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Efficacy and safety of insulin glargine 300 U/mL versus insulin glargine 100 U/mL in Asia Pacific insulin-naïve people with type 2 diabetes: The EDITION AP randomized controlled trial

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Abstract

Aim: To compare the efficacy and safety of Gla-300 versus Gla-100 in insulin-naïve people with type 2 diabetes in Asia Pacific.

Materials and Methods: In this open-label, randomized, active-controlled, 26-week study, insulin-naïve participants with type 2 diabetes inadequately controlled with non-insulin antihyperglycaemic drugs were randomized (2:1) to Gla-300 or Gla-100. The initial daily dose of basal insulin was 0.2 U/kg and was adjusted at least weekly for 8–12 weeks to a target fasting self-monitored plasma glucose (SMPG) of 4.4–5.6 mmol/L.

Results: Of the 604 participants randomized, 570 (Gla-300, n = 375; Gla-100, n = 195) completed the study. Non-inferiority of Gla-300 versus Gla-100 in HbA1c reduction from baseline to week 26 was confirmed. In the Gla-300 and Gla-100 groups, 51.1% and 52.2% of participants achieved the HbA1c target of <7.0% (rate ratio [95% CI]: 0.98 [0.84 to 1.14]) and 19.1% and 21.9% achieved the target without hypoglycaemia during the last 12 weeks of treatment (rate ratio [95% CI]: 0.87 [0.63 to 1.20]). Changes in fasting plasma glucose and 24-hour average eight-point SMPG were comparable between groups. Incidence of hypoglycaemia at any time of day was similar between treatment groups at week 26, but incidence of any nocturnal hypoglycaemia was numerically lower with Gla-300 than Gla-100 over the initial 12-week titration period and 26-week on-treatment period. Rates of adverse events were similar between groups and low for serious adverse events.

Conclusions: Glycaemic control of Gla-300 is non-inferior to Gla-100 with a similar or lower incidence and proportion of hypoglycaemia in people with type 2 diabetes in Asia Pacific, reinforcing the results in the global EDITION programme.

KEYWORDS

basal insulin, glycaemic control, hypoglycaemia, insulin analogues, insulin therapy, population study

1 | INTRODUCTION

Based on the 2017 International Diabetes Federation Global Diabetes Atlas, the Asia Pacific region has a high burden of diabetes.[1] China had the highest number of people with diabetes globally (114 million) and the highest treatment costs (110 billion international dollars). South Korea and Taiwan had approximately 3.5 and 2 million people with diabetes, respectively. However, these figures are probably an underestimate as it is believed that 54%–58% of people with diabetes in the Asia Pacific region are currently undiagnosed.[1]

Achieving glycaemic control is important for reducing microvascular and macrovascular long-term complications.[2] Local guidelines for glycaemic targets vary between regions. Guidelines of the Chinese Diabetes Society and the Chinese Taipei Diabetes Association recommend a target HbA1c of <7.0% and the Korean Diabetes Association recommend an HbA1c target of <6.5%.[3-5] Rates of glycaemic control are low in these Asia Pacific countries, with around one in three patients in China and Taiwan achieving an HbA1c of <7.0% and around one in four patients in Korea achieving an HbA1c of <6.5%.[6-9]

Many people with type 2 diabetes (T2D) may require basal insulin therapy to achieve glycaemic control as their disease progresses. However, some people delay initiating insulin therapy because of a variety of patient and physician barriers, including fear of hypoglycaemia, burdensome regimens, and insufficient access and/or communication with a general practitioner.[10] The majority of people with T2D in China delayed initiation of basal insulin,[11] and had at initiation a mean HbA1c of 9.6% (81 mmol/mol).[12] Barriers can also cause individuals to discontinue basal insulin treatment regimens.[12] Baseline characteristics can vary between populations, such as the large difference in mean body mass index (BMI) (34.8 vs. 25.3 kg/m^2) and treatment with oral antihyperglycaemic drugs such as sulphonylureas (1.2% vs. 53.9%) between Western populations in EDITION 2 and a Japanese population in EDITION JP 2 of patients with T2D; therefore it is important to investigate efficacy and safety outcomes in a variety of populations.[13,14] Given the large diabetes population in the Asia Pacific region, it is important to perform assessments in these populations.

Insulin glargine 300 U/mL (Gla-300) is a second-generation basal insulin analogue, which has a more stable and prolonged pharmacokinetic and pharmacodynamic (PK/PD) profile compared with the first-generation basal insulin analogue, insulin glargine 100 U/mL (Gla-100).[15] Results from the EDITION treat-to-target clinical trial programme conducted in Europe, North and South America, Africa and Japan showed that Gla-300 provided similar glycaemic control with lower hypoglycaemia risk versus Gla-100 in people with T2D.[13,14,16-22]

Comparative clinical trial data of insulin glargine in the Asia Pacific region are limited. The aim of the EDITION AP treat-to-target trial was to compare the efficacy and safety of Gla-300 versus Gla-100 in insulin-naïve people with T2D not adequately controlled with non-insulin antihyperglycaemic drugs in the Asia Pacific region, including China, South Korea and Taiwan.

