.67) Figure 2B]. Significant reductions with Gla-300 versus Gla-100 were also apparent when considering the percentage of participants affected by events defined by the more stringent glycaemic threshold; a 39% lower risk was observed for confirmed (<3.0 mmol/l) or severe hypoglycaemia [RR 0.61 (95% CI 0.43 to 0.87)] and a 45% lower risk for documented (<3.0 mmol/l) symptomatic hypoglycaemia [RR 0.55 (95% CI 0.37 to 0.82)] over the 6-month period (Figure 2A).

Severe Hypoglycaemia. Severe hypoglycaemia was infrequent, and events were too few for meaningful analysis. Only 4 participants (1%) in each treatment group reported severe hypoglycaemia at any time of day (24 h; Table S1).

Patterns of Hypoglycaemia by Time of Day (24 h). Figure 3 shows the distribution of hypoglycaemia by time of day, as the percentage of participants affected and as annualized event rates (panels A and C), and as differences between Gla-100 and Gla-300 during each time interval (panels B and D). Both the overall frequency of events reported and the differences between the treatment groups were greatest during the daytime, especially between 06:00 and 10:00 hours.

Participant-Reported Outcomes

Treatment satisfaction, measured by the DTSQs, improved from baseline to month 6 in both treatment groups (Table S3). There was no change in health-related quality of life (EQ-5D utility index score) from baseline to month 6 in either treatment group (data not shown). Fear of hypoglycaemia, assessed on the HFS-II, was low and decreased over the 6-month study period in both treatment groups. In the Gla-300 group, the mean (s.d.) total HFS-II score decreased from 0.49 (0.62) to 0.43 (0.48), an LS mean [standard error (s.e.)] change of −0.09 (0.02), while in the Gla-100 group the score decreased from 0.57 (0.65) to 0.48 (0.52), an LS mean (s.e.) change of −0.07 (0.02); LS mean difference was −0.02 (95% CI −0.09 to 0.04).

Change in Body Weight

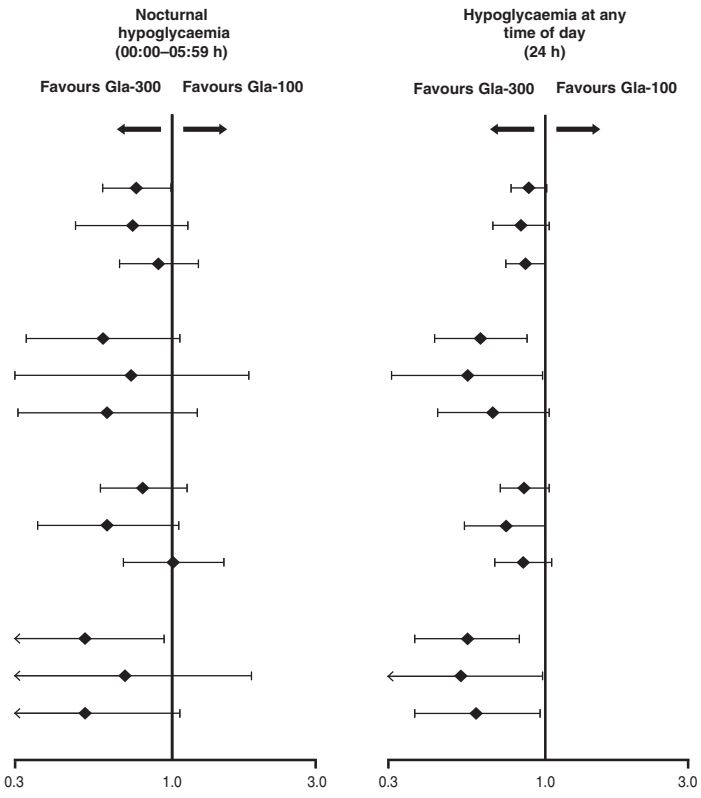
Weight gain during the treatment period was lower with Gla-300 [LS mean increase 0.49 (95% CI 0.14 to 0.83) kg] than with Gla-100 [LS mean increase 0.71 (95% CI 0.36 to 1.06) kg; non-significant].

