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Original article

Glycaemic control and hypoglycaemia with insulin glargine 300 U/mL versus insulin glargine 100 U/mL in insulin-*naïve* people with type 2 diabetes: 12-month results from the EDITION 3 trial

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ABSTRACT

Aim. – To explore if efficacy and safety findings for insulin glargine 300 U/mL (Gla-300) versus insulin glargine 100 U/mL (Gla-100), observed over 6 months in insulin-*naïve* people with type 2 diabetes, are maintained after 12 months.

Methods. – EDITION 3 was a phase 3a, randomized, multicentre, open-label, parallel-group, treat-to-target study of once-daily Gla-300 versus Gla-100 (target fasting self-monitored plasma glucose, 4.4–5.6 mmol/L [80–100 mg/dL]). Participants completing the initial 6-month treatment phase continued their previously allocated basal insulin.

Results. – Of 878 participants randomized, 337/439 (77%) and 314/439 (72%) assigned to Gla-300 and Gla-100, respectively, completed 12 months of treatment. Improved glycaemic control was sustained until 12 months in both treatment groups, with similar reductions in HbA_{1c} from baseline to month 12 (difference: −0.08 [95% confidence interval (CI): −0.23 to 0.07] % or −0.9 [−2.5 to 0.8] mmol/mol). Relative risk of experiencing ≥ 1 confirmed (≤ 3.9 mmol/L [≤ 70 mg/dL]) or severe hypoglycaemic event with Gla-300 versus Gla-100 was 0.86 (95% CI: 0.69 to 1.07) at night and 0.92 (0.82 to 1.03) at any time of day. For events with a glycaemic threshold of < 3.0 mmol/L (< 54 mg/dL) these numbers were 0.76 (0.49 to 1.19) and 0.66 (0.50 to 0.88). A similar pattern was seen for documented symptomatic events. No between-group differences in adverse events were identified.

Conclusion. – Over 12 months, Gla-300 treatment was as effective as Gla-100 in reducing HbA_{1c} in insulin-*naïve* people with type 2 diabetes, with lower overall risk of hypoglycaemia at the < 3.0 mmol/L threshold.

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Introduction

Although people with type 2 diabetes initially achieve glycaemic control with lifestyle modifications followed by non-insulin anti-hyperglycaemic agents (AHAs), as the condition progresses most will eventually require insulin therapy to maintain control [1]. Several insulin treatment protocols are available, but physiological and psychosocial barriers to starting and continuing insulin, including concerns regarding hypoglycaemia, weight gain and the lack of flexibility [2–4], may lead to delay in beginning insulin; these

Abbreviations: AHA, anti-hyperglycaemic agent; ANCOVA, analysis of covariance; DTSQs, Diabetes Treatment Satisfaction Questionnaire; EQ-5D, EuroQol 5 Dimensions; FPG, fasting plasma glucose; Gla-100, insulin glargine 100 U/mL; Gla-300, insulin glargine 300 U/mL; HFS-II, hypoglycaemia fear scale; MedDRA, Medical Dictionary for Regulatory Activities; MMRM, mixed effects model for repeated measures; PRO, participant-reported outcomes; SMPG, self-monitored plasma glucose.

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barriers may also lessen the chances of achieving and sustaining better glycaemic control through appropriate insulin dose titration.

Insulin glargine 300 U/mL (Gla-300) is characterized by flatter pharmacokinetic (PK) and pharmacodynamic (PD) profiles with longer duration of action compared with insulin glargine 100 U/mL (Gla-100), resulting in effective blood glucose control beyond 24 hours [5]. The phase 3a EDITION programme was designed to determine whether the PK and PD profiles of Gla-300 translated into clinical benefit in different populations of people with diabetes. Studies in type 2 diabetes using basal and meal-time insulin (EDITION 1) [6] or basal insulin (and non-insulin AHAs) (EDITION 2) [7] demonstrated that Gla-300 provided comparable glycaemic control to Gla-100, but with a lower rate of hypoglycaemia over 6 months. Over 12 months, sustained glycaemic control and lower hypoglycaemia risk with Gla-300 were also found in prior insulin-treated people [8,9].

EDITION 3 [10] investigated the efficacy and safety of Gla-300 versus Gla-100 in insulin-*naïve* people with type 2 diabetes whose blood glucose levels were inadequately controlled with non-insulin AHAs. In line with results from EDITION 1 and 2, the 6-month EDITION 3 results demonstrated equivalent glycaemic control with Gla-300 and Gla-100, associated with a significantly lower risk of nocturnal (00:00–05:59 h) confirmed ($\leq$ 3.9 mmol/L [$\leq$ 70 mg/dL]) or severe hypoglycaemia. Here, we present the 12-month efficacy and safety results from EDITION 3.

Materials and methods

Study design and participants

EDITION 3 was a multicentre, randomized, open-label, two-arm, parallel-group, treat-to-target phase 3a study conducted in 2012–2013, involving 878 participants with type 2 diabetes. Details of the study design have been described previously [10]. Briefly, adults $\geq$ 18 years of age with type 2 diabetes for at least 1 year prior to screening, having used non-insulin AHAs for at least 6 months prior to screening and being insulin *naïve*, were randomized 1:1 to once-daily Gla-300 (using a modified Tactipen® injector [Sanofi, Paris, France]) or Gla-100 (using a SoloSTAR® pen [Sanofi]) for a period of 12 months. Exclusion criteria included $HbA_{1c} < 7.0\%$ (< 53 mmol/mol) or $> 11.0\%$ (> 97 mmol/mol) at screening. Any non-insulin AHAs not approved for combination with insulin, and/or sulfonylureas or glinides, were discontinued at baseline.