2 | METHODS

2.1 | Study design and participants

EDITION AP (NCT02855684) was a multicentre, open-label, randomized, active-controlled, two-arm, parallel-group, 26-week, treat-to-target, non-inferiority study, in adult (aged ≥18 years) insulin-naïve participants with T2D who were not adequately controlled with non-insulin antihyperglycaemic agents. The study began on August 24, 2016 and was completed on August 6, 2018. The main exclusion criteria included HbA1c <7.0% (<53 mmol/mol) or >11% (>97 mmol/mol) at screening, T2D for less than 1 year, less than 6 months non-insulin antihyperglycaemic drugs or current/previous insulin use. Other key exclusion criteria are shown in Table S1.

2.2 | Interventions

Participants were randomized in a 2:1 ratio to once-daily Gla-300 or Gla-100. Randomization was stratified by HbA1c values at screening (<8.0% vs. ≥8.0%), use of sulphonylurea or glinides (yes vs. no) and geographical region (non-China vs. China). Treatment kits were randomized and allocated using a centralized allocation scheme (interactive voice/web response system).

Both insulins were titrated to achieve glycaemic targets according to the same titration algorithm (Table S2).

The initial daily dose of basal insulin in both treatment groups was 0.2 U/kg. Dose was adjusted at least weekly but no more than every 3 days, to a target fasting self-monitored plasma glucose (SMPG) of 4.4–5.6 mmol/L (80–100 mg/dL) while avoiding hypoglycaemia, with best efforts made to complete titration within the initial 8–12 weeks. Dose adjustments were based on median fasting SMPG values from the last three measurements, including the day of titration.

Background therapies were not changed during the study unless safety concerns necessitated dose reduction or discontinuation. The study was approved by local ethics committees and was conducted in accordance with the Declaration of Helsinki and the International Conference on Harmonization guidelines for Good Clinical Practice. All participants provided written informed consent.

2.3 | Outcomes

The primary endpoint in EDITION AP was change in HbA1c from baseline to week 26. Secondary efficacy outcomes included: proportion (%) of participants achieving target (HbA1c <7%) at week 26 and those achieving the target at week 26 without any hypoglycaemia during the last 12 weeks of the treatment period; incidence of patients with ≥1 confirmed (≤3.9 mmol/L [≤70 mg/dL]) or severe hypoglycaemia event at any time of day (24 hours) or at night (00:00–05:59 hours); change in fasting plasma glucose (FPG), eight-point SMPG, mean 24-hour plasma glucose (PG), variability of mean

24-hour PG and daily basal insulin dose from baseline to week 26; and treatment adherence.

Safety endpoints included incidence and rates of hypoglycaemia occurring at any time of day (24 hours) or during the night (00:00–05:59 hours), based on the definitions recommended by the American Diabetes Association 2005 Working Group on Hypoglycaemia,[23] and adverse events (AEs).

2.4 | Data analysis and statistics

A sample size of 600 participants (Gla-300 [n = 400] and Gla-100 [n = 200]) was chosen to ensure with >94% power that the upper confidence limit of the two-sided 95% confidence interval (CI) for the mean difference between treatments would not exceed the non-inferiority margin (0.4% HbA1c), assuming that the standard deviation (SD) is 1.3% and the true difference in HbA1c between treatments is 0.

The primary efficacy endpoint and all secondary efficacy endpoints were examined in the modified intent-to-treat (mITT) population, defined as all randomized participants who received ≥1 dose of the study drug and had a baseline and at least one postbaseline assessment of any primary or secondary efficacy variable. Safety endpoints were assessed in the safety population, defined as all participants randomized and exposed to at least one dose of the study drug.

Primary efficacy was examined using an analysis of covariance (ANCOVA) model with treatment, randomization strata of screening HbA1c (<8.0%; ≥8.0%), use of sulphonylurea or glinides (yes; no) and geographical region (non-China; China) as fixed effects, and HbA1c baseline value as a covariate. Differences between treatments and two-sided 95% CIs were estimated within the ANCOVA. A sequential stepwise closed testing approach was used to assess non-inferiority and subsequently the superiority of Gla-300 versus Gla-100 for the primary endpoint. The first step determined non-inferiority between the two treatments (shown if the upper bound of the two-sided 95% CI of the difference in mean HbA1c change from baseline to endpoint between treatments was <0.4%). If non-inferiority was shown, the following selected secondary efficacy endpoints and primary endpoint were tested in the following prioritized order: superiority in incidence of patients with at least one hypoglycaemia from baseline to endpoint; superiority in incidence of patients with at least one nocturnal hypoglycaemia from baseline to endpoint; superiority in change in HbA1c from baseline to endpoint. Testing stopped when an endpoint was found to be non-significant at the one-sided $\alpha = 0.025$ level.

Missing data were imputed using a last observation carried forward (LOCF) method. Several sensitivity analyses of HbA1c change were performed including using a mixed model or repeated measures based on all study visits to assess the impact of missing data and rescue medications.

The proportion of participants experiencing hypoglycaemic events was compared between treatment groups using a Cochran–Mantel–Haenszel method; as were the categorical target achievement outcomes. Annualized event rates of hypoglycaemia per patient-year were compared using a negative binomial model. Insulin dose, body weight and incidence of AEs were analysed descriptively.