Adverse Events

The most common adverse events were infections, cardiac events, gastrointestinal events or musculoskeletal events. These events were equally distributed between treatment groups. Injection-site reactions were reported by 17 (4%) participants treated with Gla-300 and 21 (5%) participants treated with

A

	Nocturnal hypoglycaemia (00:00–05:59 h) RR	95% CI	Hypoglycaemia at any time of day (24 h) RR	95% CI
Confirmed (≤3.9 mmol/l) or severe hypoglycaemia				
Baseline to month 6	0.76	0.59 to 0.99	0.88	0.77 to 1.01
Baseline to week 8	0.74	0.48 to 1.13	0.83	0.67 to 1.03
Week 9 to month 6	0.90	0.67 to 1.22	0.86	0.74 to 1.00
Confirmed (<3.0 mmol/l) or severe hypoglycaemia				
Baseline to month 6	0.59	0.33 to 1.06	0.61	0.43 to 0.87
Baseline to week 8	0.73	0.30 to 1.79	0.55	0.31 to 0.98
Week 9 to month 6	0.61	0.31 to 1.21	0.67	0.44 to 1.03
Documented symptomatic hypoglycaemia ≤3.9 mmol/l				
Baseline to month 6	0.80	0.58 to 1.12	0.85	0.71 to 1.03
Baseline to week 8	0.61	0.36 to 1.05	0.74	0.54 to 1.00
Week 9 to month 6	1.01	0.69 to 1.48	0.84	0.68 to 1.05
Documented symptomatic hypoglycaemia <3.0 mmol/l				
Baseline to month 6	0.51	0.27 to 0.94	0.55	0.37 to 0.82
Baseline to week 8	0.70	0.27 to 1.83	0.52	0.28 to 0.98
Week 9 to month 6	0.51	0.25 to 1.06	0.59	0.37 to 0.96



B

	Nocturnal hypoglycaemia (00:00–05:59 h) RR	95% CI	Hypoglycaemia at any time of day (24 h) RR	95% CI
Confirmed (≤3.9 mmol/l) or severe hypoglycaemia				
Baseline to month 6	0.98	0.64 to 1.48	0.75	0.57 to 0.99
Baseline to week 8	0.70	0.41 to 1.18	0.61	0.43 to 0.86
Week 9 to month 6	1.08	0.66 to 1.77	0.81	0.60 to 1.10
Confirmed (<3.0 mmol/l) or severe hypoglycaemia				
Baseline to month 6	0.61	0.33 to 1.15	0.75	0.47 to 1.22
Baseline to week 8	0.69	0.26 to 1.86	0.55	0.29 to 1.02
Week 9 to month 6	0.58	0.27 to 1.24	0.87	0.49 to 1.53
Documented symptomatic hypoglycaemia ≤3.9 mmol/l				
Baseline to month 6	0.90	0.55 to 1.48	0.62	0.44 to 0.87
Baseline to week 8	0.60	0.31 to 1.16	0.42	0.26 to 0.67
Week 9 to month 6	1.02	0.58 to 1.80	0.70	0.49 to 1.01
Documented symptomatic hypoglycaemia <3.0 mmol/l				
Baseline to month 6	0.55	0.28 to 1.07	0.55	0.35 to 0.85
Baseline to week 8	0.66	0.23 to 1.92	0.43	0.22 to 0.85
Week 9 to month 6	0.51	0.23 to 1.14	0.61	0.36 to 1.05

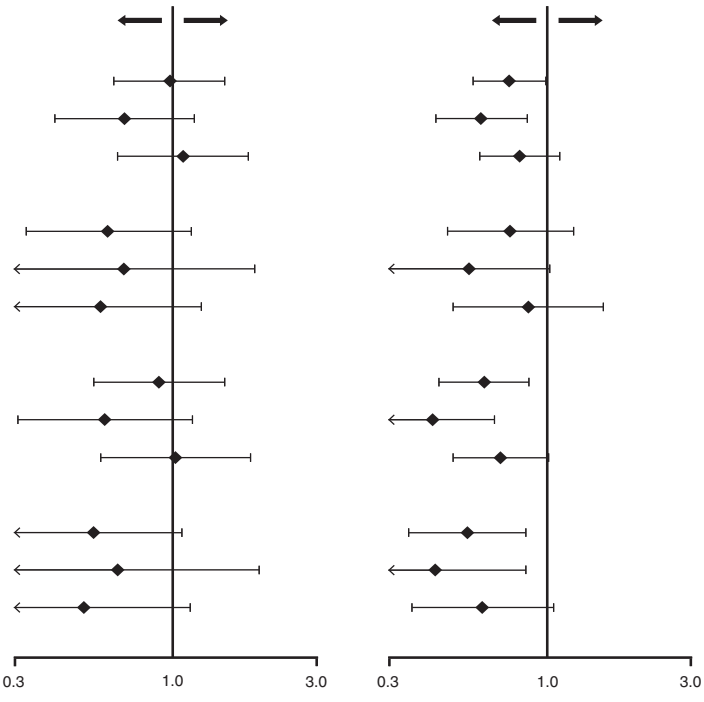


Figure 2. Hypoglycaemic events during the night (00:00–00:59 hours) or at any time of day (24 h) with glargine 300 U/ml (Gla-300) versus glargine 100 U/ml (Gla-100) during 6 months of treatment (safety population): (A) Relative risk of at least one hypoglycaemic event per participant. (B) Ratio of annualized event rates. CI, confidence interval.

