original article

One–year sustained glycaemic control and less hypoglycaemia with new insulin glargine 300 U/ml compared with 100 U/ml in people with type 2 diabetes using basal plus meal–time insulin: the EDITION 1 12–month randomized trial, including 6–month extension

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Aims: To evaluate the maintenance of efficacy and safety of insulin glargine 300 U/ml (Gla-300) versus glargine 100 U/ml (Gla-100) in people with type 2 diabetes mellitus (T2DM) using basal plus meal-time insulin for 12 months in the EDITION 1 trial.

Methods: EDITION 1 was a multicentre, randomized, open-label, two-arm, phase IIIa study. Participants completing the initial 6-month treatment period continued to receive Gla-300 or Gla-100, as previously randomized, once daily for a further 6-month open-label extension phase. Changes in glycated haemoglobin (HbA1c) and fasting plasma glucose concentrations, insulin dose, hypoglycaemic events and body weight were assessed.

Results: Of 807 participants enrolled in the initial phase, 89% (359/404) assigned to Gla-300 and 88% (355/403) assigned to Gla-100 completed 12 months. Glycaemic control was sustained in both groups (mean HbA1c: Gla-300, 7.24%; Gla-100, 7.42%), with more sustained HbA1c reduction for Gla-300 at 12 months: least squares mean difference Gla-300 vs Gla-100: HbA1c −0.17 [95% confidence interval (CI) −0.30 to −0.05]%. The mean daily basal insulin dose at 12 months was 1.03 U/kg for Gla-300 and 0.90 U/kg for Gla-100. Lower percentages of participants had ≥1 confirmed [≤3.9 mmol/l (≤70 mg/dl)] or severe hypoglycaemic event with Gla-300 than Gla-100 at any time of day [24 h; 86 vs 92%; relative risk 0.94 (95% CI 0.89–0.99)] and during the night [54 vs 65%; relative risk 0.84 (95% CI 0.75–0.94)], while the annualized rates of such hypoglycaemic events were similar. No between-treatment differences in adverse events were apparent.

Conclusion: During 12 months of treatment of T2DM requiring basal and meal-time insulin, glycaemic control was better sustained and fewer individuals reported hypoglycaemia with Gla-300 than with Gla-100. The mean basal insulin dose was higher with Gla-300 compared with Gla-100, but total numbers of hypoglycaemic events and overall tolerability did not differ between treatments.

Keywords: basal insulin, glycaemic control, insulin glargine, meal-time insulin

Introduction

Control of hyperglycaemia becomes progressively more difficult with increasing duration of type 2 diabetes mellitus (T2DM). Despite optimized use of available therapies, including insulin, some patients cannot attain or maintain desired levels of glycaemic control [1,2]. Among the barriers to success of insulin therapy are concerns about hypoglycaemia, injection

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frequency and weight gain [3,4]. Some of these difficulties may be attributable to limitations of the profiles of action of current basal insulins, and may become more apparent with the progression of diabetes and prolonged treatment.

Compared with glargine 100 U/ml (Gla-100), the new insulin glargine 300 U/ml formulation (Gla-300) has demonstrated more prolonged and stable pharmacokinetic and pharmacodynamic profiles, leading to glycaemic control beyond 24 h after injection [5]. The phase IIIa EDITION development programme was designed to determine whether this improved profile of action would lead to better results in clinical use. This programme compared the efficacy and safety of Gla-300 with that of Gla-100 in people with T2DM using basal-bolus insulin (EDITION 1) [6], people with T2DM using basal insulin and oral antihyperglycaemic drugs (EDITION 2) [7], and insulin-naïve people with T2DM (EDITION 3) [8].

The 6-month results from these studies have shown similar improvements in glycaemic control with intensified therapy with Gla-300 and Gla-100, but lower rates of hypoglycaemia with Gla-300. After 6 months in EDITION 1, people previously using basal and also meal-time insulin attained HbA1c values close to 7.3% using each regimen, but with a 22% lower relative risk of confirmed or severe nocturnal hypoglycaemia and no increase in daytime hypoglycaemia with Gla-300 [6].

In a planned extension of the EDITION 1 trial, we examined whether the pattern of similar improvement of glycaemic control with good tolerability and lower risk of nocturnal hypoglycaemia is maintained with continued use of Gla-300 for a further 6-month interval of randomized but less intensively supervised treatment.

Materials and Methods

Study Design and Population

This was a multicentre, open-label, two-arm parallel-group study conducted between 15 December 2011 and 4 September 2013 in 13 countries (three in North America and nine in Europe and South Africa) [6]. The study was registered with ClinicalTrials.gov under the number NCT01499082. The appropriate ethics committees approved the protocol and the study was conducted according to Good Clinical Practice and the Declaration of Helsinki. All participants provided written informed consent.