3 | RESULTS

3.1 | Participant disposition

Of the 802 individuals screened, 198 (24.7%) failed screening (Figure S1); the most common reason was a failure to meet the inclusion criterion related to the HbA1c range (98 participants [12.2%]). In total, 604 people with T2D (Gla-300 [n = 401] and Gla-100 [n = 203]) were randomized in 52 centres in China, South Korea and Taiwan; the greatest proportion of participants were from China (n = 474; 78.5%). Of the 604 participants randomized, 598 participants were exposed to the study drug and were included in the mITT and safety populations, and 570 participants completed the study. Treatment was adhered to on 99% of days in both treatment groups.

3.2 | Baseline characteristics

The demographic and baseline characteristics were similar in the two treatment groups (Table 1). The mean (SD) age was 58.3 (9.8) years and the majority (72.2%) of participants were aged <65 years. Overall, 5.5% of participants had moderate or severe renal impairment, with an estimated glomerular filtration rate (eGFR) below 60 mL/min/1.73 m^2, and 13.7% had diabetic nephropathy.

3.3 | Efficacy

The primary endpoint was met, with non-inferiority of Gla-300 versus Gla-100 in HbA1c reduction from baseline to week 26 being confirmed. Mean (SD) HbA1c was similar at baseline in both treatment groups (8.6% [0.9%] or 70.5 [9.8] mmol/mol with Gla-300 and 8.5% [1.0%] or 69.3 [10.9] mmol/mol with Gla-100) and decreased to 7.0% (0.8%) (53.0 [8.7] mmol/mol) in both groups (least squares [LS] mean difference 0.02% [95% CI: −0.10% to 0.14%] or 0.2 mmol/mol [95% CI: −1.1 to 1.5 mmol/mol]; Table 2, Figure 1A). The greatest between-visit reductions in HbA1c were during the first 12 weeks of treatment with LS mean (standard error [SE]) reductions of 1.4% (0.0%) (15.3 [0.0] mmol/mol) with both Gla-300 and Gla-100 (mean difference 0.01% [95% CI: −0.10% to 0.12%]; 0.11 mmol/mol [95% CI: −1.10 to 1.31 mmol/mol]).

No between-group differences were observed in the main secondary endpoints of the proportion of participants experiencing ≥1 confirmed (≤3.9 mmol/L [≤70 mg/dL]) or severe hypoglycaemic event at any time of day or at night (data not shown; $P > 0.05$ for both). As superiority of Gla-300 versus Gla-100 was not shown for the proportion of participants experiencing ≥1 confirmed (≤3.9 mmol/L [≤70 mg/dL]) hypoglycaemia event at any time of day, superiority of HbA1c reductions was not assessed.

TABLE 1 Baseline characteristics (randomized population)

Baseline characteristics	Gla-300 (N = 401)	Gla-100 (N = 203)	Total (N = 604)
Mean age, years	58.5 ± 9.6	57.9 ± 10.2	58.3 ± 9.8
Gender, % (male/female)	58.0/42.0	53.0/47.0	57.0/43.0
Mean BMI, kg/m^2	25.2 ± 3.2	25.3 ± 3.2	25.2 ± 3.2
Country/region from which participant enrolled, n (%)			
China	315 (78.6)	159 (78.3)	474 (78.5)
South Korea	77 (19.2)	34 (16.7)	111 (18.4)
Taiwan	9 (2.2)	10 (4.9)	19 (3.1)
Mean type 2 diabetes duration, years	10.7 ± 6.4	10.5 ± 5.8	10.6 ± 6.2
HbA1c,			
%	8.6 ± 0.9	8.5 ± 1.0	8.6 ± 1.0
mmol/mol	70.5 ± 9.8	69.4 ± 10.9	70.5 ± 10.9
FPG, mmol/L	9.92 ± 2.30	9.72 ± 2.18	9.85 ± 2.26
eGFR, mL/min/1.73 m^2	90.4 ± 20.5	88.7 ± 20.7	89.9 ± 20.6
Prior non-insulin antihyperglycaemic treatment, %			
Metformin	73.1	74.4	73.5
Sulphonylureas	57.9	64.0	59.9
Alpha-glucosidase inhibitors	36.4	29.1	33.9
DPP-4 inhibitors	16.2	21.2	17.9
Thiazolidinediones	9.5	11.3	10.1
Fixed-dose oral combination drugs	7.5	6.4	7.1
SGLT-2 inhibitors	3.0	4.4	3.5
Other	9.7	4.9	8.1

Abbreviations: BMI, body mass index; DPP-4, dipeptidyl peptidase-4; eGFR, estimated glomerular filtration rate; FPG, fasting plasma glucose; SD, standard deviation; SGLT-2, sodium-glucose co-transporter-2.
Note: Data are presented as mean ± SD, unless otherwise stated.

The proportions of participants achieving an HbA1c of <7% over 26 weeks was >50% in the two treatment groups (Gla-300, 51.1% vs. Gla-100, 52.2%), with ~20% (Gla-300, 19.1% vs. Gla-100, 21.9%) of participants in either group achieving an HbA1c of <7% without hypoglycaemia during the last 12 weeks of treatment (Table 2). The proportion of participants achieving an HbA1c of <6.5% over 26 weeks was 29.7% with Gla-300 and 28.4% with Gla-100.