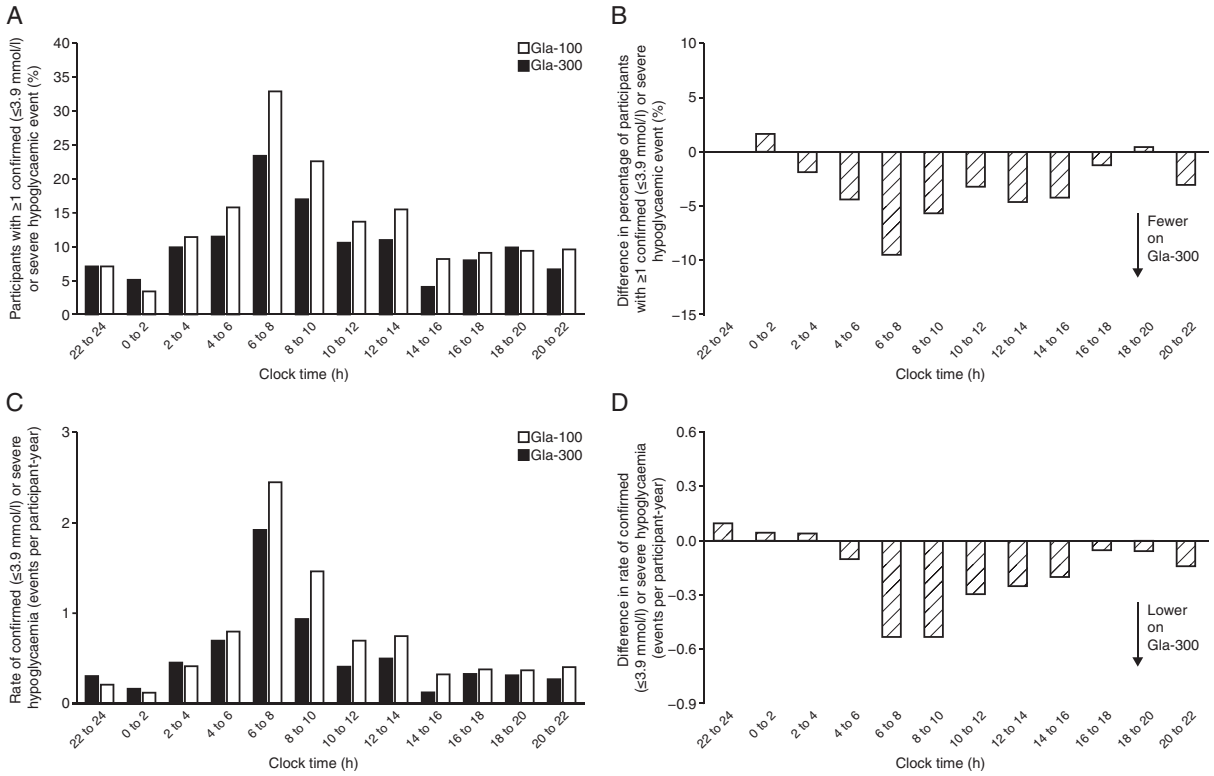


Figure 3. Confirmed (≤3.9 mmol/l) or severe hypoglycaemia during 6 months of treatment by time of the day (safety population): (A) Percentage of participants who experienced at least one event and (B) associated between-treatment differences. (C) Annualized event rates (events per participant-year) and (D) associated between-treatment differences. Gla-300, glargine 300 U/ml; Gla-100, glargine 100 U/ml.

Gla-100. Serious treatment-emergent adverse events were reported by 24 (6%) participants treated with Gla-300 and 26 (6%) participants treated with Gla-100 (Table S4). Two participants (0.5%) on Gla-300 and 6 (1.4%) on Gla-100 experienced events identified as potential major adverse cardiac events. Treatment-emergent adverse events led to withdrawal from the study in 5 participants (1%) in each treatment group. One participant in the Gla-300 group experienced a serious treatment-emergent adverse event (worsening of atherosclerotic heart disease) leading to death during the study period.