Comprehensive details of the study design and participant population have been reported previously [6]. In summary, participants ≥18 years of age with T2DM (World Health Organization definition [9]) using basal insulin plus meal-time insulin analogue were randomized (1 : 1) to receive once-daily injections of either Gla-300 or Gla-100 with meal-time insulin. Candidates were excluded if they used human meal-time insulin or any premixed or basal insulin other than insulin glargine or neutral protamine Hagedorn or had started using new glucose-lowering agents and/or weight loss drugs in the 3 months before the screening visit. Further details on exclusion criteria have been reported previously [6]. As previously described [6], once-daily injections of Gla-300 or Gla-100 in the evening were to be individually titrated once weekly throughout the study following the same dosing recommendations in both groups and seeking a fasting self-monitored plasma glucose (SMPG) of 4.4–5.6 mmol/l (80–100 mg/dl). Dose adjustments of both insulins were limited to 3-unit increments or decrements because of the characteristics of the pen injectors used. Meal-time insulin was to be adjusted at the discretion of the site investigator based on SMPG data, including, when appropriate, preprandial or 2-h postprandial plasma glucose and consideration of the carbohydrate content of the meal, with the aim of optimizing glucose patterns while limiting hypoglycaemia. Participants who completed the 6-month treatment period continued to receive either Gla-300 or Gla-100 according to initial randomization, along with their meal-time insulin, for a further 6-month open-label extension phase. After the 6-month visit, only one visit to the study site (month 9) and two phone contacts (months 7.5 and 10.5) were required for participants before their 12-month visit.

Efficacy and Safety Outcomes

At the end of the extension phase, the following efficacy outcomes were assessed: change from baseline in glycaemic control (HbA1c); fasting plasma glucose (FPG) and eight-point SMPG profiles; mean insulin dose (basal and meal-time); and treatment satisfaction scores (using the Diabetes Treatment Satisfaction Questionnaire status version [DTSQs]). The DTSQs addresses the participant's satisfaction with treatment (six items) as well as perceived hyperglycaemia (one item) and perceived hypoglycaemia (one item) [10]. The safety outcomes assessed included change from baseline in body weight, the percentage of participants experiencing ≥1 hypoglycaemic event, annualized rates of hypoglycaemic events, and the occurrence of other adverse events. All hypoglycaemic events were categorized according to the American Diabetes Association definitions [11]: (i) severe hypoglycaemia (an event requiring the assistance of another person to actively administer carbohydrate, glucagon or other resuscitative actions); (ii) documented symptomatic hypoglycaemia [an event during which typical symptoms of hypoglycaemia are confirmed by a measured plasma glucose concentration of ≤3.9 mmol/l (≤70 mg/dl)]; and (iii) asymptomatic hypoglycaemia confirmed by a measured plasma glucose concentration of ≤3.9 mmol/l (≤70 mg/dl). For the main analysis of hypoglycaemic outcomes, the confirmed (with or without symptoms) and severe categories were combined and recorded as percentage of participants with ≥1 event and as events per participant-year over the 12-month study period. In addition to the threshold of ≤3.9 mmol/l (≤70 mg/dl), hypoglycaemic events with a plasma glucose of <3.0 mmol/l (<54 mg/dl) were analysed independently.

Data Analysis and Statistics

The efficacy measures, including insulin dose, were analysed in 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 at least one post-baseline efficacy assessment during the main 6-month on-treatment period). Analysis of change from baseline to month 12 of key efficacy endpoints was performed using a mixed-effects model for repeated measures.

Safety variables, including body weight, were analysed descriptively using the safety population (defined as all participants randomized and exposed to ≥1 dose of study insulin), as previously described [6]. The change in weight from baseline to month 12 was analysed using an analysis of covariance model adjusted by HbA1c strata and world region. Analysis of rate ratio based on the number of events per participant-year was based on an overdispersed Poisson regression model adjusted on HbA1c strata using treatment period as offset.