Mean baseline FPG (SD) values were 9.97 (2.30) and 9.79 (2.17) mmol/L in the Gla-300 and Gla-100 groups, respectively. The LS mean reductions in FPG from baseline to week 26 were 3.37 mmol/L for Gla-300 and 3.60 mmol/L for Gla-100 and were comparable between treatment groups (LS mean difference 0.23 mmol/L [95% CI: −0.03 to 0.50 mmol/L]; Table 2). The majority of the mean FPG decrease [SD] occurred in the first 12 weeks (3.15 [2.32] mmol/L for Gla-300 and 3.44 [2.30] mmol/L for Gla-100).

The eight-point SMPG profiles in both groups showed a marked decrease between baseline and week 26 (Figure 1B), with the LS mean change in 24-hour average PG being similar between groups (Table 2). The variability (coefficient of variation [CV]) of mean 24-hour PG increased from baseline to week 26 and was comparable in the two treatment groups (LS mean change [SE]: Gla-300, 5.91% [0.75%]; Gla-100, 5.18% [0.92%]; LS mean difference between groups 0.74% [95% CI: −1.14% to 2.62%]). No participants in either treatment group required rescue therapy during the 6-month on-treatment period.

3.4 | Hypoglycaemia

The proportion of participants with T2D experiencing ≥1 severe and/or confirmed (≤3.9 mmol/L [≤70 mg/dL]) hypoglycaemia during the 26-week treatment period was not significantly different between the two treatment groups for events reported at any time of day (relative risk [RR] [95% CI] Gla-300 vs. Gla-100: 0.94 [0.85–1.05]) and between 00:00 and 05:59 hours (RR [95% CI] Gla-300 vs. Gla-100: 0.84 [0.70–1.02]; Table 2). Furthermore, the incidence of all categories of hypoglycaemia at any time of day (24 hours) was similar between treatment groups at week 26 (Figure 2A). However, ancillary analysis showed that during the initial 12 weeks the incidence of any hypoglycaemia, documented (≤3.9 mmol/L [70 mg/dL]) symptomatic hypoglycaemia,and confirmed (≤3.9 mmol/L [70 mg/dL]) or severe hypoglycaemia at anytime of day (24 hours), was lower with Gla-300 versus Gla-100.

For nocturnal (00:00 to 05:59 hours) hypoglycaemia, the incidence of any hypoglycaemia or documented (≤3.9 mmol/L [70 mg/dL]) symptomatic hypoglycaemia was lower with Gla-300 versus Gla-100 at 6 months (Figure 3A). At 12 weeks, the incidence of any hypoglycaemia, documented (≤3.9 mmol/L [70 mg/dL]) symptomatic hypoglycaemia or confirmed (≤3.9 mmol/L [70 mg/dL]) or severe nocturnal hypoglycaemia was lower with Gla-300 versus Gla-100. The rate of all categories of any time of day (24 hours) and nocturnal (00:00 to 05:59 hours) hypoglycaemia were similar between treatment groups at week 26 at either threshold (Figures 2B and 3B). No remarkable differences were seen in incidence or rates of any category of hypoglycaemia at the lower threshold of <3.0 mmol/L (<54 mg/dL).

The incidence of severe hypoglycaemia was low (one participant [0.5%] in the Gla-100 group).

3.5 | Insulin dose, body weight and treatment compliance

Mean daily basal insulin dose at baseline was comparable between Gla-300 (12.2 U [0.18 U/kg]) and Gla-100 (12.3 U [0.18 U/kg]). At week 26, the mean daily basal insulin dose increased to 24.2 U (0.34 U/kg) with Gla-300 and 20.9 U (0.29 U/kg) with Gla-100 (Figure S2).

TABLE 2 Glycaemic control and the proportion of patients experiencing hypoglycaemia (modified intent-to-treat [mITT] population)

