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New insulin glargine 300 U/ml versus glargine 100 U/ml in Japanese people with type 2 diabetes using basal insulin and oral antihyperglycaemic drugs: glucose control and hypoglycaemia in a randomized controlled trial (EDITION JP 2)

Y. Terauchi[1], M. Koyama[2], X. Cheng[3], Y. Takahashi[2], M. C. Riddle[4], G. B. Bolli[5] & T. Hirose[6]

[1] *Graduate School of Medicine, Yokohama City University, Yokohama, Japan*
[2] *Sanofi, Tokyo, Japan*
[3] *Sanofi, Beijing, China*
[4] *Oregon Health & Science University, Portland, OR, USA*
[5] *Perugia University Medical School, Perugia, Italy*
[6] *Toho University School of Medicine, Tokyo, Japan*

Aims: To compare the efficacy and safety of insulin glargine 300 U/ml (Gla-300) with glargine 100 U/ml (Gla-100) in Japanese people with type 2 diabetes using basal insulin plus oral antihyperglycaemic drug(s) [OAD(s)].

Methods: The EDITION JP 2 study (NCT01689142) was a 6-month, multicentre, open-label, phase III study. Participants (n = 241, male 61%, mean diabetes duration 14 years, mean weight 67 kg, mean body mass index 25 kg/m^2, mean glycated haemoglobin (HbA1c) 8.02 %, mean basal insulin dose 0.24 U/kg/day) were randomized to Gla-300 or Gla-100, while continuing OAD(s). Basal insulin was titrated to target fasting self-monitored plasma glucose 4.4—5.6 mmol/l. The primary efficacy endpoint was HbA1c change over 6 months. Safety endpoints included hypoglycaemia and weight change.

Results: Gla-300 was non-inferior to Gla-100 for HbA1c reduction [least squares (LS) mean difference 0.10 (95% confidence interval [CI] −0.08, 0.27) %]. The mean HbA1c at month 6 was 7.56 and 7.52 % with Gla-300 and Gla-100, respectively. Nocturnal confirmed (≤3.9 mmol/l) or severe hypoglycaemia risk was 38% lower with Gla-300 versus Gla-100 [relative risk 0.62 (95% CI 0.44, 0.88)]; annualized rates were 55% lower at night [rate ratio 0.45 (95% CI 0.21, 0.96)] and 36% lower at any time [24 h; rate ratio 0.64 (95% CI 0.43, 0.96)]. Severe hypoglycaemia was infrequent. A significant between-treatment difference in weight change favoured Gla-300 [LS mean difference −1.0 (95% CI −1.5, −0.5) kg; p = 0.0003]. Adverse event rates were comparable between groups.

Conclusions: Japanese people with type 2 diabetes using basal insulin plus OAD(s) experienced less hypoglycaemia with Gla-300 than with Gla-100, while glycaemic control did not differ.

Keywords: basal insulin, glycaemic control, insulin analogues, phase III study, randomized trial, type 2 diabetes

Introduction

While type 2 diabetes can initially be controlled in most people with lifestyle modification and oral antihyperglycaemic drug (OAD) treatment, disease progression often leads to a requirement for insulin therapy [1]. Nevertheless, a number of barriers may reduce adherence to insulin regimens, and patients and physicians might be wary of intensifying therapy because of fear of hypoglycaemia [2,3], which probably contributes to the inadequate glycaemic control that is observed in many people [3]. The global prevalence of diabetes is increasing rapidly,

including in Japan, where changing lifestyles have led to a rapid rise in type 2 diabetes over the last few decades [4–6]. There is considerable need, therefore, for improved management strategies that can help to reduce the burden attributable to diabetes.

Since the market authorization of insulin glargine 100 U/ml [Gla-100 (Lantus®; Sanofi, Paris, France)] in 2000 (Gla-100 was licensed in Japan in 2003), long-acting basal insulin analogues have had a considerable positive impact on diabetes management [7]. Nevertheless, quality of life for people with diabetes might be further improved by therapies that can achieve and maintain glycaemic control, lower hypoglycaemia risk and increase injection interval flexibility. New insulin glargine 300 U/ml (Gla-300) may help to address these needs; studies in both Japanese and Western populations [8,9] have shown more stable and prolonged pharmacokinetic and pharmacodynamic profiles with Gla-300 versus Gla-100, and persistence of glycaemic control beyond 24 h in people with type 1 diabetes. Gla-300 was licensed in the USA, Europe and Japan in 2015 (as Toujeo® in the USA and Europe; as Lantus® XR in Japan).

Correspondence to: Yasuo Terauchi, Yokohama City University Graduate School of Medicine, Department of Endocrinology and Metabolism, 3–9 Fukuura, Kanazawa-ku, Yokohama, 236-0004, Japan.
E-mail: terauchi@yokohama-cu.ac.jp

The phase IIIa EDITION programme compared Gla-300 with Gla-100 in several different populations, and has shown that Gla-300 is as effective as Gla-100 in achieving glycaemic control in type 1 and type 2 diabetes [10–14]. In addition, a lower hypoglycaemia risk was observed over 6 months in multinational type 2 diabetes populations treated with Gla-300 combined with mealtime insulin (EDITION 1) or OAD(s) (EDITION 2), and in insulin-naïve people (EDITION 3) [10–12]. The present study, EDITION JP 2 (NCT01689142), investigated the efficacy and safety of Gla-300 versus Gla-100 in Japanese people with type 2 diabetes who were already using basal insulin and OAD(s).