Results

Participant Characteristics and Disposition

Of 807 participants randomized in the initial treatment phase, 404 were assigned to Gla-300 and 403 to Gla-100. In the Gla-100 group, 1 participant did not receive study treatment
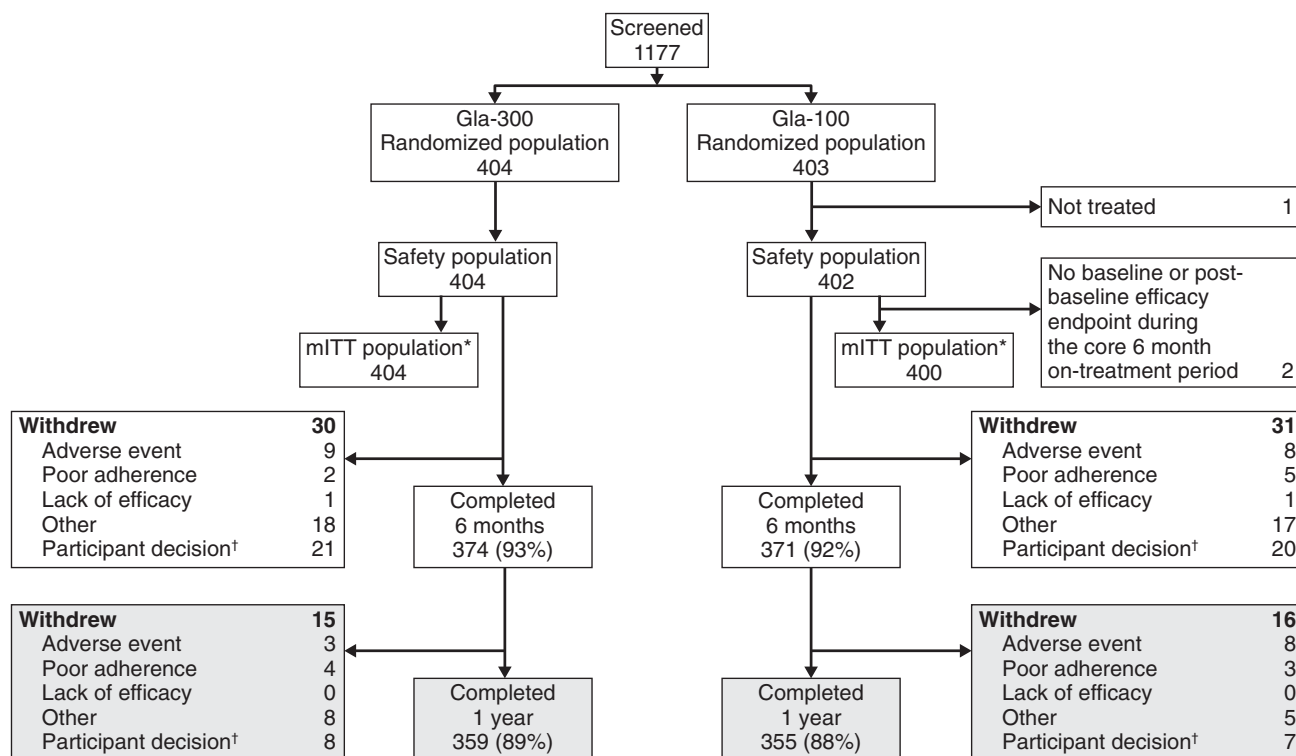
Figure 1. Participant flow diagram for EDITION 1. Upper portion with open boxes shows flow during the main 6-month study; shaded boxes below indicate flow during the extension phase up to 12 months. Gla-100, glargine 100 U/ml; Gla-300, glargine 300 U/ml; mITT, modified intention-to-treat. *During the main 6-month on-treatment period; †Not mutually exclusive with the reason for treatment discontinuation.

and was not included in the safety and mITT populations. Two participants who had no baseline or post-baseline efficacy endpoint during the main 6-month on-treatment period were also excluded from the mITT population (Figure 1). Similar proportions of participants in the two treatment groups completed the initial 6-month study, 93% using Gla-300 and 92% using Gla-100, and 89 and 88%, respectively, completed 12 months. The reasons for withdrawal did not differ between treatment groups (Figure 1).

As previously reported [6], the demographic characteristics at baseline were similar in both treatment groups. Overall, 53% of participants were men, the mean [standard deviation (s.d.)] participant age was 60 (8.6) years and the mean (s.d.) duration of diabetes was 16 (7.5) years. The participants' mean (s.d.) body mass index was 36.6 (6.4) kg/m^2, HbA1c 8.15 (0.78)%, [65.6 (8.5) mmol/mol]), FPG 8.86 (2.90) mmol/l [159.5 (52.3) mg/dl] and basal insulin dose 0.67 (0.27) U/kg/day.

Glycaemic Response

The improvement in glycaemic control observed at 6 months, as measured by HbA1c (Figure 2A) and FPG (Figure 2B), was maintained through to the end of the study in both groups. At month 12 the mean (s.d.) HbA1c with Gla-300 was 7.24 (0.93)% [55.6 (10.2) mmol/mol] and with Gla-100 it was 7.42 (0.94)% [57.6 (10.3) mmol/mol]. The least squares (LS) mean change from baseline was −0.86% (−9.4 mmol/mol) with Gla-300 and −0.69% (−7.5 mmol/mol) with Gla-100. The LS mean

difference between reductions with Gla-300 and Gla-100 at month 12 was −0.17 (95% CI −0.30 to −0.05)%, equivalent to −1.9 (95% CI −3.2 to −0.5) mmol/mol (p = 0.007).

A similar pattern in change of laboratory-measured clinic-collected FPG at month 6 was observed at month 12. The mean change from baseline was −1.6 mmol/l (−29.6 mg/dl) for Gla-300 and −1.4 mmol/l (−26.0 mg/dl) for Gla-100; the LS mean difference between reductions with Gla-300 versus Gla-100 was −0.34 (95% CI −0.69 to 0.01) mmol/l [−6.1 (95% CI −12.5 to 0.2) mg/dl; p = 0.058]. Although the overall reductions in the eight-point SMPG profile from baseline to month 12 were similar between treatments, lowering of blood glucose at the post-dinner and bedtime measurements was greater with Gla-300 (Figure S1).