Daily basal insulin was started at 0.2 U/kg body weight, and then adjusted once weekly, aiming for a fasting self-monitored plasma glucose (SMPG) of 4.4–5.6 mmol/L (80–100 mg/dL) in the absence of hypoglycaemia (Table S1; see supplementary material associated with this article online). If, after dose titration, laboratory-measured fasting plasma glucose (FPG) or HbA_{1c} were above the target without reasonable explanation, and if appropriate action failed to correct this, intensification of therapy was to be considered, namely rescue medication chosen by investigator discretion. Participants who completed the 6-month treatment period continued to receive either Gla-300 or Gla-100, according to initial randomization, for a further predefined 6-month extension phase.

Appropriate local or national ethics committees approved the study protocol. The study was registered with ClinicalTrials.gov (NCT01676220) and was conducted according to Good Clinical Practice and the Declaration of Helsinki.

Outcomes

The primary efficacy endpoint in EDITION 3, change in HbA_{1c} from baseline to month 6, has been previously reported [10]. For the 12-month on-treatment period, the efficacy outcomes were: change from baseline to month 12 in HbA_{1c}, FPG, pre-breakfast SMPG, 8-point SMPG profiles and basal insulin dose. Safety/tolerability outcomes included the percentage of participants experiencing $\geq$ 1 hypoglycaemic event, annualized rates of hypoglycaemic events, change from baseline to month 12 in body weight, and the occurrence of other adverse events (AEs). Other safety information such as clinical laboratory data and vital signs were recorded throughout the study.

Hypoglycaemic events were categorized based on American Diabetes Association definitions [11]:

- severe hypoglycaemia;
- documented symptomatic hypoglycaemia (typical symptoms of hypoglycaemia and a measured plasma glucose concentration of $\leq$ 3.9 mmol/L [$\leq$ 70 mg/dL]);
- and asymptomatic hypoglycaemia (measured plasma glucose concentration of $\leq$ 3.9 mmol/L [$\leq$ 70 mg/dL] in the absence of typical symptoms of hypoglycaemia).

The confirmed (with or without symptoms) and severe categories were combined and analysed as 'confirmed or severe' hypoglycaemia. In addition, hypoglycaemic events with a plasma glucose measurement of $<$ 3.0 mmol/L ($<$ 54 mg/dL) were analysed.

Hypoglycaemia was assessed as events occurring during the night (00:00–05:59 h) and at any time of day (24 h), and also by the following subgroups: age ($<$ 65 years; 65–75 years; $\geq$ 75 years), randomization stratum of HbA_{1c} at screening ($< 8.0\%$; $\geq 8.0\%$), BMI at baseline (< 30 kg/m^2; ≥ 30 kg/m^2), duration of diabetes ($<$ 10 years; $\geq$ 10 years). An additional post hoc exploratory analysis was by prior sulfonylurea use (within the 3 months prior to screening or within the run-in period).

Bicomposite efficacy endpoints (post hoc, exploratory) were also assessed, defined as the percentage of participants achieving HbA_{1c} target ($< 7.0\%$) at month 12 without hypoglycaemia (confirmed or severe, or documented symptomatic, at both glycaemic thresholds) at night (00:00–05:59 h) and at any time of day (24 h) over 12 months of treatment.

Participant-reported outcomes (PRO) included treatment satisfaction (using the Diabetes Treatment Satisfaction Questionnaire [DTSQs, status version]) [12–14], health-related quality of life (using the EuroQol 5 Dimensions [EQ-5D] questionnaire) [15], and behaviours and worries related to fear of hypoglycaemia (using the hypoglycaemia fear scale [HFS-II]) [16].

Data analysis and statistics

The efficacy and PRO analyses used the modified intent-to-treat (mITT) population, namely all randomized participants who received $\geq$ 1 dose of study insulin and had both a baseline and $\geq$ 1 post-baseline efficacy assessment. Safety analyses used the safety population, comprising all participants randomized and exposed to $\geq$ 1 dose of study insulin.

For all efficacy outcomes other than change in basal insulin dose, 8-point SMPG, and pre-breakfast SMPG, a mixed effects model for repeated measures (MMRM) analysis was conducted. Change in body weight was assessed using an analysis of covariance (ANCOVA) model. Bicomposite efficacy endpoints were compared using a Cochran–Mantel–Haenszel method stratified by randomization strata of screening HbA_{1c} (< 8.0 and $\geq 8.0\%$). AEs were analysed descriptively and coded using the Medical Dictionary for Regulatory Activities (MedDRA) system.

The Cochran–Mantel–Haenszel method was used to analyse the percentage of participants with at least one hypoglycaemic event, and an overdispersed Poisson regression model using treatment period (expressed in years) as offset and stratified by randomization strata of screening HbA_{1c} (< 8.0 and $\geq 8.0\%$) was used to analyse the hypoglycaemic event rate.

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Results

Study population

As previously reported [10], 878 participants were randomized to receive Gla-300 ($n = 439$) or Gla-100 ($n = 439$) (Fig. 1); of these, 435 and 438 respectively, formed the safety population, while 432 and 430 participants, comprised the mITT population. Baseline characteristics have been reported previously, and were similar between-treatment groups [10]. The discontinuation rate was similar in the Gla-300 ($n = 84$; 19%) and Gla-100 ($n = 102$; 23%) groups, with 337 and 314 participants completing the 12-month study without the need for rescue therapy. The majority of discontinuations in the Gla-300 ($n = 57$) and Gla-100 ($n = 78$) groups were made at the participant's request. Perceived lack of efficacy accounted for the discontinuation of three participants (0.7%) in the Gla-300 group and one participant (0.1%) in the Gla-100 group. Rescue therapy was required by 15 (3.4%) and 26 (5.9%) participants in the Gla-300 and Gla-100 groups, respectively, more frequently being a fast-acting insulin analogue in both treatment groups (Gla-300 $n = 12$; Gla-100 $n = 19$).