Time point	Parameter	Gla-300 (N = 397)	Gla-100 (N = 201)
	HbA1c, % [mmol/mol]		
Baseline	Mean ± SD	8.6 ± 0.9 [70.5 ± 9.8]	8.5 ± 1.0 [69.3 ± 10.9]
Week 12*	Mean ± SD	7.2 ± 0.8 [55.2 ± 8.7]	7.2 ± 0.8 [55.2 ± 8.7]
	LS mean change from baseline to week 12 ± SE	−1.4 ± 0.0 [−15.3 ± 0.0]	−1.4 ± 0.0 [−15.3 ± 0.0]
	LS mean difference (95% CI)	0.01 (−0.10 to 0.12) [0.11 (−1.10 to 1.31)]	
Week 26†	Mean ± SD	7.0 ± 0.8 [53.0 ± 8.7]	7.0 ± 0.8 [53.0 ± 8.7]
	LS mean change from baseline to week 26 ± SE	−1.5 ± 0.1 [−16.4 ± 1.1]	−1.5 ± 0.1 [−16.4 ± 1.1]
	LS mean difference (95% CI)	0.02 (−0.10 to 0.14) [0.22 (−1.10 to 1.53)]	
Week 26‡	**Achieved HbA1c target <7.0%, n (%)**	203 (51.1)	105 (52.2)
	RR (95% CI) Gla-300 vs. Gla-100	0.98 (0.84 to 1.14)	
Week 26‡	**Achieved HbA1c target with no hypoglycaemia during the last 12 weeks of treatment**	76 (19.1)	44 (21.9)
	RR (95% CI) Gla-300 vs. Gla-100	0.87 (0.63 to 1.20)	
	FPG, mmol/L	**N = 385**	**N = 196**
Baseline	Mean ± SD	10.0 ± 2.3	9.8 ± 2.2
Week 12§	Mean ± SD	6.8 ± 1.6	6.4 ± 1.4
	Mean change from baseline to week 12 ± SD*	−3.2 ± 2.3	−3.4 ± 2.3
Week 26†	Mean ± SD	6.7 ± 1.7	6.5 ± 1.4
	LS mean change from baseline to week 26 ± SE	−3.4 ± 0.1	−3.6 ± 0.1
	LS mean difference (95% CI)	0.23 (−0.03 to 0.50)	
	Mean change in 24-hour average plasma glucose	**N = 373**	**N = 189**
Baseline	Mean ± SD	10.9 ± 2.3	10.6 ± 2.4
Week 12§	Mean ± SD	8.3 ± 1.6	8.3 ± 1.7
	Mean change from baseline to week 12 ± SD¶	−2.5 ± 2.1	−2.3 ± 2.3
Week 26†	Mean ± SD	8.3 ± 1.6	8.4 ± 1.9
	LS mean change from baseline to week 26 ± SE	−2.4 ± 0.1	−2.3 ± 0.1
	LS mean difference (95% CI)	−0.11 (−0.39 to 0.17)	
	Proportion of patients with ≥1 severe and/or confirmed (≤3.9 mmol/L [≤70 mg/dL]) hypoglycaemia during the 26-week treatment period	**N = 397**	**N = 201**
Anytime	N (%)	207 (68.0)	146 (72.6)
	RR (95% CI) Gla-300 vs. Gla-100	0.94 (0.85–1.05)	
	P-value	0.2838	
Nocturnal	N (%)	148 (37.3)	90 (44.8)
	RR (95% CI) Gla-300 vs. Gla-100	0.84 (0.70 to 1.02)	
	P-value	0.0864	

Abbreviations: CI, confidence interval; FPG, fasting plasma glucose; LS, least squares; RR, relative risk; SD, standard deviation; SE, standard error; SMPG, self-monitored plasma glucose.

Note: *missing data imputed using MMRM approach; †last observation carried forward (LOCF) used for missing data; ‡patients for whom no data were available were assumed to not have achieved target; §observed case data provided; ¶descriptive statistics only.

Mean (SD) body weight increased in the Gla-300 and Gla-100 groups from 68.3 (11.7) and 68.8 (11.5) kg at baseline to 70.0 (12.1) and 70.7 (11.5) kg at week 26. The mean (SD) increase in body weight from baseline to week 26 was 1.75 (2.49) kg with Gla-300 and 1.69 (2.51) kg with Gla-100.

3.6 | Safety

The percentage of participants experiencing treatment-emergent AEs was similar for Gla-300 (49.6%) and Gla-100 (49.8%), as was the incidence of serious AEs (5.5% for both treatment groups). Injection site

reactions were rare, rated as mild in intensity, and a similar incidence was observed between treatment groups (Gla-300: 1.8%, Gla-100: 0.5%). The percentage of participants experiencing serious AEs leading to treatment discontinuation was low and similar in the Gla-300 and Gla-100 groups (Table S3).

There were three fatal events, two (0.5%) in the Gla-300 group and one (0.5%) in the Gla-100 group. The two fatal events in the Gla-300 group were caused by gastric cancer (not related to the study drug) and cardiorespiratory arrest in a person with a previous history of coronary heart disease, which was considered related to the study drug. One case in the Gla-100 group was reported as cause of death unknown.

4 | DISCUSSION

The primary endpoint of non-inferiority in HbA1c reduction was achieved, with Gla-300 providing comparable glycaemic control with Gla-100; this was accompanied by similar incidence and rates of hypoglycaemia over the entire 26-week study period for both basal insulins. Furthermore, a trend towards numerically lower incidence and rates of hypoglycaemia with Gla-300 versus Gla-100 was seen during the initial 12-week titration period; this was observed despite similar HbA1c reductions observed at 12 weeks between treatment groups. Overall, both basal insulin treatments had HbA1c target (<7.0%) achievement rates of >50% (Gla-300, 51.1% vs. Gla-100, 52.2%), and ~20% (Gla-300, 19.1% vs. Gla-100, 21.9%) of participants in either group achieved the HbA1c target without any hypoglycaemic events during the last 12 weeks of the treatment period.

These results in an Asia Pacific population confirm the findings of previous randomized clinical trials comparing Gla-300 and Gla-100. The EDITION 1–3 (which recruited people with T2D living in countries across Europe, the United States, Russia and South America) and EDITION JP 2 (which recruited Japanese people with T2D) trials showed comparable glycaemic control with Gla-300 and Gla-100 and lower risk of hypoglycaemia during the 8-week titration period.[13,14,16-20] Rates of HbA1c target (<7.0%) attainment were greater with both administered basal insulin treatments than previously reported rates with oral antihyperglycaemic drugs.[6-9] However, in Korea, guidelines recommend an HbA1c target of <6.5%, against which the achievement rates reported here are slightly lower than those reported elsewhere.[9] In addition, comparing this study with EDITION 3 (which also assessed insulin-naïve patients with T2D but in Western regions), patients with T2D in the Asia Pacific region had lower mean (SD) baseline BMI (25.2 [3.2] kg/m^2) than patients with T2D in Western regions (33.0 [6.7] kg/m^2).[18]