Insulin Dose

During 12 months of treatment, the daily basal insulin dose in both treatment groups increased from a baseline value of 0.67 U/kg (Figure 2C). The increase in dose occurred predominantly during the first 12 weeks, with only a gradual slight increase between week 12 and month 12. At month 12, the mean (s.d.) daily basal insulin dose was 1.03 (0.40) U/kg with Gla-300 and 0.90 (0.35) U/kg with Gla-100. The mean (s.d.) daily meal-time insulin dose at 12 months was 0.55 (0.36) and 0.56 (0.38) U/kg with Gla-300 and Gla-100, respectively, and the corresponding values for the total daily insulin dose were 1.58 (0.66) and 1.45 (0.62) U/kg. Because the mean meal-time
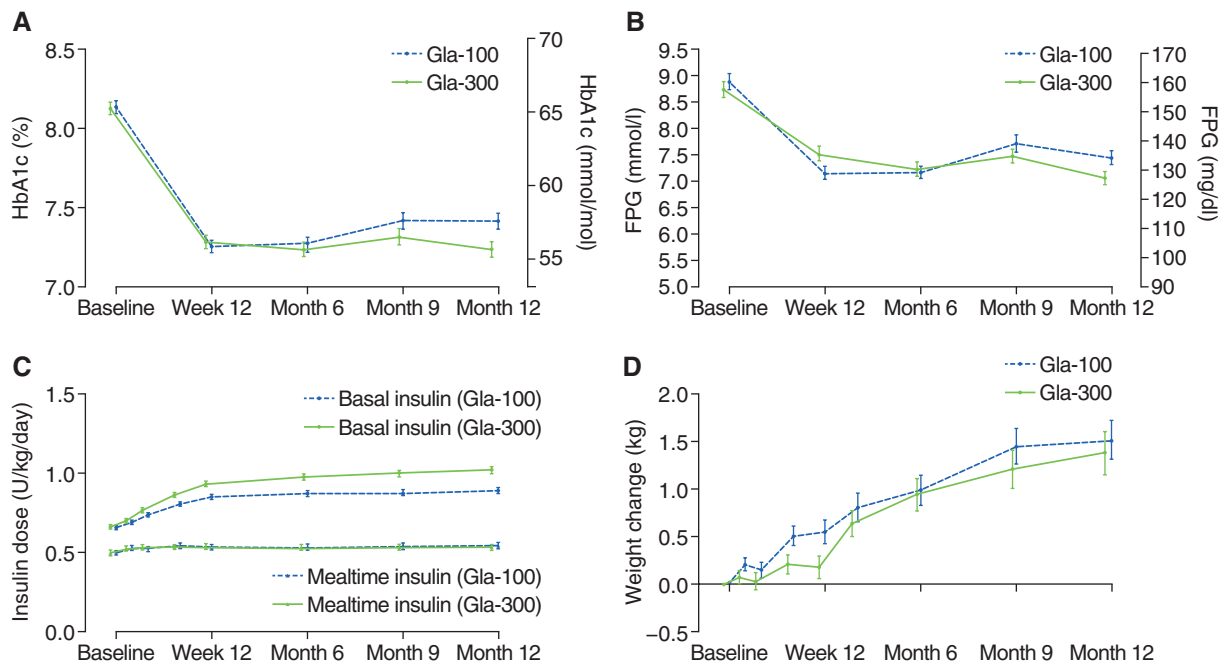
Figure 2. Clinical measures (mean ± standard error) during treatment by visit. (A) glycated haemoglobin (HbA1c) in the modified intention-to treat (mITT) population. (B) Laboratory-measured clinic-collected fasting plasma glucose (FPG) in the mITT population. (C) Daily basal insulin and meal-time insulin dose in the mITT population. (D) Weight change from baseline in the safety population. Gla-100, glargine 100 U/ml; Gla-300, glargine 300 U/ml.

insulin dose was similar for the two treatment groups throughout the study, the changes in total daily insulin dose from baseline [0.40 (0.39) U/kg with Gla-300 and 0.29 (0.39) U/kg with Gla-100] were mainly driven by the differences in the basal insulin doses.

Weight Change

The mean (s.d.) weight change from baseline to the last on-treatment value was 1.2 (3.8) kg with Gla-300 and 1.4 (3.5) kg with Gla-100; LS mean difference for Gla-300 versus Gla-100: −0.2 (95% CI −0.7 to 0.3) kg (Figure 2D).

Treatment Satisfaction

At month 12, the improvements in mean (s.d.) total DTSQ score (0–36) from baseline for Gla-300 and Gla-100 were similar at 2.98 (5.77) and 2.59 (5.44), respectively. Improvements in perceived frequency of hypoglycaemia (item 3) and perceived convenience (item 4) were also similar between groups [mean (s.d.) changes 0.31 (1.83) vs 0.21 (1.82) and 0.52 (1.39) vs 0.48 (1.24), respectively].