Glycaemic response

The improvement in glycaemic control observed at 6 months, measured by HbA_{1c} (Fig. 2A) and FPG (Fig. 2B), was maintained to month 12 and was similar with the two treatments. At month 12, mean (SD) HbA_{1c} was 7.13 (1.00) % (54.4 [10.9] mmol/mol) with Gla-300 and 7.24 (0.97) % (55.6 [10.6] mmol/mol) with Gla-100. The least squares (LS) mean difference in HbA_{1c} change from baseline to month 12 for Gla-300 versus Gla-100 was −0.08 (95% confidence interval [CI]: −0.23 to 0.07) % (−0.9 [95% CI: −2.5 to 0.8] mmol/mol)) (Table S2; see supplementary material associated with this article online). LS mean difference in FPG change for Gla-300 versus Gla-100 was 0.07 (95% CI: −0.26 to 0.40) mmol/L (1.32 [95% CI: −4.62 to 7.26] mg/dL) (Table S2; see supplementary material associated with this article online).

Pre-breakfast SMPG decreased in both treatment groups, with the largest decrease occurring during the first 12 weeks. Mean (SD) pre-breakfast SMPG levels were very similar in the two treatment groups at month 12: Gla-300, 6.19 (1.21) mmol/L (111.5 [21.8] mg/dL); Gla-100, 6.18 (1.37) mmol/L (111.4 [24.7] mg/dL). Eight-point SMPG profiles decreased markedly for both Gla-300 and Gla-100 during the study, and at month 12 the plasma glucose profiles were similar in the two treatment groups (Fig. 2C).

Insulin dose

Daily basal insulin dose increased up to month 12 in both treatment groups, but to a greater extent in the Gla-300 group (Fig. 2D). The mean (SD) basal insulin dose at month 12 was 0.67 (0.33) U/kg/day in the Gla-300 group and 0.56 (0.27) U/kg/day in the Gla-100 group (20% higher with Gla-300). Forty-five percent of the dose difference at month 12 was reached by week 12.

Hypoglycaemia

Nocturnal (00:00–05:59 h) confirmed (≤ 3.9 mmol/L [≤ 70 mg/dL]) or severe hypoglycaemia

The percentage of participants experiencing ≥ 1 nocturnal confirmed or severe hypoglycaemic event over the 12-month treatment period was 25% with Gla-300 and 29% with Gla-100

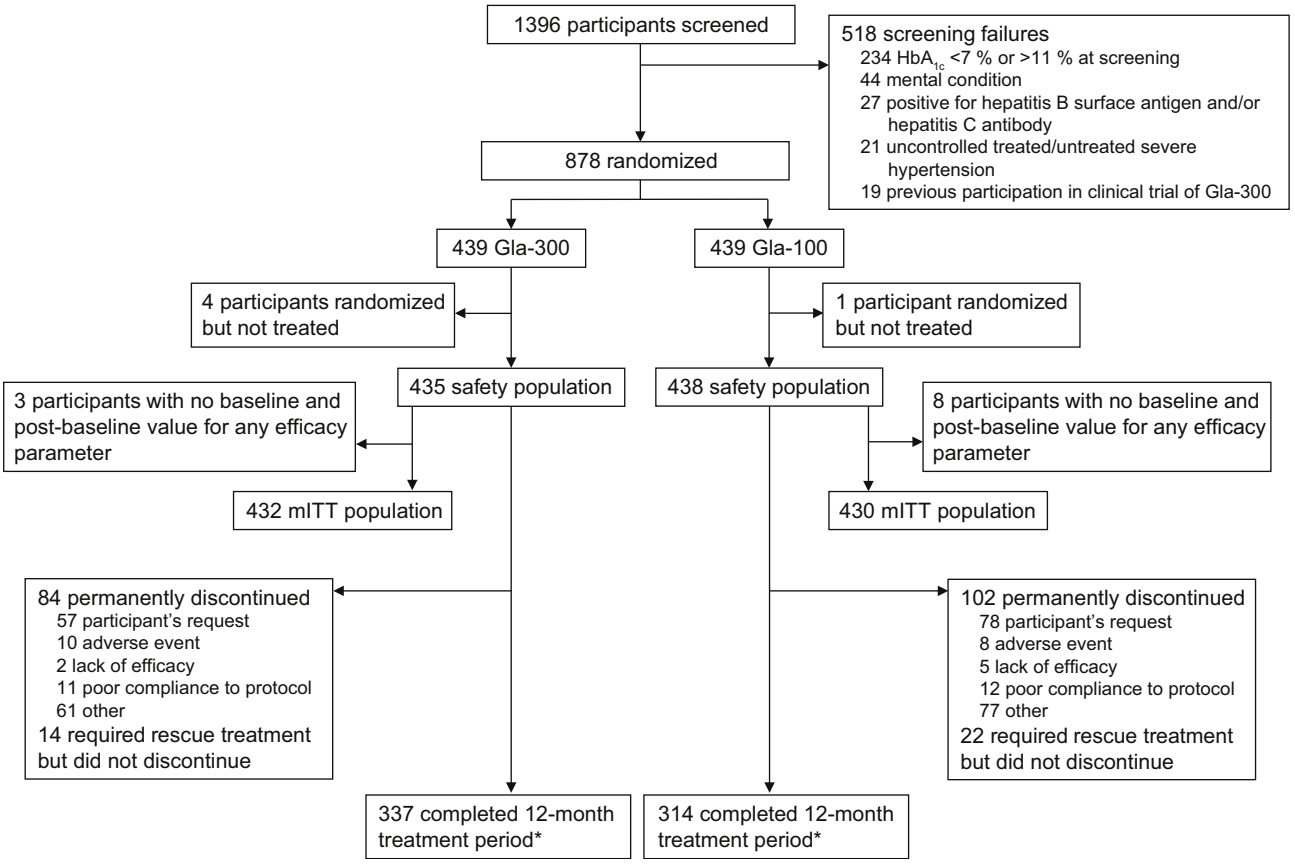

Fig. 1. Participant flow diagram. *The 12-month completed population included all patients who completed the 12-month on-treatment period and who did not permanently discontinue the study medication and did not start rescue therapy during the 12-month on-treatment period. mITT: modified intent-to-treat.