Materials and Methods

Research Design

EDITION JP 2 was a multicentre, randomized, open-label, two-arm, parallel-group, phase III study in Japanese people with type 2 diabetes treated with basal insulin and OAD(s). The study comprised a screening phase, 6-month treatment period, a pre-planned 6-month safety extension and follow-up. Results from the main 6-month treatment period are presented here. The study was approved by appropriate ethics committees and conducted in accordance with Good Clinical Practice [15] and the Declaration of Helsinki [16]. Written informed consent was obtained from all participants before study commencement.

Participants

Adults with type 2 diabetes diagnosed for ≥1 year and treated with basal insulin and OAD(s) for ≥6 months were recruited as outpatients at 22 centres in Japan. The key inclusion criterion was HbA1c ≥7.0 and ≤10.0 % at screening. Exclusion criteria at screening were age <18 years, body mass index (BMI) ≥35 kg/m^2, use of premixed insulins or insulin detemir ≥2 times per day, use of glucagon-like peptide-1 receptor agonists in the previous 3 months, use of an insulin pump within the last 6 months, use of mealtime insulin for ≥10 days in the previous 3 months, severe hypoglycaemia resulting in coma/seizures, and/or hospitalization for diabetic ketoacidosis in the last 6 months.

Randomization and Masking

Participants were randomized (1 : 1) to Gla-300 or Gla-100, stratified by HbA1c [<8.0 or ≥8.0 % (<64 or ≥64 mmol/mol)] and treatment with sulphonylurea/glinide (yes or no) at screening. Owing to the differences in the injection devices, this was an open-label study and blinding was not possible; however, samples taken for measurements relating to efficacy parameters at the central laboratory were anonymized to ensure objective data collection.

Interventions

Participants were trained in the use of glucose meters to monitor their plasma glucose [self-monitored plasma glucose (SMPG)] levels and record them in a diary, and in insulin pen use and the dose titration schedule. Glucose meters

automatically converted the blood glucose measurements into plasma glucose values. Once-daily subcutaneous injections of Gla-300 [using a modified TactiPen® pen injector (Haselmeier GmbH, Zürich, Switzerland)] or Gla-100 [using a SoloSTAR® pen (Sanofi, Paris, France)] were self-administered at the same time each evening (defined as the period from immediately after the evening meal to bedtime). The initial daily dose of Gla-300 or Gla-100 was equal to the total daily basal insulin dose on the day before the baseline visit for participants previously receiving Gla-100 (once or twice daily), once-daily insulin detemir or neutral protamine Hagedorn (NPH) insulin, or 80% of the total daily NPH insulin dose on the day before the baseline visit for participants previously receiving NPH insulin twice daily. Owing to differences in the delivery pen scaling, starting doses of Gla-300 and Gla-100 were rounded down to the nearest 1.5 and 1.0 U, respectively. Basal insulin doses were titrated to a fasting SMPG target of 4.4–5.6 mmol/l (80–100 mg/dl) with adjustments made at least once per week, but not more often than every 3–4 days. Uptitrations of 1.5 or 1.0 U (minimum dose increments possible for each pen) were made for Gla-300 and Gla-100, respectively, when the median fasting SMPG over the previous 3 days was >5.6 and <7.8 mmol/l (>100 and <140 mg/dl) and uptitrations of 3.0 or 2.0 U, respectively, were made for median fasting SMPG ≥7.8 mmol/l (≥140 mg/dl; Table S1). Downtitration of 3.0 U of either treatment was made when median fasting SMPG over the previous 3 days was ≥3.3 and <4.4 mmol/l (≥60 and <80 mg/dl), or at the investigators' discretion when the median fasting SMPG was <3.3 mmol/l (<60 mg/dl) or when >2 symptomatic or any severe hypoglycaemia episodes occurred in the preceding week (Table S1). After week 12, rescue antidiabetic medication could be used at the investigators' discretion if fasting plasma glucose (FPG) and HbA1c could not be lowered below the threshold values, <11 mmol/l (<200 mg/dl) and <8.5 % (<69.4 mmol/mol), respectively. Participants in both groups continued OAD(s) throughout the study, with doses of sulphonylureas/glinides adjusted if ≥2 symptomatic or one severe hypoglycaemic episodes occurred.