Findings from two large real-world evidence studies of US electronic health records of people with T2D are also in agreement with the present study. The DELIVER 2 study showed that, in patients previously treated with basal insulin, Gla-300 provided comparable HbA1c reductions with other basal insulins, but with lower rates of severe hypoglycaemia.[24] LIGHTNING predicted lower rates of severe hypoglycaemia with Gla-300 versus first-generation basal insulin analogues, Gla-100 and insulin detemir, in insulin-naïve people with T2D.[25]

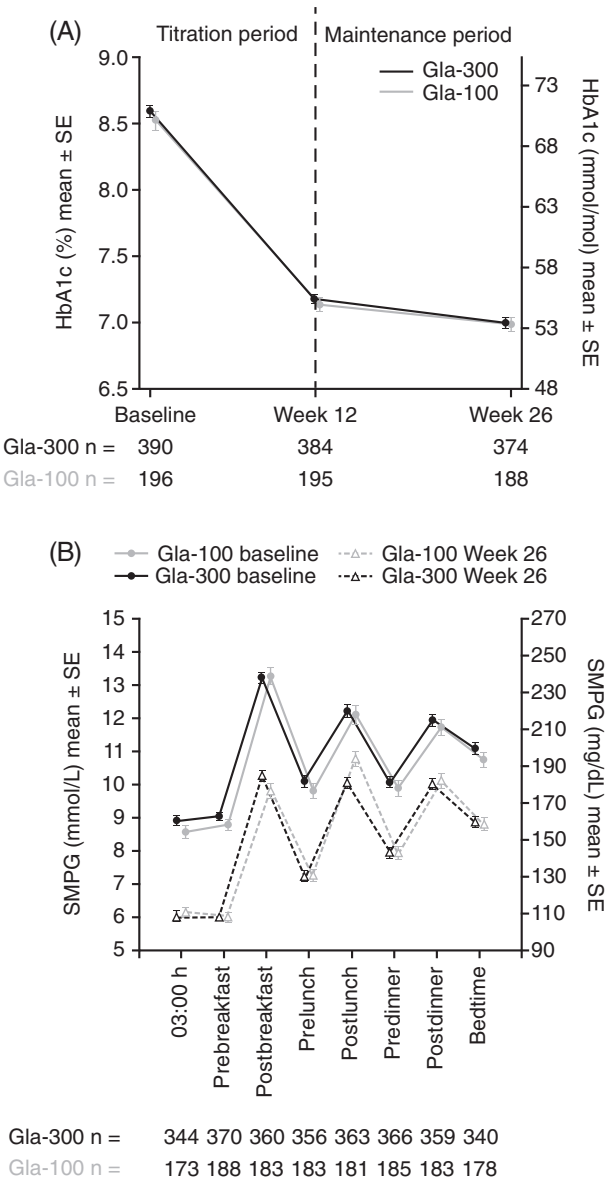

FIGURE 1 Mean change in (A) HbA1c and (B) eight-point self-monitored plasma glucose (SMPG) profiles. SE, standard error

Interestingly, the recent BRIGHT treat-to-target randomized controlled trial comparing efficacy and safety of the two second-generation basal insulin analogues, Gla-300 and insulin degludec 100 U/mL (IDeg-100), also showed a reduced risk of hypoglycaemia with Gla-300 during the 12-week active titration period in insulin-naïve individuals with uncontrolled T2D; this was accompanied by comparable glycaemic control between the two insulins.[26] The majority of dose increases, HbA1c reductions and FPG reductions occurred within the first 12 weeks, which is consistent with best efforts being made to achieve glycaemic targets within the initial 12 weeks.

Reducing the risk of hypoglycaemia within the initial weeks of starting basal insulin therapy can have important implications for