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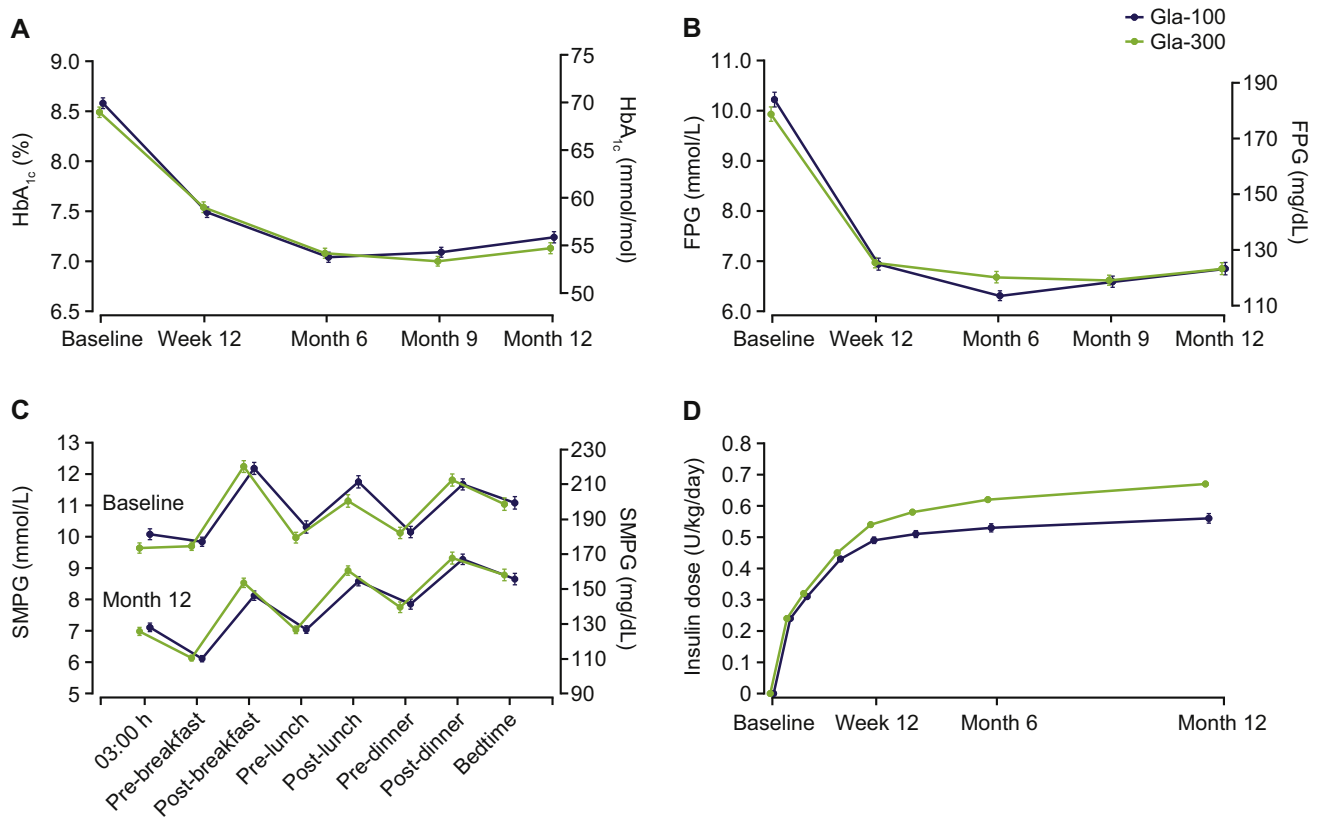

Fig. 2. Clinical measures (mean ± SE) during 12 months of treatment. A. HbA_{1c}, by visit. B. Laboratory-measured FPG, by visit. C. Eight-point SMPG profile at baseline and at month 12. D. Daily basal insulin dose, by visit. mITT population. FPG: fasting plasma glucose; mITT: modified intent-to-treat; SE: standard error; SMPG: self-monitored plasma glucose.

(relative risk [RR]: 0.86 [95% CI: 0.69 to 1.07]) (Fig. 3A). The number of participants needed to be treated in order to prevent one participant from experiencing such an event over 1 year was 24. Annualized rates of nocturnal confirmed or severe hypoglycaemic events were similar in the two insulin groups over the 12-month treatment period (Gla-300 1.33 events/participant-year vs. Gla-100 1.36 events/participant-year; RR: 0.98 [95% CI: 0.69 to 1.40]) (Fig. 3B).

Any time of day confirmed (≤ 3.9 mmol/L [≤ 70 mg/dL]) or severe hypoglycaemia

Over 12 months, the percentage of participants who experienced ≥ 1 confirmed or severe hypoglycaemic event occurring any time of day was 56% with Gla-300 and 61% with Gla-100 (RR: 0.92 [95% CI: 0.82 to 1.03]) (Fig. 3A). The number of participants needed to be treated in order to prevent one participant from experiencing ≥ 1 confirmed or severe hypoglycaemic event at any time of day over 1 year was 21. Annualized rates of hypoglycaemic events were similar with Gla-300 and Gla-100 (7.14 events/participant-year vs. 8.11 events/participant-year; RR: 0.88 [95% CI: 0.70 to 1.11]) (Fig. 3B).