Outcomes

In this treat-to-target study, non-inferiority of Gla-300 to Gla-100 was assessed for the primary endpoint, HbA1c change from baseline to month 6. Secondary endpoints included change from baseline to month 6 in laboratory-measured FPG, average pre-injection SMPG (taken ≤30 min before each basal insulin injection), mean eight-point SMPG profile, daily basal insulin dose, and percentage of participants achieving the HbA1c target of <7.0 %. The percentage of participants with FPG <5.6 mmol/l (<100 mg/dl) at month 6 was an exploratory endpoint. Hypoglycaemic events, categorized using the American Diabetes Association definitions [17], were analysed according to the time of day that they occurred [any time of day (24 h) or nocturnal (00:00–05:59 h)] and by study period (full 6-month study period, baseline to week 8 and week 9 to month 6). Briefly, hypoglycaemic categories included: *any hypoglycaemia* (all asymptomatic and symptomatic events whether confirmed by SMPG or not); *documented symptomatic*
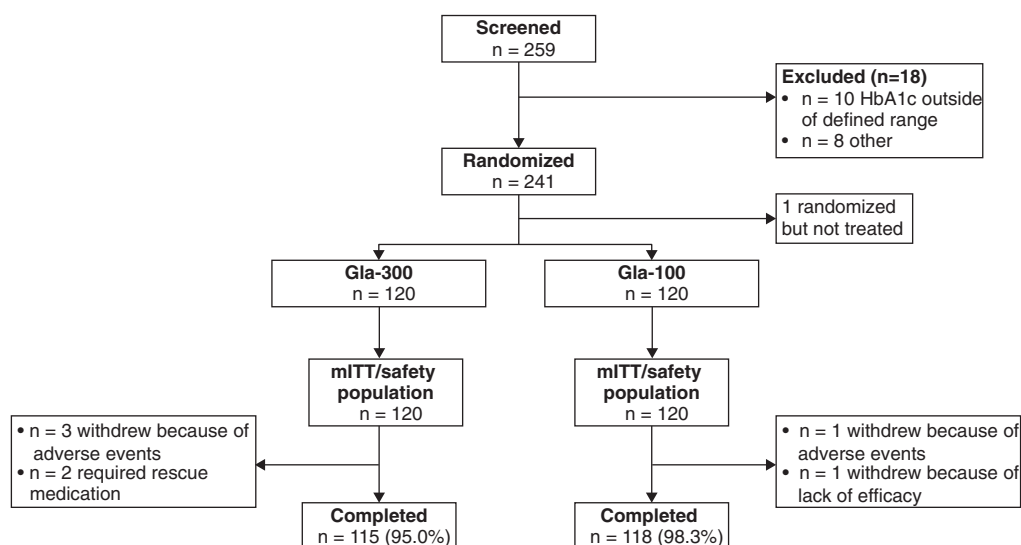
Figure 1. Flow of participants through the main 6-month period of the EDITION JP 2 study: modified intention-to-treat (mITT) and safety populations. Gla-100; insulin glargine 100 U/ml; Gla-300; insulin glargine 300 U/ml; HbA1c, glycated haemoglobin.

hypoglycaemia [symptomatic events with SMPG ≤3.9 mmol/l (≤70 mg/dl)]; *asymptomatic hypoglycaemia* [events without symptoms confirmed by SMPG ≤3.9 mmol/l (≤70 mg/dl)]; *severe hypoglycaemia* (events requiring assistance by another person). *Confirmed or severe hypoglycaemia* included documented symptomatic, asymptomatic and severe events. Hypoglycaemic events at the stricter plasma glucose threshold of <3.0 mmol/l (<54 mg/dl) were analysed separately. Other safety endpoints were occurrence of injection site and hypersensitivity reactions, changes in vital signs (including body weight), and occurrence of other adverse events (AEs).

Data Analysis and Statistics

The sample size was planned to ensure sufficient power for the primary endpoint; a sample of 240 evaluable participants was estimated to give >90% power for the upper confidence limit of the difference between the two treatments in change from HbA1c from baseline to month 6 not to exceed 0.4 % (4.4 mmol/mol), assuming the standard deviation (SD) was 0.90 % (9.8 mmol/mol), for a true difference of 0.0 %, and that all participants were evaluable.

Efficacy endpoints were analysed using the modified intention-to-treat (mITT) population, which included all randomized participants who received ≥1 dose of study treatment, and had a baseline and at least one subsequent assessment for any of the efficacy variables. For the primary endpoint, non-inferiority of Gla-300 to Gla-100 would be shown if the upper limit of the two-sided confidence interval (CI) for the difference in mean change in HbA1c from baseline was lower than the predefined margin of 0.4 %.

The safety population included all participants randomized and exposed to ≥1 dose of study treatment. Hypoglycaemia was analysed as the percentage of participants experiencing ≥1 event (with relative risk) and the number of events per participant-year (with rate ratio). Between-treatment differences in body weight and annualized rates of hypoglycaemia

were analysed post hoc. Further details on statistical analyses are provided in Appendix S1. The significance level was defined as a two-sided p-value <0.05.

Results

Participants

Participants were enrolled from September 2012 and the last participant completed the 6-month treatment period in November 2013. Of 259 individuals screened, 241 were randomized; 121 to Gla-300 and 120 to Gla-100. One participant left the Gla-300 group before receiving any study treatment (Figure 1); the remaining 240 participants were included in the mITT and safety populations. The baseline characteristics of the randomized population did not differ between the Gla-300 and Gla-100 groups (Table 1); mean age was 61 years and 61% of participants were male. Mean body weight (67 kg), BMI (25 kg/m^2) and duration of type 2 diabetes (14 years) also did not differ between the groups. Most participants were using insulin glargine before the study commenced, nearly all with a once-daily regimen. Biguanides, sulphonylureas and dipeptidyl peptidase-4 inhibitors were continued during the study by 57% (136/240), 52% (125/240), and 42% (101/240) of participants, respectively. From the Gla-300 and Gla-100 groups, 5.0 and 1.7%, respectively, did not complete 6 months of treatment (Figure 1). Discontinuation because of AEs was reported for three participants in the Gla-300 group [duodenal ulcer haemorrhage (serious AE; discontinued on day 50); generalized pruritus (AE; discontinued on day 116); gastric ulcer (serious AE; discontinued on day 29)] and one participant in the Gla-100 group [tibia fracture (serious AE; discontinued on day 49)]. Discontinuation because of lack of efficacy was reported for none of the participants in the Gla-300 group and one participant in the Gla-100 group.