Discussion

In this phase IIIa study, the efficacy and safety of Gla-300 were investigated over 6 months in a population of insulin-naïve people with type 2 diabetes with inadequately controlled blood glucose on oral glucose-lowering drugs, with any sulphonylureas or glinides discontinued at randomization. Improvements in overall glycaemic control were superimposable with Gla-300 and Gla-100 as indicated by HbA1c values that approached 7.0 % (53 mmol/mol) at month 6 in both groups. This equivalent reduction in HbA1c is in line with the EDITION 1 and 2 studies [13,14], conducted in people already on insulin. The mean change in laboratory-measured FPG from baseline to month 6 was greater in the Gla-100 group than in the Gla-300 group. In addition to the more gradual decrease in pre-breakfast SMPG with Gla-300, this small difference (0.39 mmol/l) may reflect differences in the pharmacokinetic and pharmacodynamic profiles of Gla-300 versus Gla-100, with Gla-300 delivering a more even activity throughout the 24-h period compared with Gla-100 [12].

Superiority of Gla-300 over Gla-100 was not demonstrated with respect to the predefined main secondary endpoint, as the percentage of participants with ≥1 nocturnal confirmed (≤3.9 mmol/l) or severe hypoglycaemic event from week 9 to month 6 was not different between treatment groups. Nevertheless, with Gla-300 relative to Gla-100, the risk of experiencing at least one nocturnal event that was severe or confirmed ≤3.9 mmol/l was 24% lower over the entire 6-month treatment period [RR 0.76 (95% CI 0.59 to 0.99)]. In addition, when hypoglycaemia at any time of day (24 h) was compared between treatments, and assessed as annualized rates, the relative reduction with Gla-300 was 25% [RR 0.75 (95% CI 0.57 to 0.99)]. Notably, in EDITION 3, these benefits in terms of lower hypoglycaemia risk were observed in the absence of sulphonylureas, which in previous studies of starting basal insulin were associated with greater rates of hypoglycaemia [8].

A possible explanation for the different findings of the EDITION 3 study, in terms of the main secondary endpoint, compared with the first two studies in the EDITION programme, is that the overall numbers of hypoglycaemic events were substantially lower in EDITION 3, leading to lower statistical power to detect between-treatment differences. This presumably reflects the difference between the population in EDITION 3 (insulin-naïve, likely retaining greater endogenous insulin secretion, with a known diabetes duration shorter than

that in EDITION 1 and EDITION 2) and the populations in EDITION 1 and EDITION 2, who had been taking insulin for a number of years. These differences predict greater hypoglycaemia risk [22] in the latter studies compared with the present study whenever glycaemic control is optimized with insulin.

In the EDITION 3 study, hypoglycaemic events both on Gla-300 and Gla-100 occurred most frequently between 06:00 and 10:00 hours. Reasons for a concentration of events at this time of day presumably include increasing alertness and attention to glucose testing, but also the fact that people eat breakfast at varying times but not often before 06:00 hours. Hence, the interval between 06:00 and 10:00 hours often includes a period of prolonged fasting, during which the long-lasting effects of bedtime injections of insulin might occur; however, as in EDITION 1 and EDITION 2, EDITION 3 used a more specific and standardized definition of nocturnal hypoglycaemia (00:00–05:59 hours) than some previous studies [8], which instead used a more individualized criterion (after bedtime insulin injection until the morning glucose measurement, breakfast or administration of any oral glucose-lowering drug). The greatest between-treatment difference in risk of hypoglycaemia in EDITION 3, favouring Gla-300, was evident during the 06:00–10:00 hours interval (Figure 3), reflecting the more evenly distributed glucose-lowering activity of Gla-300 compared with Gla-100 [12]. Thus, it is possible that the risk reduction of hypoglycaemia with Gla-300 at night in EDITION 3 is underestimated because of the nocturnal definition, which excluded events that occurred later than 06:00 hours but still before breakfast.

The lower percentage of participants affected by, and lower annualized rate of, hypoglycaemia with Gla-300 versus Gla-100 was more evident during the first 8 weeks of treatment, corresponding to the time when the greatest insulin dose titration occurred. This finding is consistent with the EDITION 1 and 2 studies [13,14]. Regardless of the explanation, this result suggests safer and easier titration with Gla-300. In addition, there were no differences in participant-reported outcomes between treatment groups. Indeed, overall satisfaction with treatment and health-related quality of life were good throughout the study, and fear of hypoglycaemia was very low at baseline and decreased further over the main treatment period.