Severe hypoglycaemia

There were no reports of nocturnal (00:00–05:59 h) severe hypoglycaemia with Gla-300, while three participants (0.7%) reported such events with Gla-100. Six participants in the Gla-300 group (1.4%) and nine in the Gla-100 group (2.1%) reported severe hypoglycaemia at any time of day (24 h).

Other definitions of hypoglycaemia

The percentage of participants experiencing ≥ 1 documented symptomatic (≤ 3.9 mmol/L [≤ 70 mg/dL]) hypoglycaemic event during the 12-month treatment period was 19% and 21% with Gla-300 and Gla-100 at night (00:00–05:59 h), and 39% and 44% at any time of day (24 h) (Fig. 3A). Annualized rates of the any time of day events showed a statistically significant 27% reduction in rate with Gla-300 versus Gla-100 at any time of day (24 h) (Fig. 3B).

Using the more stringent glycaemic threshold (< 3.0 mmol/L [< 54 mg/dL]) for confirmed or severe hypoglycaemia, 7.1% and 9.4% of participants receiving Gla-300 and Gla-100, respectively, reported nocturnal (00:00–05:59 h) hypoglycaemia over 12 months (Fig. 3A; RR: 0.76 [95% CI: 0.49 to 1.19]), while 14% and 22% of participants reported hypoglycaemia at any time of day (24 h) (RR: 0.66 [0.50 to 0.88]; for documented symptomatic hypoglycaemia, RR: 0.65 [0.47 to 0.90]) (Fig. 3A). Annualized rates at this lower glycaemic threshold were also numerically lower, at night (00:00–05:59 h) and at any time of day (24 h), with Gla-300 than with Gla-100 for confirmed or severe hypoglycaemia, and for documented symptomatic hypoglycaemia (Fig. 3B).

Pattern of hypoglycaemia by time of day (24 h)

The percentage of participants experiencing ≥ 1 confirmed (≤ 3.9 mmol/L [≤ 70 mg/dL]) or severe hypoglycaemic event was lower in the Gla-300 group than in the Gla-100 group throughout most of the day (Fig. 4), suggesting that Gla-300 reduced the risk of hypoglycaemia beyond the protocol-defined nocturnal period (although no statistical testing of differences was performed).

Hypoglycaemia by subgroup

The percentage of participants with ≥ 1 confirmed (≤ 3.9 mmol/L [≤ 70 mg/dL]) or severe hypoglycaemic event at any time of day (24 h) over 12 months of treatment was numerically lower with Gla-300 than Gla-100 for all subgroups (age, HbA_{1c} stratum, BMI at baseline, and duration of diabetes) (Fig. 5).

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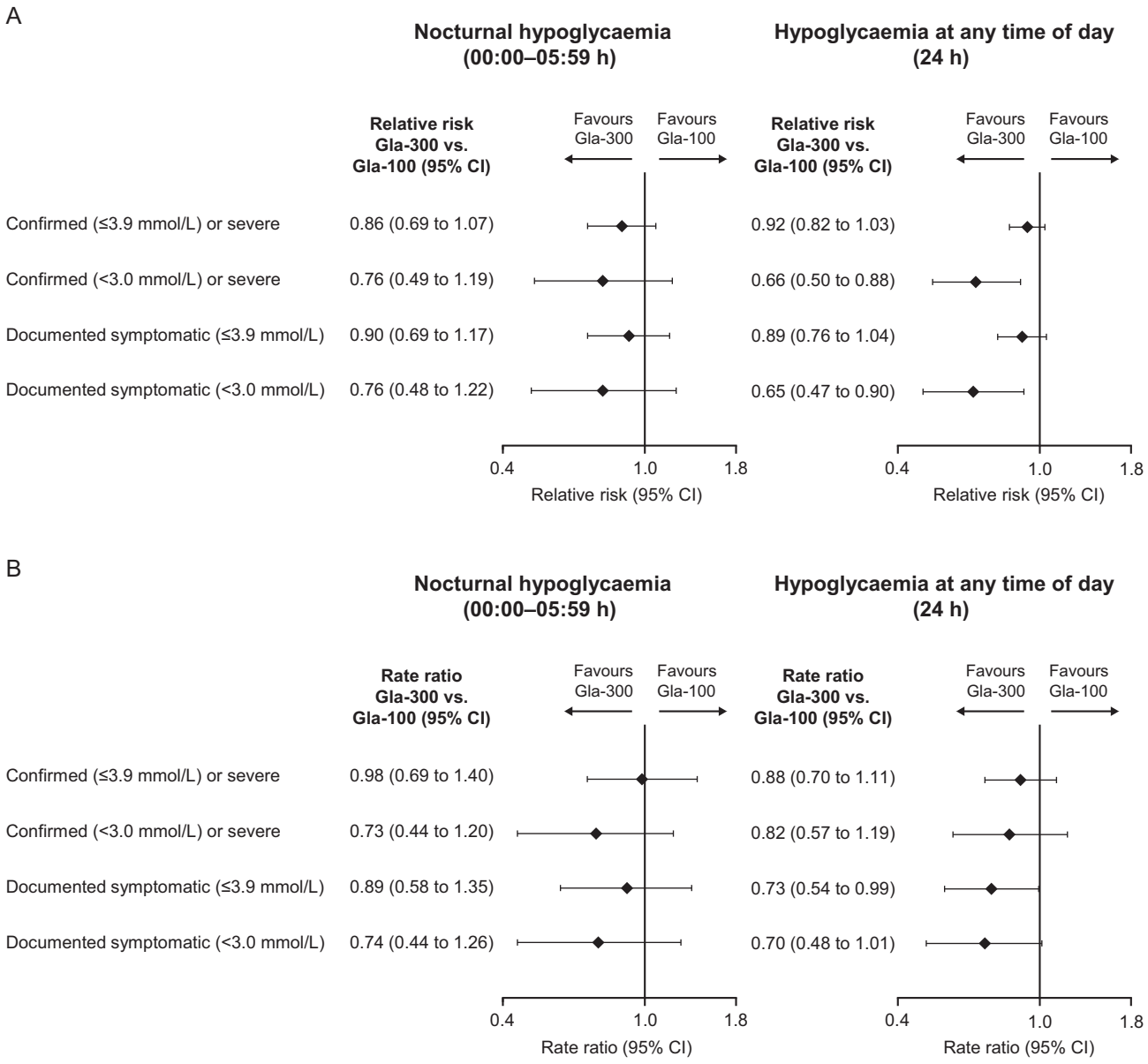