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Table 1. Baseline characteristics of the randomized population.

	Gla-300 (N = 121)	Gla-100 (N = 120)	All (N = 241)
Age, mean (s.d.) years	61.1 (10.8)	60.5 (12.0)	60.8 (11.4)
Male, n (%)	77 (63.6)	70 (58.3)	147 (61.0)
Duration of type 2 diabetes, mean (s.d.) years	14.0 (8.0)	13.9 (8.7)	14.0 (8.3)
Body weight, mean (s.d.) kg	67.4 (13.6)	65.9 (12.8)	66.7 (13.2)
BMI, mean (s.d.) kg/m^2	25.7 (4.0)	24.8 (3.6)	25.3 (3.8)
C-peptide, mean (s.d.) nmol/l	0.38 (0.28)	0.32 (0.20)	0.35 (0.24)
FPG, mean (s.d.) mmol/l	7.7 (2.1)*	7.4 (1.9)†	7.6 (2.0)‡
HbA1c, mean (s.d.)			
mmol/mol	63.8 (7.9)	64.6 (8.4)	64.1 (8.1)
%	7.99 (0.72)	8.06 (0.77)	8.02 (0.74)
Previous basal insulin type, n (%)			
Insulin glargine	118 (98.3)*	110 (91.7)*	228 (95.0)§
NPH insulin	0 (0.0)*	0 (0.0)*	0 (0.0)§
Insulin detemir	2 (1.7)*	10 (8.3)*	12 (5.0)§
Previous basal insulin daily injection number, n (%)			
Once daily	118 (98.3)*	116 (96.7)*	234 (97.5)§
Twice daily	2 (1.7)*	4 (3.3)*	6 (2.5)§
Previous daily basal insulin dose, mean (s.d.)			
U/kg/day	0.25 (0.14)†	0.24 (0.12)†	0.24 (0.13)¶
U/day	16.8 (10.5)†	16.1 (8.8)†	16.4 (9.7)¶
Previous OAD treatment**, n (%)			
Biguanides	70 (57.9)	71 (59.2)	141 (58.5)
Sulphonylureas	64 (52.9)	66 (55.0)	130 (53.9)
Dipeptidyl peptidase-4 inhibitors	51 (42.1)	53 (44.2)	104 (43.2)
α-glucosidase inhibitors	43 (35.5)	26 (21.7)	69 (28.6)
Thiazolidinediones	12 (9.9)	9 (7.5)	21 (8.7)
Glinides	11 (9.1)	12 (10.0)	23 (9.5)

BMI, body mass index; FPG, fasting plasma glucose; Gla-100; insulin glargine 100 U/ml; Gla-300; insulin glargine 300 U/ml; HbA1c, glycated haemoglobin; OAD, oral antihyperglycaemic drug; NPH, neutral protamine Hagedorn; s.d., standard deviation.

*N = 120.

†N = 119.

‡N = 239.

§N = 240.

¶N = 238.

**Therapies used within 3 months before the screening visit and from screening to the first injection of test medication.

Glycaemic Control

The decrease in HbA1c from baseline to month 6 did not differ between treatment groups (Figure 2A and Table S2). The least squares (LS) mean difference between the groups at month 6 was 0.10 (95% CI −0.08 to 0.27) % [1.1 (95% CI −0.9 to 3.0) mmol/mol], confirming non-inferiority of Gla-300 for the primary endpoint. No between-treatment difference was noted for the decrease in laboratory-measured FPG across the study period (Figure 2B and Table S2). The LS mean difference between Gla-300 and Gla-100 at month 6 was 0.04 (95% CI −0.40 to 0.49) mmol/l [0.8 (95% CI −7.3 to 8.8) mg/dl].