Hypoglycaemia

Any Time of Day. Over 12 months, fewer participants reported ≥1 confirmed [≤3.9 mmol/l (≤70 mg/dl)] or severe hypoglycaemic event, at any time of day (24 h), with Gla-300 compared with Gla-100 [86 vs 92%, respectively (Table 1); relative risk 0.94 (95% CI 0.89–0.99)]. The cumulative number of confirmed [≤3.9 mmol/l (≤70 mg/dl)] or severe hypoglycaemic events per participant increased at similar rates

for the two groups throughout the period of observation (Figure 3A), and the event rates did not differ between treatments [22 vs 21 per participant-year; rate ratio 1.06 (95% CI 0.89–1.27)].

Nocturnal. Fewer participants experienced ≥1 nocturnal (00:00–05:59 hours) confirmed [≤3.9 mmol/l (≤70 mg/dl)] or severe hypoglycaemic event with Gla-300 than with Gla-100 [54 vs 65% (Table 1); relative risk 0.84 (95% CI 0.75–0.94)], during the 12-month study period. The cumulative number of confirmed [≤3.9 mmol/l (≤70 mg/dl)] or severe hypoglycaemic events per participant increased more rapidly in the Gla-100 group for the first 6 months, after which the curves were roughly parallel (Figure 3B). Annualized rates of nocturnal confirmed [≤3.9 mmol/l (≤70 mg/dl)] or severe hypoglycaemia did not differ significantly between treatments [2.88 vs 3.19 events per participant-year; rate ratio 0.90 (95% CI 0.70–1.16); Table 1].

Other Hypoglycaemia Categories. Fewer participants reported ≥1 documented symptomatic hypoglycaemic event [≤3.9 mmol/l (≤70 mg/dl)] in the Gla-300 group compared with the Gla-100 group at any time of day or during the night (Table 1).

When the more stringent hypoglycaemia threshold [<3.0 mmol/l (<54 mg/dl)] was applied to the categories of documented symptomatic and confirmed or severe hypoglycaemia, no significant between-treatment differences were seen (Table 1).

Severe hypoglycaemia (any time of day) was reported by 6.7% of Gla-300- and 7.5% of Gla-100-treated participants (Table 1).

Table 1. Hypoglycaemia over 12 months in the EDITION 1 study (safety population).

	Hypoglycaemia at any time of day (24 h)				Nocturnal hypoglycaemia (00:00–05:59 hours)			
	Gla-300 (N = 404)	Gla-100 (N = 402)	RR*	95% CI	Gla-300 (N = 404)	Gla-100 (N = 402)	RR*	95% CI
Total participant-years	378.91	376.37			378.91	376.37		
Overall number of events	8708	8247			1146	1290		
Confirmed or severe hypoglycaemia								
≤3.9 mmol/l (≤70 mg/dl)								
Participants ≥1 event, n (%)	347 (85.9)	368 (91.5)	0.94	0.89–0.99	220 (54.5)	260 (64.7)	0.84	0.75–0.94
Events, n (events per participant-year)	8464 (22.34)	7900 (20.99)	1.06	0.89–1.27	1092 (2.88)	1202 (3.19)	0.90	0.70–1.16
<3.0 mmol/l (<54 mg/dl)								
Participants ≥1 event, n (%)	222 (55.0)	238 (59.2)	0.93	0.82–1.05	96 (23.8)	106 (26.4)	0.90	0.71–1.14
Events, n (events per participant-year)	1227 (3.24)	1050 (2.79)	1.16	0.87–1.54	234 (0.62)	229 (0.61)	1.01	0.68–1.52
Severe hypoglycaemia								
Participants ≥1 event, n (%)	27 (6.7)	30 (7.5)	0.90	0.54–1.48	10 (2.5)	13 (3.2)	0.77	0.34–1.73
Events, n (events per participant-year)	72 (0.19)	54 (0.14)	1.32	0.46–3.81	15 (0.04)	18 (0.05)	0.83	0.29–2.38
Documented symptomatic hypoglycaemia								
≤3.9 mmol/l (≤70 mg/dl)								
Participants ≥1 event, n (%)	302 (74.8)	333 (82.8)	0.90	0.84–0.97	180 (44.6)	230 (57.2)	0.78	0.68–0.89
Events, n (events per participant-year)	4573 (12.07)	4404 (11.70)	1.03	0.84–1.27	695 (1.83)	938 (2.49)	0.74	0.56–0.97
<3.0 mmol/l (<54 mg/dl)								
Participants ≥1 event, n (%)	186 (46.0)	204 (50.7)	0.91	0.79–1.05	80 (19.8)	92 (22.9)	0.87	0.66–1.13
Events, n (events per participant-year)	831 (2.19)	784 (2.08)	1.05	0.78–1.43	179 (0.47)	191 (0.51)	0.93	0.59–1.47
Asymptomatic hypoglycaemia								
≤3.9 mmol/l (≤70 mg/dl)								
Participants ≥1 event, n (%)	285 (70.5)	295 (73.4)	0.96	0.88–1.05	118 (29.2)	125 (31.1)	0.94	0.76–1.16
Events, n (events per participant-year)	3694 (9.75)	3307 (8.79)	1.11	0.86–1.43	368 (0.97)	237 (0.63)	1.54	0.96–2.47
<3.0 mmol/l (<54 mg/dl)								
Participants ≥1 event, n (%)	89 (22.0)	82 (20.4)	1.08	0.83–1.41	17 (4.2)	16 (4.0)	1.06	0.54–2.06
Events, n (events per participant-year)	311 (0.82)	201 (0.53)	1.54	0.93–2.53	35 (0.09)	19 (0.05)	1.82	0.77–4.31