Fig. 3. Hypoglycaemia over 12 months. A. Relative risk of participants experiencing ≥ 1 hypoglycaemic event. B. Annualized rates (events per participant-year). Safety population. CI: confidence interval.

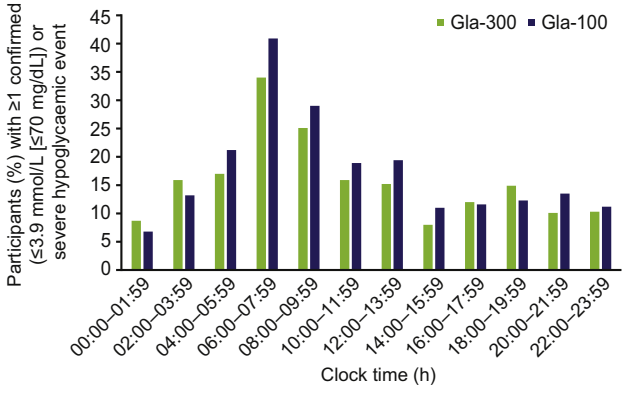

Fig. 4. Percentage of participants experiencing ≥ 1 confirmed (≤ 3.9 mmol/L [≤ 70 mg/dL]) or severe hypoglycaemic event during 12 months of treatment by time of the day. Safety population.

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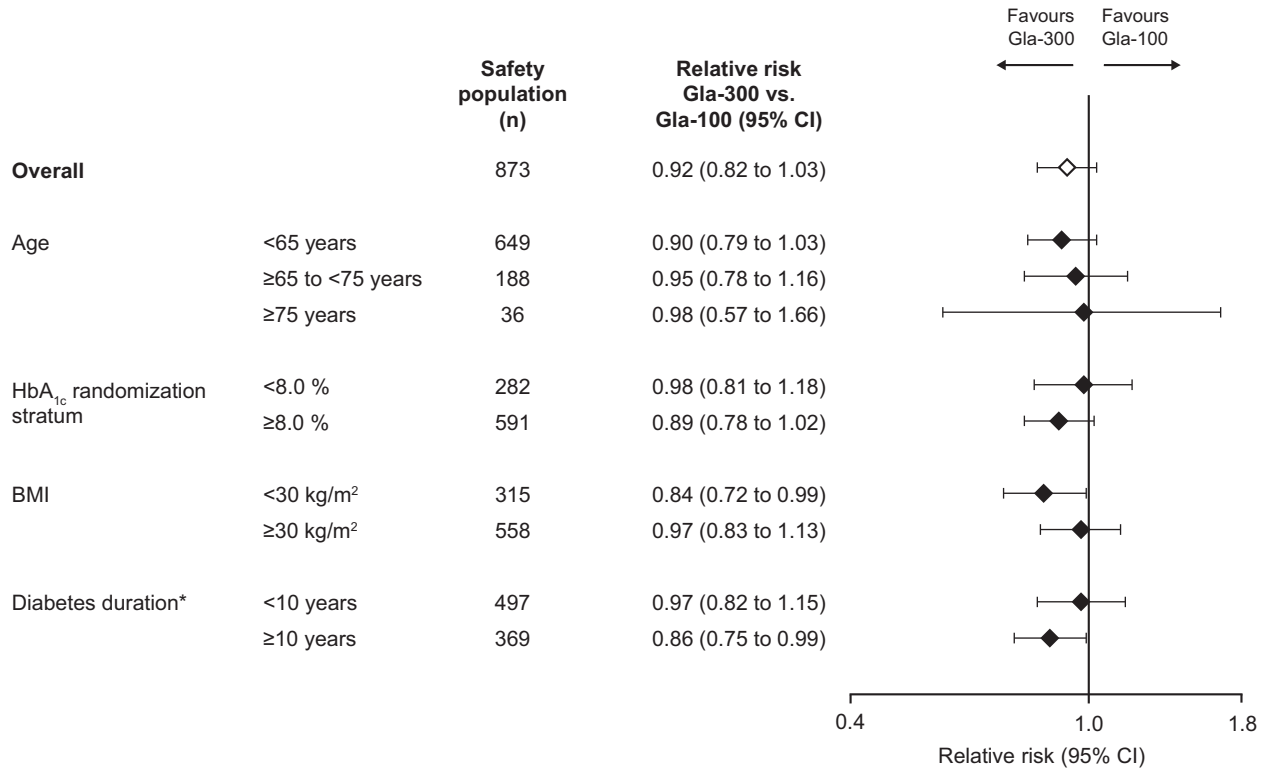

Fig. 5. Relative risk of participants experiencing at least one confirmed (≤ 3.9 mmol/L [≤ 70 mg/dL]) or severe hypoglycaemic event at any time of day (24 h) by subgroup during the 12-month on-treatment period. Safety population. BMI: body mass index.