The percentages of participants achieving the HbA1c target of <7.0 % for Gla-300 and Gla-100 were 25% (30/120) and 24% (29/120), respectively, with 23% (28/120) and 23% (27/120) of participants achieving the target without any confirmed
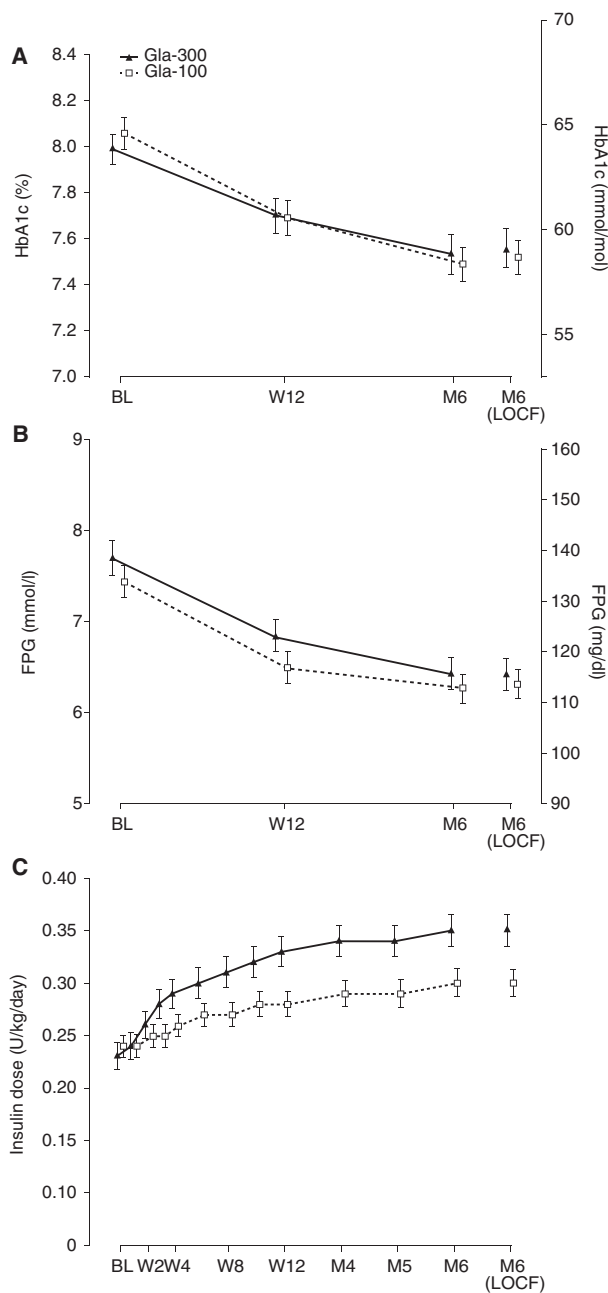

Figure 2. Glycaemic control and insulin dose endpoints across the 6-month study period [all modified intention-to-treat (mITT) population]. (A) glycated haemoglobin (HbA1c). (B) Laboratory-measured fasting plasma glucose (FPG). (C) Daily basal insulin dose; data are shown as mean ± standard error. BL, baseline; W, week; M, month; Gla-100; insulin glargine 100 U/ml; Gla-300; insulin glargine 300 U/ml.

[<3.0 mmol/l (<54 mg/dl)] or severe hypoglycaemic events (Table S2). In addition, 34% (40/118) and 40% (48/119) of participants achieved the FPG target of <5.6 mmol/l (<100 mg/dl) at month 6 with Gla-300 and Gla-100, respectively (Table S2).

At month 6, mean eight-point SMPG profiles showed a decrease in SMPG from baseline at all time points for both treatments, but relatively small differences were observed between treatments (Figure S1). Between baseline and month 6,

average pre-injection SMPG values increased in both treatment groups. LS mean change (standard error) from baseline to month 6 was 0.7 (0.29) mmol/l [13 (5.2) mg/dl] with Gla-300 and 0.9 (0.29) mmol/l [17 (5.2) mg/dl] with Gla-100 (Table S2).

Change in Basal Insulin Dose

Basal insulin doses increased from 16 U/day (0.23 U/kg/day) to 24 U/day (0.35 U/kg/day) with Gla-300 and from 16 U/day (0.24 U/kg/day) to 20 U/day (0.30 U/kg/day) with Gla-100 over 6 months (Figure 2C). Based on U/kg/day values, 92% of the total change in Gla-300 dose and 83% of the total change in Gla-100 dose had occurred by month 4.

Hypoglycaemia

During the 6-month treatment period 682 hypoglycaemic events were reported in the Gla-300 group and 1066 events in the Gla-100 group (Table S3).

Confirmed [≤3.9 mmol/l (≤70 mg/dl)] or Severe Hypoglycaemia. Fewer participants receiving Gla-300 versus Gla-100 experienced ≥1 nocturnal (00:00–05:59 h) confirmed or severe hypoglycaemic event [28% (34/120) vs 46% (55/120)] over 6 months, with the greatest difference between groups observed between week 9 and month 6 [25% (30/118) vs 44% (52/119); Figure 3A and Table S4]. Annualized rates of nocturnal hypoglycaemia were also lower with Gla-300 than Gla-100 (two vs five events per participant-year; p = 0.040; Figure 3A and B and Table S3). Over the first 12 weeks, the cumulative mean number of nocturnal events per participant did not differ between the two treatments, whereas it was lower with Gla-300 over the remainder of the 6-month period (Figure 3C).

Over 6 months, a numerically lower percentage of participants using Gla-300 than Gla-100 experienced ≥1 confirmed or severe hypoglycaemic event at any time of day [24 h; 65% (78/120) vs 77% (92/120)], with a significant difference observed during the first 8 weeks of the study [38% (45/120) vs 55% (66/120); Figure 3A and Table S4]. A 36% rate reduction was also observed in the number of hypoglycaemic events per participant-year at any time of day (24 h; 10 vs 17 events per participant-year; p = 0.030; Figure 3A and D and Table S3) and the cumulative mean number of events per participant was lower over the entire 6-month study period with Gla-300 than with Gla-100 (Figure 3E).

