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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.

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; $\geq$ 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.