For participants with baseline BMI < 30 kg/m^2 the RR was 0.84 (95% CI: 0.72 to 0.99), while for those with a diabetes duration of ≥ 10 years the RR was 0.86 (95% CI: 0.75 to 0.99). No heterogeneity of treatment effect across subgroups was observed. Similar results were observed for the percentage of participants with ≥ 1 confirmed (≤ 3.9 mmol/L [≤ 70 mg/dL]) or severe hypoglycaemic event at night (00:00–05:59 h) (data not shown). In addition, no heterogeneity of treatment effect was observed for the post hoc analysis of hypoglycaemia (percentage of participants with ≥ 1 confirmed [≤ 3.9 mmol/L (≤ 70 mg/dL)] or severe event at night or at any time of day [24 h]) by sulfonylurea subgroup.

Bicomposite endpoints

The percentage of participants reaching an HbA_{1c} target of < 7.0% without nocturnal (00:00–05:59 h) confirmed (≤ 3.9 mmol/L [≤ 70 mg/dL]) or severe hypoglycaemia was 23% in the Gla-300 group versus 19% in the Gla-100 group (Responder Ratio: 1.24 [95% CI: 0.96 to 1.61]). For those without nocturnal documented symptomatic (≤ 3.9 mmol/L [≤ 70 mg/dL]) hypoglycaemia, the percentage of participants was 28% versus 24% (Responder Ratio 1.19 [95% CI: 0.96 to 1.49]) (Table S3; see supplementary material associated with this article online). Similar differences between Gla-300 and Gla-100 were observed for hypoglycaemia at any time of day (24 h), and hypoglycaemia confirmed at the lower glycaemic threshold of < 3.0 mmol/L (< 54 mg/dL) (Table S3; see supplementary material associated with this article online). In these analyses the between-treatment difference did not reach statistical significance, except for the percentage of participants achieving an HbA_{1c} target of < 7.0% without documented symptomatic (< 3.0 mmol/L [< 54 mg/dL]) hypoglycaemia (Responder Ratio: 1.25 [95% CI: 1.01 to 1.54]) (Table S3; see supplementary material associated with this article online).

Participant-reported outcomes

Overall satisfaction with treatment, measured by the DTSQs (possible score range 0–36), was high in both treatment groups. The mean (SD) Total Treatment Satisfaction scores were similar in the two groups at baseline (Gla-300, 27.2 [7.1]; Gla-100, 26.3 [7.1]) and at month 12 (32.1 [4.7] and 31.7 [5.0]). Health-related quality of life (EQ-5D utility index score) remained stable in both treatment groups throughout the 12-month study (data not shown). As previously reported, fear of hypoglycaemia was very low at baseline [10], and decreased further to month 12 in both treatment groups. The mean (SD) total HFS-II score decreased from 0.52 (0.63) to 0.42 (0.47) in the Gla-300 group, and from 0.61 (0.68) to 0.47 (0.53) in the Gla-100 group.

Weight change

The mean (SD) change in body weight from baseline to last on-treatment value was small and similar in both groups: 0.97 (4.32) kg in the Gla-300 group and 1.20 (4.16) kg in the Gla-100 group. LS mean difference (95% CI) for Gla-300 versus Gla-100 was −0.24 (−0.81 to 0.33) kg.

Adverse events

Overall, 63% of participants in both treatment groups experienced an AE during the 12-month on-treatment period (Table S4; see supplementary material associated with this article online). The most commonly reported of these were infections (38% in the Gla-300 group vs. 37% in the Gla-100 group), gastrointestinal disorders (20% vs. 19%) and musculoskeletal disorders (17% vs. 17%). The percentages of participants reporting injection site reactions, treatment-emergent serious adverse events, and treatment-emergent adverse events leading to withdrawal

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from the study were also similar in the two treatment groups (Table S4; see supplementary material associated with this article online). Twelve participants (four in the Gla-300 group and eight in the Gla-100 group) were identified as experiencing potential major adverse cardiac events over the 12-month on-treatment period. As previously reported, one participant, in the Gla-300 group, died as a result of a serious treatment-emergent adverse event (worsening of atherosclerotic heart disease) [10].

Discussion

The findings of EDITION 3 reported here are in keeping with the sustained glycaemic control observed with Gla-100 and Gla-300 between months 6 and 12 in the EDITION 1 and 2 studies (in people already using basal insulin, or basal plus meal-time insulin) [8,9]. Similarly to the 12-month results of the EDITION 1 trial [8], HbA_{1c} levels were better sustained over 12 months with Gla-300 versus Gla-100, although the between-treatment difference was not statistically significant in EDITION 3 (as it was in EDITION 1). Thus, in a population of insulin-*naïve* people with type 2 diabetes, Gla-300 and Gla-100 provided equivalent overall glycaemic control at 12 months, and similar to that observed at 6 months [10]. No new safety signals were detected.

As observed over the first 6 months [10], the percentage of participants reporting nocturnal confirmed or severe, or documented symptomatic, hypoglycaemia over 12 months was similar or lower in the Gla-300 group versus the Gla-100 group, regardless of the glycaemic threshold used. However, there was a lack of statistical significance for many of the between-group differences, at least partly due to the low overall numbers of hypoglycaemic events in EDITION 3, as evidenced by wide confidence intervals in the estimates of relative risk. The use of an insulin-*naïve* study population with a relatively low risk of hypoglycaemia [17], presumably due to participants having greater endogenous insulin secretion, may have contributed to the lower number of hypoglycaemic events in EDITION 3 compared with EDITION 1 and 2, where Gla-300 did reduce the risk of hypoglycaemia, particularly at night, compared with Gla-100. Furthermore, the discontinuation of sulfonylureas at baseline in EDITION 3 is likely to have lowered the occurrence of hypoglycaemia, as indirectly suggested by the results of studies with similar design where sulfonylureas were continued [18–20].