Distribution of Hypoglycaemic Events Over 24 h. The pattern of confirmed or severe hypoglycaemic events shown by time of day (Figure 3F) suggests a benefit of Gla-300 over Gla-100 for reducing hypoglycaemia risk between 00:00 and 13:59 h, with the most pronounced between-treatment difference observed between 02:00 and 06:59 h.

Other Hypoglycaemia Categories. Similar patterns of reduction in hypoglycaemic events to those described above were observed across other hypoglycaemia definitions (Figure 3A and Tables S3 and S4).

Severe Hypoglycaemia. Severe hypoglycaemia was infrequent during the 6-month period, with 2.5% (3/120) of participants receiving Gla-300 and 1.7% (2/120) receiving Gla-100 experiencing ≥1 event at any time of day (24 h; Table S4), corresponding to 0.05 and 0.03 events per participant-year, respectively (Table S3). During the 6-month on-treatment period, 0.8% (1/120) of participants receiving Gla-300 and 1.7% (2/120) receiving Gla-100 experienced ≥1 severe hypoglycaemic event during the night (annualized rates of 0.02 and 0.03 events per participant-year, respectively).

Body Weight

The LS mean change (standard error) in weight between baseline and month 6 was −0.6 (0.2) and 0.4 (0.2) kg for the Gla-300 and Gla-100 groups, respectively. At month 6 there was a significant between-treatment difference in weight change, LS mean difference (95% CI) −1.0 (−1.5 to −0.5) kg, p = 0.0003 (Figure S2).

Adverse Events

During the study, comparable numbers of participants experienced treatment-emergent AEs with Gla-300 and Gla-100 [58% (70/120) vs 57% (68/120)]. Treatment-emergent severe AEs were infrequent, occurring in 4.2% (5/120) and 3.3% (4/120) of participants using Gla-300 and Gla-100, respectively. Three (2.5%) participants receiving Gla-300 and one (0.8%) receiving Gla-100 permanently discontinued therapy owing to treatment-emergent AEs. The most frequently reported AEs are shown in Table S5.

Injection site and hypersensitivity reactions, were reported by 1.7% (2/120) and 9.2% (11/120) of participants receiving Gla-300, and 0.8% (1/120) and 8.3% (10/120) of participants receiving Gla-100, respectively. None of the events was considered serious. No deaths were recorded as a result of either treatment, but one participant (0.8%) receiving Gla-100 experienced a major adverse cardiovascular event.

Discussion

Studies in several Western populations with type 2 diabetes in the EDITION programme (EDITION 1, 2 and 3) have shown no difference in glycaemic control but less hypoglycaemia with Gla-300 than Gla-100 [10–12]. The results from the present study are consistent with previous EDITION studies and extend these findings to Japanese people with type 2 diabetes.