Gla-100, glargine 100 U/ml; Gla-300, glargine 300 U/ml; CI, confidence interval.
*RR, relative risk for participants with ≥1 hypoglycaemic event and rate ratio for hypoglycaemic events per participant-year.

Adverse Events

Overall, 72% of participants in the Gla-300 and 69% in the Gla-100 treatment groups reported treatment-emergent adverse events (Table S1). Injection site reactions were reported by 12 (3.0%) and 6 (1.5%) participants in the Gla-300 and Gla-100 groups, respectively. Serious adverse events occurred in 13% of participants using Gla-300 and 15% using Gla-100. Discontinuation of treatment because of an adverse event occurred in 2.2 and 3.5% of participants using Gla-300 and Gla-100. Six participants had serious treatment-emergent adverse events with fatal outcome during the study [2 participants in the Gla-300 group (bronchopneumonia, n = 1; bronchogenic carcinoma, n = 1) and four in the Gla-100 group (intoxication with medication after recurrent depression, n = 1; myocardial infarction, n = 1; worsening chronic heart failure, n = 1; acute pulmonary arrest, n = 1)]. Three additional participants died after discontinuation of study medication [2 participants in the Gla-300 group (infective thrombosis, n = 1; pulmonary embolism, n = 1) and one in the Gla-100 group (unknown cause)]. None of these events were considered related to study medication.

Discussion

The results of the 6-month extension of the EDITION 1 study are largely consistent with the observations from the core 6-month study [6]. Adherence to both Gla-300 and Gla-100 as part of a basal-bolus treatment regimen continued to be very good, with nearly 90% of enrolled participants completing 12 months of follow-up. Both regimens provided sustained glycaemic control with mean levels at 12 months (7.24% with Gla-300 and 7.42% with Gla-100) that were similar to those observed at the end of 6 months [6]. The present observations also confirm that a 14% higher dose of Gla-300 [representing an 8% increase in total average insulin dose (basal plus meal-time insulin)] compared with Gla-100 was required to maintain these levels of glycaemic control, without leading to a higher risk of hypoglycaemia. The cause of the difference in insulin dosage is not known; however, as the main active molecule circulating after injection of both Gla-300 and Gla-100 is the same M1 metabolite [12,13], an effect at the subcutaneous depot seems most likely. Potentially, a longer residence time for Gla-300 in the subcutaneous space, which is consistent with the more stable and prolonged pharmacokinetic and pharmacodynamic profiles [5], might lead to an increase of enzymatic inactivation at that injection site. In addition, the slight further increase of dose of Gla-300 during the extension period, when the study participants were more responsible for dosing decisions, is consistent with the participants having greater confidence in increasing the dose at given levels of glucose.