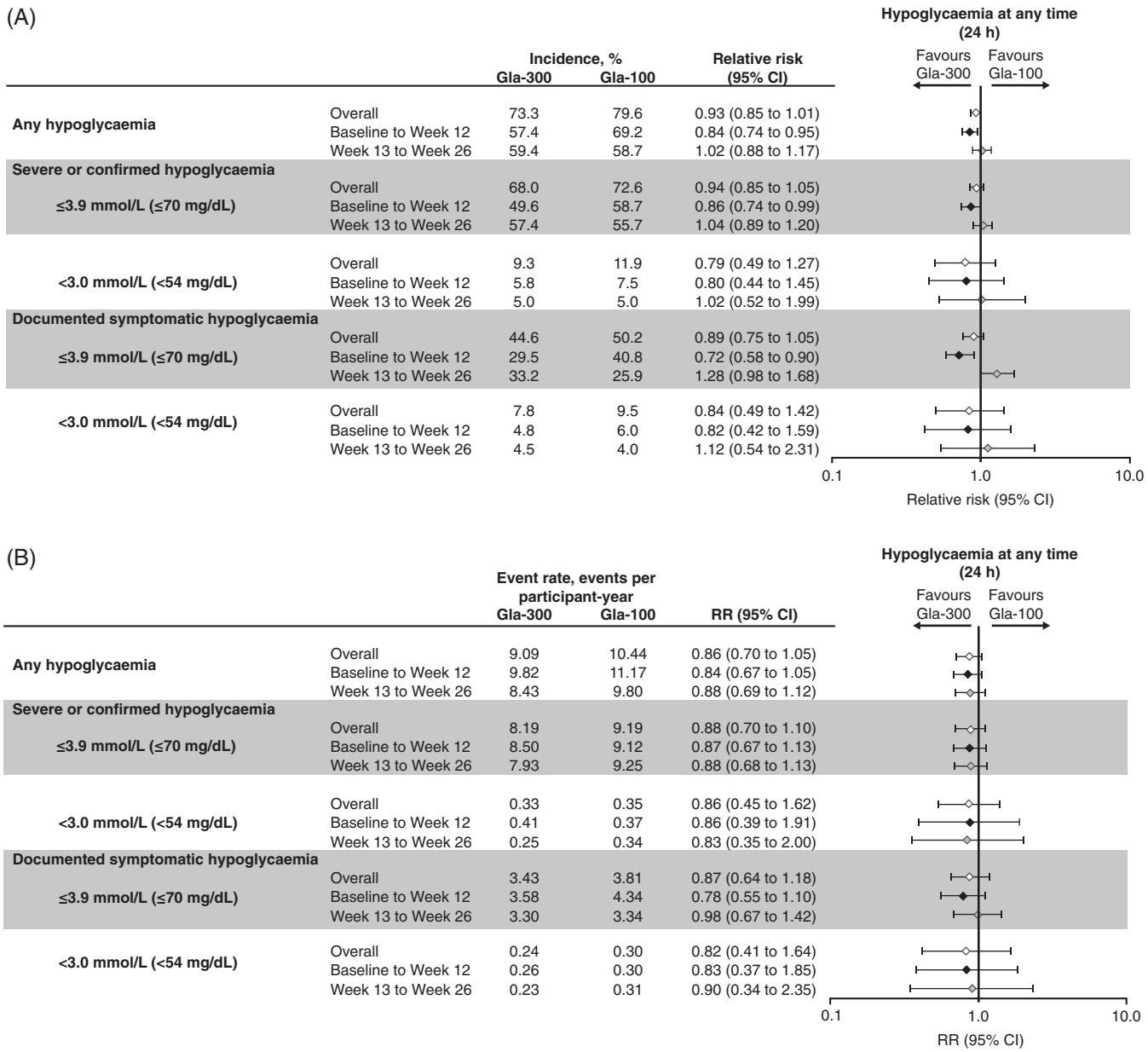

FIGURE 2 (A) Incidence and (B) event rate per participant-year of hypoglycaemia at any time of day (24 hours). CI, confidence interval; RR, rate ratio

adherence to therapy and long-term clinical outcomes. Hypoglycaemia occurs frequently during the titration period[27] and hypoglycaemic events within this period can lead to a higher risk of hypoglycaemia in the longer term.[28] As the analysis of hypoglycaemia during the titration period was ancillary analysis, the study was not designed for these comparisons. However, it is important to note that the reduced incidence and risk of hypoglycaemia observed with Gla-300 versus Gla-100 in some categories—especially nocturnal hypoglycaemia—indicate a safety profile which may present fewer barriers to optimal insulin titration. Fear of hypoglycaemia is a barrier to insulin initiation and optimal titration in insulin-naïve people with T2D.[29] Delay in insulin initiation, suboptimal titration and poor glucose control are issues in the treatment of diabetes in Asia as in other regions.[11] The ORBIT real-world evidence study showed that ~50% of patients did not have their insulin dose up-titrated within the first 3 months after starting insulin therapy.[12] Early glycaemic control increases the likelihood of achieving targets in the longer term,[28] and promotes improved glycaemic outcomes in the longer term.[2] Therefore, it is especially important to minimize the risk of hypoglycaemia occurring during the first few weeks of basal insulin therapy. The observed reduction in some incidence and risk of hypoglycaemia with Gla-300 versus Gla-100 could reflect differences in pharmacokinetic/pharmacodynamic profiles. For example, the steady-state profile of Gla-100 has greater glucose-lowering activities than Gla-300 in the first postdosing hours, reflecting a less steady blood glucose concentration, which may, in turn, affect hypoglycaemic risk.[15]