In the present study, Gla-300 was non-inferior to Gla-100 for the primary endpoint, HbA1c reduction over 6 months. Similarly, no between-treatment differences were observed in the secondary and exploratory glycaemic control endpoints. Furthermore, the changes in HbA1c and FPG levels, and the proportions of participants attaining glycaemic targets in the present study were consistent with treat-to-target studies in Japanese populations using other basal insulin analogues [18–20]; however, the eight-point SMPG profiles showed a greater rise in SMPG after meals, particularly after dinner, in the present study compared with EDITION 1, 2 and 3. This difference may be partially explained by greater impairment of β-cell
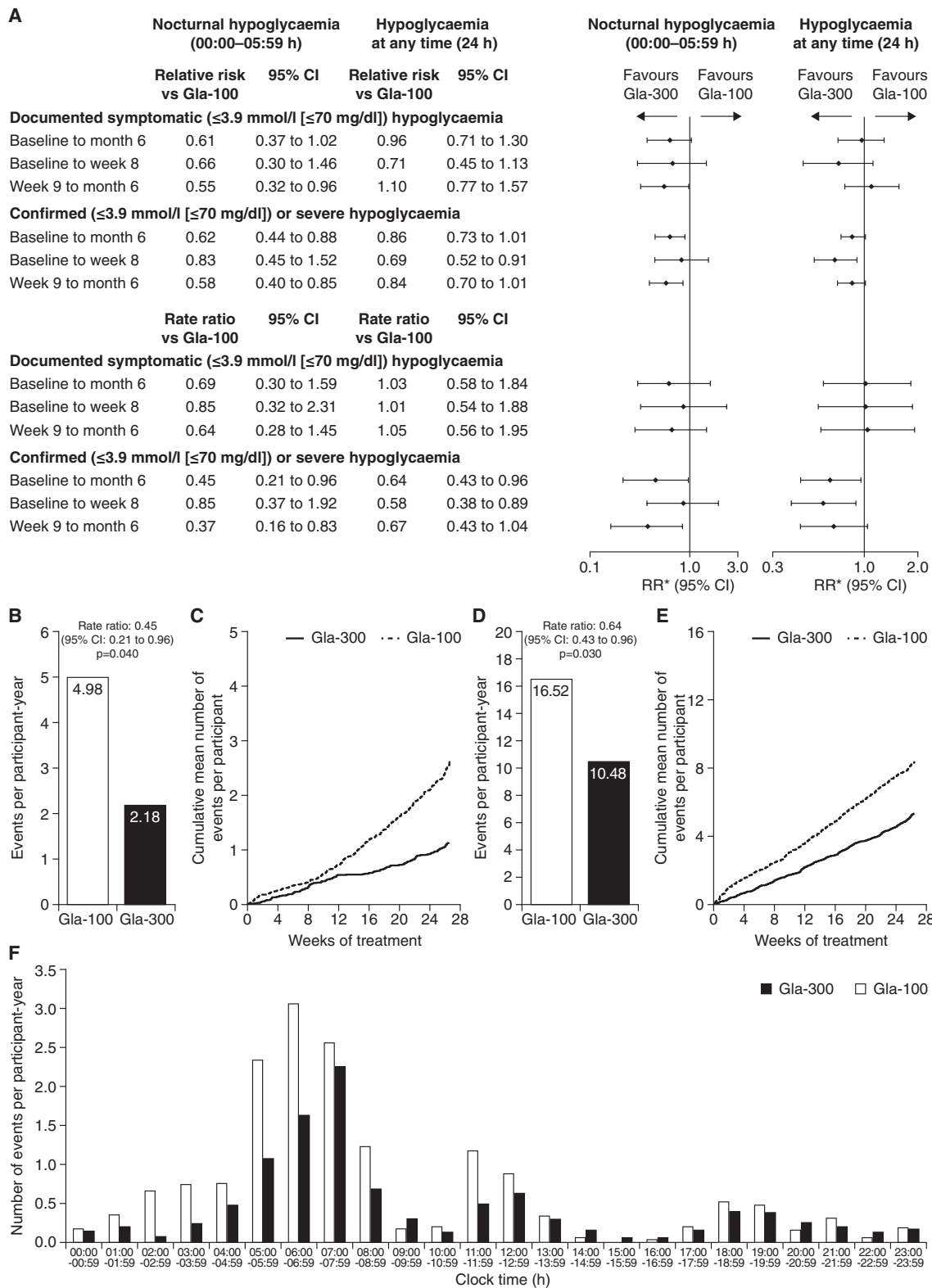
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	Nocturnal hypoglycaemia (00:00–05:59 h)		Hypoglycaemia at any time (24 h)	
	Relative risk vs Gla-100	95% CI	Relative risk vs Gla-100	95% CI
Documented symptomatic (≤3.9 mmol/l [≤70 mg/dl]) hypoglycaemia				
Baseline to month 6	0.61	0.37 to 1.02	0.96	0.71 to 1.30
Baseline to week 8	0.66	0.30 to 1.46	0.71	0.45 to 1.13
Week 9 to month 6	0.55	0.32 to 0.96	1.10	0.77 to 1.57
Confirmed (≤3.9 mmol/l [≤70 mg/dl]) or severe hypoglycaemia				
Baseline to month 6	0.62	0.44 to 0.88	0.86	0.73 to 1.01
Baseline to week 8	0.83	0.45 to 1.52	0.69	0.52 to 0.91
Week 9 to month 6	0.58	0.40 to 0.85	0.84	0.70 to 1.01
	Rate ratio vs Gla-100	95% CI	Rate ratio vs Gla-100	95% CI
Documented symptomatic (≤3.9 mmol/l [≤70 mg/dl]) hypoglycaemia				
Baseline to month 6	0.69	0.30 to 1.59	1.03	0.58 to 1.84
Baseline to week 8	0.85	0.32 to 2.31	1.01	0.54 to 1.88
Week 9 to month 6	0.64	0.28 to 1.45	1.05	0.56 to 1.95
Confirmed (≤3.9 mmol/l [≤70 mg/dl]) or severe hypoglycaemia				
Baseline to month 6	0.45	0.21 to 0.96	0.64	0.43 to 0.96
Baseline to week 8	0.85	0.37 to 1.92	0.58	0.38 to 0.89
Week 9 to month 6	0.37	0.16 to 0.83	0.67	0.43 to 1.04

Figure 3. Confirmed [≤3.9 mmol/l (≤70 mg/dl)] or severe hypoglycaemia over the 6-month study period (safety population). (A) Relative risk of experiencing ≥1 hypoglycaemic event and rate ratio of hypoglycaemic events during the night (00:00–05:59 h) and at any time of day (24 h). (B) Nocturnal (00:00–05:59 h) annualized rates (events per participant-year). (C) Cumulative mean number of nocturnal (00:00–05:59 h) events per participant. (D) Annualized rates (events per participant-year) at any time of day (24 h). (E) Cumulative mean number of events at any time of day (24 h) per participant. (F) Number of confirmed [≤3.9 mmol/l (≤70 mg/dl)] or severe hypoglycaemic events per participant-year by time of the day. CI, confidence interval; Gla-100; insulin glargine 100 U/ml; Gla-300; insulin glargine 300 U/ml; *RR, relative risk/rate ratio.

function in the Japanese as compared to the Western population [21].