Some additional observations from this study extend the findings of the earlier report of 6-month results. At the end of
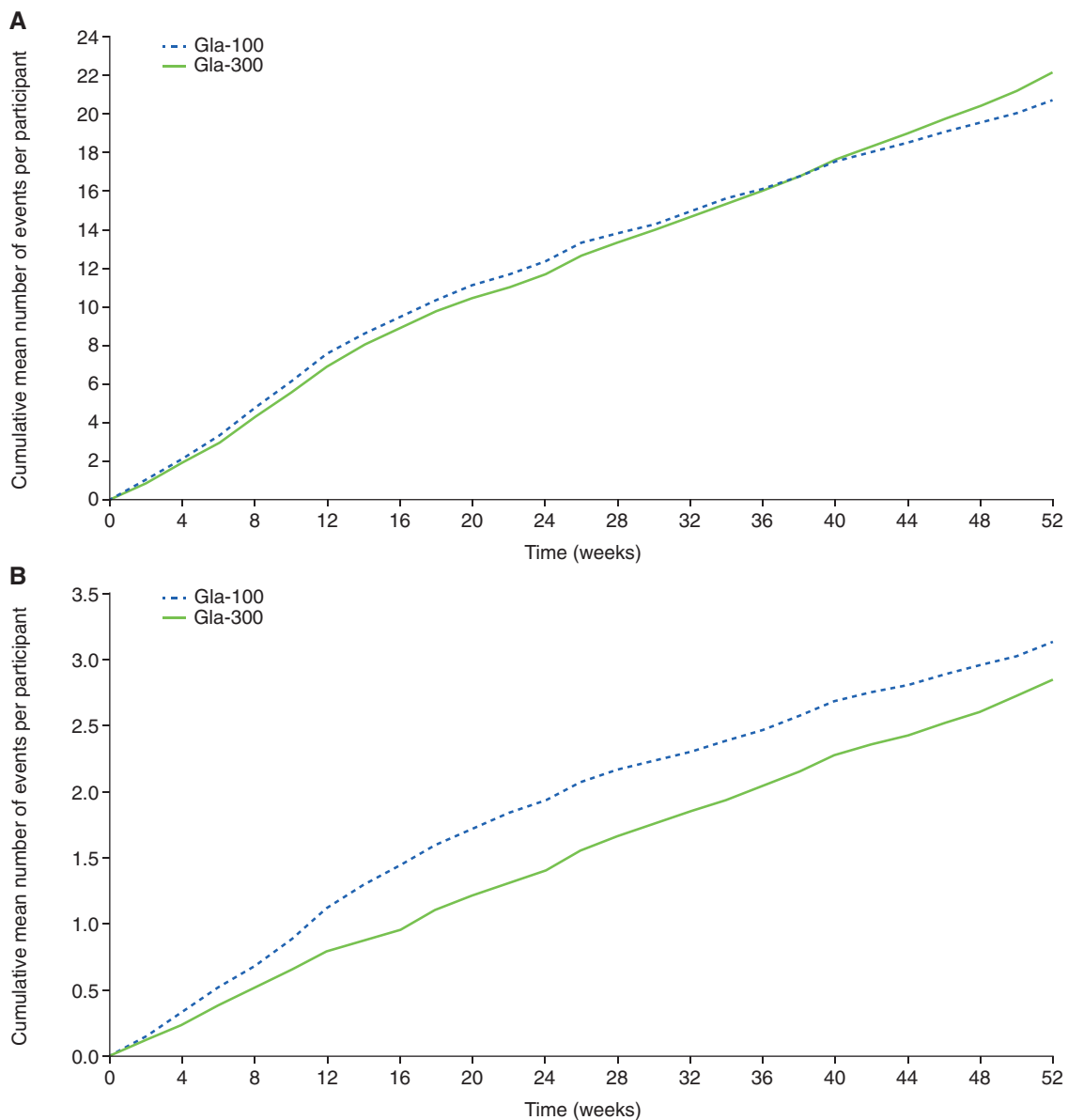
Figure 3. Cumulative mean numbers of confirmed [≤3.9 mmol/l (≤70 mg/dl)] or severe hypoglycaemic events per participant during the 12-month study period (safety population). (A) Events occurring at any time of day (24 h). (B) Nocturnal events (00:00–05:59 hours). Gla-100, glargine 100 U/ml; Gla-300, glargine 300 U/ml [Correction added on May 29: In Figure 3A, the values of Gla-100 and Gla-300 were previously incorrect and these have now been amended in this version].

the first 6 months there was a between-treatment difference in risk of hypoglycaemia, especially at night, favouring Gla-300. The lower risk of nocturnal hypoglycaemia was maintained over the 12-month period, although the difference was attenuated over time. Overall, the numbers of participants affected by hypoglycaemia at any time of the day were equivalent or lower with Gla-300, depending on the category of hypoglycaemia reported. The annualized rates of hypoglycaemia were similar or slightly higher with Gla-300 than with Gla-100 during the full extension period across the categories, mostly owing to more hypoglycaemic events being reported during the daytime. Insufficient adjustment of the meal-time insulin dose may have influenced the frequency of daytime hypoglycaemic events and

contributed to the observed rates of hypoglycaemia in the treatment groups.

Although the reduction of HbA1c from baseline showed no tendency to differ between the groups treated with Gla-300 or Gla-100 for the first 6 months, by the end of the 12 months a small but significant difference favouring Gla-300 was found [LS mean difference −0.17 (95% CI −0.30 to −0.05)%, p = 0.007]. Examination of the HbA1c patterns over time (Figure 2A) suggests that the less intensive follow-up of participants in the extension period led to a modest initial worsening of control in both arms at 9 months, and this persisted at 12 months with Gla-100 but not with Gla-300. The patterns of HbA1c were consistent with similar trends for FPG

[LS mean difference −0.34 (95% CI −0.69 to 0.01) mmol/l; p = 0.058] at month 12, and also in the late-evening measurements on the eight-point glucose profiles at month 12. Thus, waning of the lower risk of hypoglycaemia with Gla-300 during the second 6 months of treatment occurred concurrently with apparent improvement in glycaemic control. These differences in glycaemic control are modest, and the period of extension was still limited; however, they do suggest that, as duration of treatment increased, the advantage of Gla-300 in terms of risk of hypoglycaemia may have improved the participants' ability to make appropriate decisions regarding timing and adjustment of basal and meal-time insulin doses. Further study of the relationships between the frequency of nocturnal hypoglycaemia during titration of Gla-300, risk of daytime hypoglycaemia, and attained HbA1c seems warranted.