Some weight gain was experienced by both treatment groups, although less than that observed in other studies initiating basal insulin with [8] or without [23] sulphonylureas. This increase in body weight tended to be less with Gla-300 compared with Gla-100, consistent with the results of EDITION 2 [14], as well as those of EDITION 4 in subjects with type 1 diabetes [24]. At present, this observation remains without a plausible hypothesis. Also, consistent with the EDITION 1 [13] and EDITION 2 studies [14] was the higher daily dose needed with Gla-300 compared with Gla-100 (on average 17%). This higher dose probably reflects the slightly lower 24-h exposure seen in pharmacokinetic–pharmacodynamic studies at equal doses [12] due to reduced absorption of the more concentrated insulin from the s.c. depot. This has also been observed with other insulins that precipitate in the s.c. space, such as NPH and semilente [25].

As with EDITION 1 and 2, the strengths of the present study include its relatively large number of enrolled participants and closely supervised titration scheme. Limitations include the open-label nature of the protocol, the relatively short duration of the study and the limited generalizability of the results to other populations with diabetes mellitus.

In conclusion, Gla-300 demonstrated equivalent glycaemic control compared with Gla-100 in insulin-naïve people with type 2 diabetes. Although the percentage of participants with ≥1 nocturnal confirmed (≤3.9 mmol/l) or severe hypoglycaemic event from week 9 to month 6 (the main secondary endpoint) was not significantly different between treatment groups, Gla-300 reduced hypoglycaemia risk compared with Gla-100 over the full 6-month study period. Taken in light of the similar results found by the previous EDITION studies, the present findings may have clinical implications for the successful starting and maintenance of basal insulin therapy using Gla-300.

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Conflict of Interest

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. G. B. B. has received honoraria for advising and lecturing from Sanofi, Eli Lilly and Novartis. M. C. R. has received research grant support from Amylin, Eli Lilly and Sanofi and honoraria for consulting and/or speaking from Amylin, Bristol-Myers Squibb–AstraZeneca Alliance, Elcelyx, Eli Lilly, Hoffmann-La Roche, Sanofi and Valeritas. These dualities of interest have been reviewed and managed by Oregon Health & Science University. R. M. B. has received research support from, or been a consultant or member of a scientific advisory board for, Abbott Diabetes Care, Amylin, Bayer, Becton Dickinson, Boehringer Ingelheim, Bristol-Myers Squibb–AstraZeneca Alliance, Calibra, DexCom, Eli Lilly, Halozyme, Hygieia, Johnson & Johnson, Medtronic, Merck, Novo Nordisk, Roche, Sanofi and Takeda. His employer, non-profit Park Nicollet Institute, contracts for his services and no personal income goes to R. M. B. He has inherited Merck stock. He has been a volunteer for the American Diabetes Association and the Juvenile Diabetes Research Foundation. M. Z. and K. S. are employees of Sanofi. H. G. is an employee of EXPERIS IT, contracted to Sanofi. P. D. H. has received funding for self or affiliated institutions from AntriaBio, Bristol-Myers Squibb–AstraZeneca Alliance, Eli Lilly, GlaxoSmithKline, Hanmi, Janssen/Johnson & Johnson, Merck (MSD), Novo Nordisk, Roche Diagnostics, Roche Pharma, Sanofi, Skyepharma and Takeda.

G. B. B., M. C. R., R. M. B. and P. D. H. were involved in development of Gla-300, the design of the study programme and development of the present study's protocol, and were involved in writing, reviewing and editing the manuscript. M. Z. and Isabel Muehlen-Bartmer of Sanofi contributed to the design and treatment considerations for the trial. M. Z., K. S. and H. G. were involved in the analysis and interpretation of the data, and in reviewing and editing the manuscript.

Supporting Information

Additional Supporting Information may be found in the online version of this article:

Appendix S1. Further details of statistical analyses.

Appendix S2. List of investigators.

Figure S1. Participant flow diagram.

Figure S2. Eight-point self-monitored plasma glucose (SMPG) profile at baseline and at the end of treatment (modified intention-to-treat population).

Figure S3. Cumulative mean numbers of confirmed (plasma glucose ≤3.9 mmol/l) or severe hypoglycaemic events per participant during the main 6-month treatment period (safety population).

Table S1. Hypoglycaemic events (% participants affected) for Gla-300 versus Gla-100 during 6 months of treatment, by intervals of time of day (safety population).

Table S2. Hypoglycaemic events and event rates (per participant-year of exposure) for Gla-300 versus Gla-100 during 6 months of treatment, by intervals of time of day (safety population).

Table S3. Assessment of treatment satisfaction using the Diabetes Treatment Satisfaction Questionnaire (status version, DTSQs) (modified intention-to-treat population).

Table S4. Treatment-emergent serious adverse events (safety population).

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