That Gla-300 may cause less hypoglycaemia than Gla-100 in people who are at higher risk of events is supported by the findings of the subgroup analyses; over 12 months people generally considered to be at higher risk of hypoglycaemia [21,22] (those with a lower BMI [< 30 kg/m^2], and those with longer diabetes duration [≥ 10 years]), experienced a significantly reduced risk of hypoglycaemia with Gla-300 versus Gla-100 (Fig. 5). While these exploratory results should be interpreted with caution (as heterogeneity of treatment effect between the subgroups was not detected), the data suggest that further investigation to determine the potential advantages of Gla-300 in such high-risk populations may be warranted.

The observation that statistically significant differences between Gla-300 and Gla-100 in hypoglycaemic risk were found for the proportion of people experiencing hypoglycaemia with a < 3.0-mmol/L glycaemic threshold, when this was not found for the conventional ≤ 3.9 mmol/L cut-off, may be important. In terms of statistical power this finding is paradoxical, as the number of people affected is smaller with the tighter cut-off, and the confidence intervals wider (Fig. 3). One possible explanation may be that with a population in relatively tight blood glucose control, excursions below 4.0 mmol/L but above 3.0 mmol/L are common, while excursions below 3.0 mmol/L are more likely to result from a less than flat 24-hour insulin delivery, or more erratic absorption, features that are improved with Gla-300 versus Gla-100 [5].

In EDITION 3, patient satisfaction, as measured by DTSQs, was good in both the Gla-300 and Gla-100 treatment groups. Notably, fear of hypoglycaemia was low at baseline and decreased further, up to month 12, in both groups. This result is useful, given that in some geographical regions many people may discontinue insulin therapy shortly after starting it [23], possibly due to experience or fear of hypoglycaemia.

The results at month 12 in EDITION 3 confirm those previously reported at month 6 [10]. However, the possible difference in FPG and HbA_{1c} at month 6 (non-significant) with Gla-300 versus Gla-100 was reversed at month 12. This result was associated with (and likely explained by) a possibly greater dose of both Gla-300 and Gla-100 at month 12 versus month 6, with a higher dose for Gla-300 versus Gla-100 at month 12 (+20%), compared with month 6 (+17%). Indirectly, these differences suggest that in EDITION 3 insulin titration was actively continued in both groups until month 12.

In this 12-month analysis of EDITION 3, the percentage of participants achieving an HbA_{1c} target of $< 7.0\%$, without hypoglycaemia, was higher with Gla-300 than with Gla-100 for all hypoglycaemia categories analysed. Although often not statistically significant, these differences between the insulins are consistent with the lower risk of confirmed (< 3.0 mmol/L) or severe hypoglycaemia with Gla-300. These data suggest that for insulin-*naïve* people with diabetes beginning basal insulin therapy, Gla-300 may enable more to reach glycaemic targets without an increased risk of hypoglycaemia, compared with Gla-100. Further studies in people at higher risk of hypoglycaemia are warranted to determine if all people with type 2 diabetes may achieve similar glycaemic targets with Gla-300 without an increased risk of hypoglycaemia.

The higher dose of Gla-300 compared with Gla-100 required to maintain glycaemic control over 12 months in EDITION 3 is similar to that reported for the 12-month EDITION 1 and 2 results [8,9]. While the reason for this dose difference remains uncertain, it is likely that the increased dose may be explained by a longer residence time of Gla-300 than Gla-100 in the subcutaneous depot [5], giving the opportunity for greater enzymatic inactivation of the glargine molecule.

In EDITION 3, a predefined time interval of 00:00–05:59 h was used as the nocturnal window. However, hypoglycaemic events occurred most frequently between 06:00 and 10:00, a time which includes both a period of fasting and the post-breakfast period for some people. This finding suggests that evening injections of long-acting insulins may increase the risk for hypoglycaemia primarily in the second half of the morning, and that Gla-300 reduces such a risk versus Gla-100. As such, while the use of a 00:00–05:59 h definition of the nocturnal window may be more specific for the fasting nocturnal period, the midnight–10:00 h window is more clinically relevant as it includes the time period during which the highest number of hypoglycaemic events are reported (06:00 and 10:00 h).

Limitations of the current study include its open-label design (due to the different pen injectors), and the fact that contact between trial staff and participants was, as in usual clinical practice, relatively infrequent during the extension period. While the drop-out rates may be of note, they were not particularly high for this kind of study. Owing to the relatively small number of hypoglycaemic events reported, the power to detect significant differences in hypoglycaemia risk and rates was low. Care should also be taken when extending the current findings to other populations, such as people with type 1 diabetes.

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Conclusions

The 12-month results of EDITION 3 in insulin-*naïve* people with type 2 diabetes demonstrate achievement of glycaemic control in people treated with Gla-300 or Gla-100, accompanied by a lower risk of hypoglycaemia below 3.0 mmol/L (both confirmed or severe and documented symptomatic events) for Gla-300 versus Gla-100. In the context of similarly positive results observed in other EDITION studies of people with type 2 diabetes [8,9], these findings suggest that regardless of the disease stage, long-term treatment with Gla-300 may have benefits over Gla-100.

Disclosure of interest

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Appendix A. Supplementary data

Supplementary materials (Tables S1–S4) associated with this article can be found at http://www.sciencedirect.com at http://dx.doi.org/10.1016/j.diabet.2017.04.007.

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