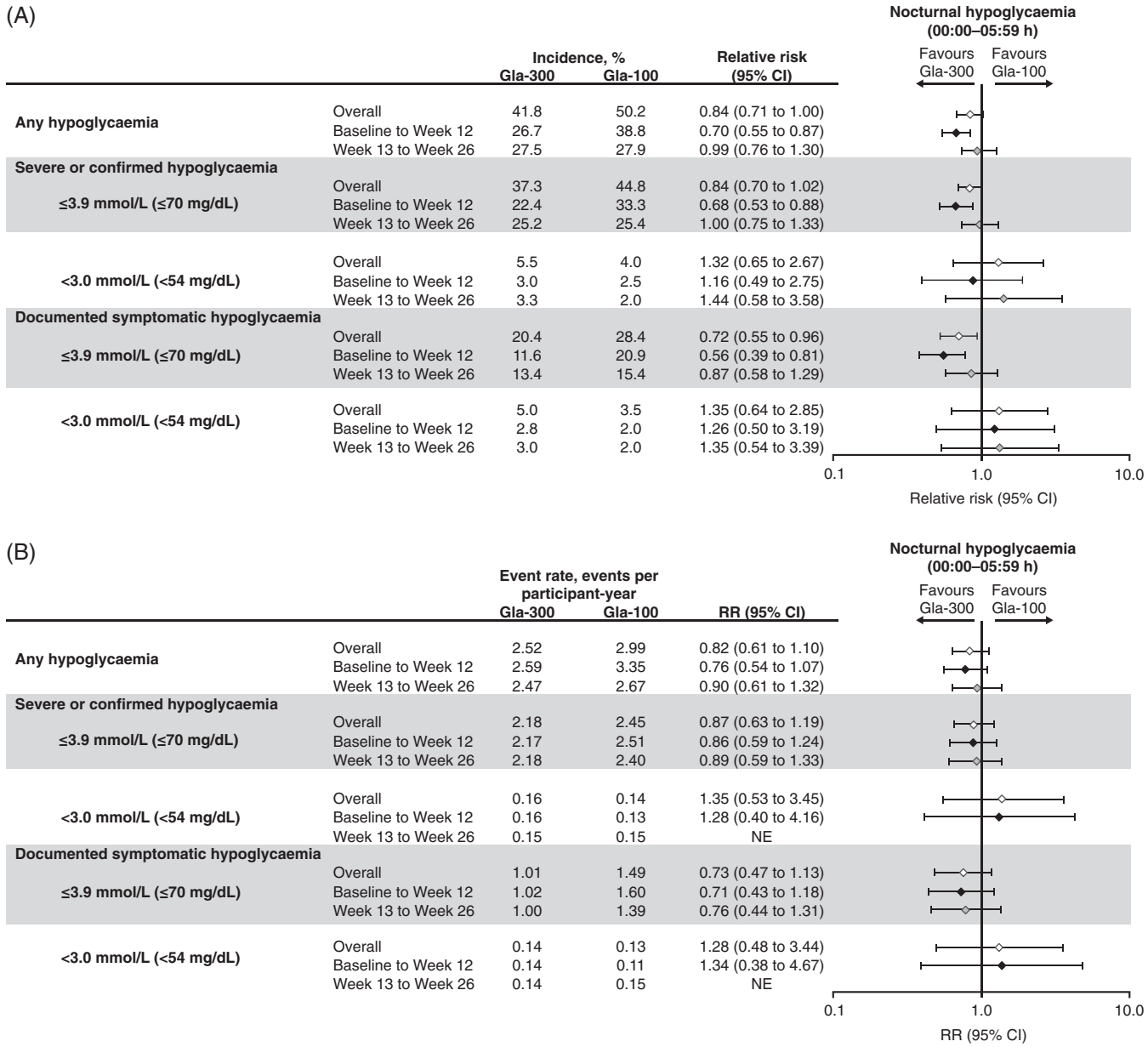

FIGURE 3 (A) Incidence and (B) event rate per participant-year of nocturnal hypoglycaemia (00:00 to 05:59). CI, confidence interval; NE, not evaluable; RR, rate ratio

The safety profiles of Gla-300 and Gla-100 in EDITION AP were similar. Treatment-emergent AEs occurred in 49.6% and 49.8% of participants receiving Gla-300 and Gla-100, respectively, in EDITION AP, similar to the incidence of treatment-emergent AEs in the EDITION 2 and 3 and JP 2 studies in insulin-naïve T2D populations: 51%–59% in EDITION 2, and 57%–58% in EDITION JP 2.[13,14] As with the wider EDITION programme, EDITION AP reported slightly higher basal insulin doses with Gla-300 versus Gla-100.[13,14,18] Despite the greater insulin dose, similar glycaemic control and similar risk of hypoglycaemia over the 26-week study period were observed in the present analysis, which is consistent with the lower 24-hour exposure observed with Gla-300 versus Gla-100.[15] This may reflect lower bioavailability because of Gla-300 remaining in the subcutaneous depot for longer than Gla-100.[30]

The strengths of this study include the randomized, head-to-head design, and also that it is the first study comparing Gla-300 versus Gla-100 in a currently understudied Asia Pacific population. The limitations include the open-label study design that reflects difficulties in blinding the two insulins, which has the potential to introduce bias.

In conclusion, EDITION AP confirms the efficacy and safety profile of Gla-300 in Asian people with T2D, which was also observed in the global EDITION programme. Results show comparable glycaemic control with similar incidence of any hypoglycaemia. Incidence of any, documented, and severe or confirmed nocturnal hypoglycaemia was lower during the first 12 weeks compared with Gla-100. By reducing the risk of hypoglycaemia during the initial insulin titration period,

Gla-300 may increase the confidence of individuals in managing and titrating their insulin compared with Gla-100.

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CONFLICT OF INTEREST

L.J. has received honoraria and consultancy fees from Sanofi. S.S. is an employee of Sanofi. E.N. is an employee and shareholder of Sanofi. E.S.K., X.D., L.L. and G.Y. have nothing to declare.

AUTHOR CONTRIBUTIONS

All authors interpreted the results, revised the manuscript, and approved the final version of the manuscript. L.J. 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.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of this article.

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