As in the other EDITION studies, Gla-300 treatment was associated with less hypoglycaemia compared with Gla-100. Overall, the between-treatment difference in confirmed [≤3.9 mmol/l (≤70 mg/dl)] or severe hypoglycaemia, favouring Gla-300, was most pronounced at night. Occurrence of hypoglycaemia thus defined at any time of day (24 h) was also reduced with Gla-300 versus Gla-100 across the entire 6 months, including the first 8 weeks, when most of the basal insulin titration occurred. When analysed by clock time over 24 h, the lower frequency of hypoglycaemia with Gla-300 extended beyond the night and into the daytime hours, with a trend for fewer events than with Gla-100 between 00:00 and 13:59 h. This is consistent with the more stable and prolonged action of Gla-300 previously described in pharmacokinetic and pharmacodynamic studies [8,9], and supports the hypoglycaemia risk reduction beyond 06:00 h already reported in Western type 2 diabetes populations [11,12]. This reduction in hypoglycaemia risk may help to reduce the barrier to both initiating and maintaining insulin therapy, which is often related to fear of hypoglycaemia in people with type 2 diabetes.

The proportion of participants receiving sulphonylurea therapy before randomization was higher in the present study than in EDITION 2, which was the global EDITION study most similar in design and which also enrolled participants previously receiving basal but not mealtime insulin. This reflects differences in regional clinical practice, with sulphonylurea therapy more commonly used for type 2 diabetes in Japan [22]. It is noteworthy that approximately half the participants in the present study continued sulphonylurea therapy; this was not permitted per protocol in EDITION 2. Nevertheless, annualized rates of hypoglycaemia were not higher overall in the present study than in EDITION 2 [11]. The potential impact of sulphonylurea use on hypoglycaemia rates in Japanese participants receiving Gla-300 warrants further investigation.

The annualized rate of nocturnal confirmed [≤3.9 mmol/l (≤70 mg/dl)] or severe hypoglycaemia was 55% lower with Gla-300 than Gla-100 in the Japanese population studied here, which was similar to EDITION 2 (48% lower with Gla-300 than Gla-100); however, the corresponding annualized rates for such events at any time of day (24 h) were 36% lower with Gla-300 versus Gla-100 in the present study compared with a 23% difference in EDITION 2. Why these findings differed between the two studies is unknown, but there are plausible possibilities. One relates to the large differences in body weight and BMI between the populations. At enrolment, mean body weight was ~67 kg in this study and 98 kg in EDITION 2, with mean values for BMI of 25 and 38 kg/m^2, respectively. Not surprisingly, the participants in the present study, who had lower body weight and BMI, required lower doses of insulin than those in EDITION 2; 24 U/day with Gla-300 and 20 U/day with Gla-100 in this study versus 91 and 82 U/day in EDITION 2. The potential relevance of these differences lies in previous observations that lower BMI and lower insulin dose requirement are independent risk factors for hypoglycaemia with Gla-100 [23]. Hence, in a type 2 diabetes population with lower BMI and low basal insulin requirement, such as the Japanese people in the present study, the advantage of Gla-300 may be even more evident than in the Western populations studied in the EDITION programme.

In line with observations from other studies in the EDITION programme, a greater relative dose of Gla-300 than Gla-100 (17%) was required in the present study, although glycaemic control did not differ between treatments. This may point towards slower absorption from the more compact subcutaneous depot resulting in greater local degradation and lower bioavailability.

Previous studies in Japanese type 2 diabetes populations have shown increases in body weight with Gla-100 and insulin degludec [18,19]. In the present study, as in other EDITION studies in type 2 diabetes populations [11,12], less weight gain was observed with Gla-300 (−0.6 kg) than with Gla-100 (+0.4 kg). The reason for this between-treatment difference is unknown but warrants further investigation in this Japanese population.

As expected given the clinical experience with Gla-100 [24] and the fact that Gla-300 and Gla-100 contain the same insulin glargine molecule, Gla-300 was well tolerated over the 6-month study period, with no new safety concerns apparent.

The strengths of the present study include adequate power to show non-inferiority of Gla-300 and sufficient duration to allow observation of any effects of switching to Gla-300. The main limitation was the open-label design, which was unavoidable owing to use of different injection devices and volumes for the Gla-300 and Gla-100 treatments, and the resulting possibility of unequal titration behaviour.

In conclusion, as previously shown in Western type 2 diabetes populations, there was no between-treatment difference in glycaemic control, with less hypoglycaemia and weight gain with Gla-300 versus Gla-100, in this population of Japanese people with type 2 diabetes using basal insulin plus OAD(s). Risk of hypoglycaemia at any time (24 h) was lower with Gla-300 than with Gla-100 across the entire study, particularly at night, and during the first 8 weeks of treatment.

Acknowledgements

Conflict of Interest

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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. Mean eight-point self-monitored plasma glucose profiles at baseline and month 6 (LOCF) in modified intention-to-treat population.

Figure S2. Change in body weight over the 6-month study period (safety population).

Table S1. Basal insulin adjustment schedule during the 6-month study period.

Table S2. Glycaemic responses over the 6-month study period (modified intention-to-treat population).

Table S3. Number of events (events per participant-year) for hypoglycaemia at all definitions across the 6-month study period (safety population).

Table S4. Number (percentage) of participants experiencing ≥1 hypoglycaemic event at all definitions over 6 months (safety population).

Table S5. Most commonly experienced treatment-emergent adverse events (TEAEs), treatment-emergent severe adverse events and TEAEs leading to permanent treatment discontinuation during the 6-month study period (safety population).

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