The tolerability of both Gla-300 and Gla-100 continued to be very good throughout the 12-month period, with similar numbers of participants experiencing adverse events and no new problems observed. This was not unexpected, given that Gla-300 and Gla-100 are different formulations of the same molecule with the same active circulating metabolite [12,13]. The high proportion of participants completing the extension study further supports the tolerability of both Gla-300 and Gla-100.

Beyond the limitations discussed in the initial 6-month study report, which are also applicable to the 12-month study [6], notably the unavoidable open-label nature of treatment, there is additional potential for biased reporting of safety and efficacy outcomes in an extension study.

In summary, in this challenging population of people with obesity, long duration of T2DM and the need for both basal and meal-time insulin treatment, the improved glycaemic control reported in the 6-month study was maintained up to 12 months, without any new safety concerns. Whether even longer-term treatment with Gla-300 would lead to better glycaemic control with equivalent or lower frequency of hypoglycaemia in this or other populations is unknown, but might be examined in future investigations.

Conflict of Interest

M.C.R. has received research grant support from Amylin, Eli Lilly, Novo Nordisk, and Sanofi, honoraria for consulting and/or speaking from Amylin, Bristol-Myers Squibb–AstraZeneca Alliance, Elcelyx, Eli Lilly, Sanofi and Valeritas. These dualities of interest have been reviewed and managed by Oregon Health and Science University. H. Y.-J. has received honoraria for consulting and speaking from Boehringer Ingelheim, Eli Lilly, Merck (MSD) and Sanofi. G. B. B. has received honoraria for advising and lecturing from Eli Lilly, Novartis and Sanofi. M. Z. and I. M.-B. are employees of Sanofi. S. C. is an employee of Keyrus Biopharma. P. D. H. has received funding for self or affiliated institutions: AntriaBio; Biocon; Bristol-Myers Squibb–AstraZeneca Alliance; Eli Lilly; GlaxoSmithKline; Hanmi; Janssen/Johnson & Johnson; Merck (MSD); Novo Nordisk; Roche Diagnostics; Roche Pharma; Sanofi; Skyepharma; and Takeda.

M.C.R. is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. 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. M. C. R., H. Y.-J., G. B. B. and P. D. H. contributed to protocol design, analysis and interpretation of the data and manuscript writing. M. Z. and I. M.-B. of Sanofi contributed to the design and treatment considerations for the trial and were involved in the analysis and interpretation of the data, and writing and reviewing the manuscript. S. C. was involved in the analysis and interpretation of data, and reviewed the manuscript.

Supporting Information

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

Figure S1. Eight-point profiles of self-monitored plasma glucose at baseline and month 12 (mean ± standard error; modified intention-to treat population).

Table S1. Adverse events (safety population).

References

1. 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): S43–52.

2. Tibaldi JM. Evolution of insulin development: focus on key parameters. Adv Ther 2012; **29**: 590–619.

3. Korytkowski M. When oral agents fail: practical barriers to starting insulin. Int J Obes Relat Metab Disord 2002; **26**(Suppl. 3): S18–24.

4. Garber AJ. Will the next generation of basal insulins offer clinical advantages? Diabetes Obes Metab 2014; **16**: 483–491.

5. Becker RH, Dahmen R, Bergmann K, Lehmann A, Jax T, Heise T. New insulin glargine 300 units.mL^{-1} provides a more even activity profile and prolonged glycemic control at steady state compared with insulin glargine 100 units.mL^{-1}. Diabetes Care 2015; **38**: 637–643.

6. Riddle MC, Bolli GB, Ziemen M, Muehlen-Bartmer I, Bizet F, Home PD. 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). Diabetes Care 2014; **37**: 2755–2762.

7. Yki-Jarvinen H, Bergenstal R, Ziemen M et al. New insulin glargine 300 units/mL versus glargine 100 units/mL in people with type 2 diabetes using oral agents and basal insulin: glucose control and hypoglycemia in a 6-month randomized controlled trial (EDITION 2). Diabetes Care 2014; **37**: 3235–3243.

8. Bolli GB, Riddle MC, Bergenstal RM et al. New insulin glargine 300 U/ml compared with glargine 100 U/ml in insulin-naive people with type 2 diabetes on oral glucose-lowering drugs: a randomized controlled trial (EDITION 3). Diabetes Obes Metab 2015; **17**: 386–394.

9. WHO. 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.

10. 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.

11. American Diabetes Association. Defining and reporting hypoglycemia in diabetes: a report from the American Diabetes Association Workgroup on Hypoglycemia. Diabetes Care 2005; **28**: 1245–1249.

12. Steinstraesser 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 2014; **16**: 873–876.

13. Lucidi P, Porcellati F, Candeloro P et al. Glargine metabolism over 24 h following its subcutaneous injection in patients with type 2 diabetes mellitus: a dose-response study. Nutr Metab Cardiovasc Dis 2014; **24**: 709–716.