

ORIGINAL ARTICLE

Glycaemic control, hypoglycaemia, and weight change with insulin glargine 300 U/mL versus insulin glargine 100 U/mL in Japanese adults with type 2 diabetes: A 12-month comparison by concomitant sulphonylurea and/or glinide use

Yasuo Terauchi MD¹  | Matthew C. Riddle MD²  | Takahisa Hirose MD³ | Masayoshi Koyama⁴ | Xi Cheng⁵ | Yoshinori Takahashi⁴ | Geremia B. Bolli MD⁶ 

¹Department of Endocrinology and Metabolism, Yokohama City University School of Medicine, Yokohama, Japan

²Division of Endocrinology, Diabetes & Clinical Nutrition, Oregon Health and Science University, Portland, Oregon

³Division of Diabetes, Metabolism and Endocrinology, Department of Medicine, Toho University School of Medicine, Tokyo, Japan

⁴Sanofi, Tokyo, Japan

⁵Sanofi, Beijing, China

⁶Department of Medicine, Division of Internal Medicine and Endocrine and Metabolic Sciences, Perugia University Medical School, Perugia, Italy

Correspondence

Yasuo Terauchi, MD, PhD, Yokohama City University Graduate School of Medicine, Department of Endocrinology and Metabolism, 3-9 Fukuura, Kanazawa-ku, Yokohama 236-0004, Japan.

Email: terauchi@yokohama-cu.ac.jp

Funding information

This study was funded by Sanofi

Aim: To explore if clinical effects and hypoglycaemia risks associated with insulin glargine 300 U/mL (Gla-300) and 100 U/mL (Gla-100) differed by sulphonylurea and/or glinide (SU/G) treatment.

Methods: A post hoc subgroup analysis of 12-month treatment data from the EDITION Japan 2 trial, a randomized, open-label, phase 3 study of Japanese people with type 2 diabetes receiving once-daily Gla-300/Gla-100 + oral antihyperglycaemic drugs. Participants previously receiving SU/G (+SU/G) were compared with those not taking SU/G (-SU/G). Endpoints included HbA1c, hypoglycaemia and body weight.

Results: For +SU/G (n = 152, 63%), HbA1c was reduced from baseline to month 12 for Gla-300 (8.1% to 7.6%) and Gla-100 (8.2% to 7.8%). For -SU/G (n = 89, 37%), reductions were 7.8% to 7.4%, and 7.9% to 7.5% for Gla-300 and Gla-100, respectively. A lower annualized rate of hypoglycaemia with Gla-300 versus Gla-100 was observed at night (00:00–05:59 hours; p = 0.0001) and any time of day (24 hour; p = 0.0015). Irrespective of the insulin used, the incidence and rate of confirmed (≤ 3.9 mmol/L [≤ 70 mg/dL]) or severe hypoglycaemia appeared higher in +SU/G versus -SU/G; overall, a reduced incidence of nocturnal hypoglycaemia, and rate of hypoglycaemia at any time, was observed in -SU/G versus +SU/G. In the -SU/G subgroup, body weight gain differences were observed between Gla-300 and Gla-100 (p < 0.0001).

Conclusions: Participants with prior and continued SU/G use had similar therapeutic responses with basal insulin but greater risk of hypoglycaemia than those not using SU/G; hypoglycaemia risk was lower with Gla-300 than Gla-100 in both subgroups.

KEYWORDS

basal insulin, glycaemic control, hypoglycaemia, insulin therapy, sulphonylureas, type 2 diabetes

1 | INTRODUCTION

As observed globally in recent years,¹ the prevalence of diabetes has increased in Japan, with the increase in type 2 diabetes (T2DM) being attributed to both lifestyle changes² and genetic factors.³ Additionally, there are differences in the epidemiology of T2DM between Japan and Western countries.³ In Japan, T2DM is an important cause of morbidity and mortality,^{4,5} and also a considerable economic burden,

with health expenditure in 2015 totalling 29 billion US dollars.⁶ Therefore, there was a need to investigate management strategies for T2DM in Japan. The EDITION Japan 2 (EDITION JP 2) trial was conducted to compare the efficacy and safety of insulin glargine 300 U/mL (Gla-300) with insulin glargine 100 U/mL (Gla-100) in Japanese people with T2DM who were previously treated with basal insulin plus oral antihyperglycaemic drugs (OADs).⁷ Over 12 months, Gla-300 provided comparable glycaemic control with less

hypoglycaemia versus Gla-100, consistent with the global EDITION study programme.^{8–10}

Unlike the other EDITION trials in adults with T2DM (EDITION 1, 2 and 3),^{8,11,12} concomitant sulphonylurea or glinide treatment was permitted in the EDITION JP 2 trial (53.9% and 9.5% of people used sulphonylurea and glinide during the trial, respectively).¹³ Guidelines published by the Japanese Diabetes Society indicate sulphonylurea as one of the treatment options, along with insulins, OADs, or glucagon-like peptide receptor agonists for glycaemic control in people with T2DM.^{14,15} Although sulphonylureas are commonly used in Japan,^{16,17} they are associated with increased risk of hypoglycaemia.¹⁸ It is therefore important to investigate whether an increased risk of hypoglycaemia resulting from treatment with a sulphonylurea in people with T2DM titrating to target on basal insulin influenced the advantages of Gla-300 over Gla-100 observed in the EDITION JP 2 trial. The current post hoc analysis aimed to explore whether the observations on glycaemic control and hypoglycaemia with Gla-300 versus Gla-100 observed in the EDITION JP 2 trial applied equally to participants who received concomitant sulphonylurea and/or glinide treatment during the trial, and those who did not.

2 | MATERIALS AND METHODS

2.1 | Study design and participants

A post hoc analysis was performed on data from the EDITION JP 2 trial (NCT01689142).⁷ As the EDITION JP 2 trial design has been previously described,¹³ it is only briefly summarized here. EDITION JP 2 was a 6-month randomized, open-label, parallel-group, phase 3, multicentre trial in Japanese adults with uncontrolled T2DM receiving basal insulin and OADs. The 6-month treatment period was followed by a predefined 6-month extension phase.

Participants were randomized 1:1 to Gla-300 or Gla-100 stratified by screening HbA1c (<8.0% vs. ≥8.0%) and sulphonylurea and/or glinide use (yes vs. no). Participants continued with the same OAD treatment during the trial as received prior to entry; for sulphonylurea/glinide, doses were to be adjusted if two or more symptomatic, or one or more severe hypoglycaemic events occurred. Dietary and lifestyle counselling was provided by a medically qualified person throughout the trial, and while adherence to these recommendations was discussed with each participant throughout the study, this was not an outcome measure. For the current analyses, data were grouped according to whether participants received concomitant sulphonylurea and/or glinide treatment (+SU/G) or not (-SU/G) during the 12-month on-treatment period.

2.2 | Outcomes

The following efficacy endpoints were analysed: change from baseline to month 12 in HbA1c, laboratory-measured fasting plasma glucose (FPG), mean 7-point self-monitored plasma glucose (SMPG) profiles at baseline and month 12, 24-hour average 7-point SMPG, average pre-injection SMPG, and daily basal insulin dose. Safety endpoints included the number of participants with one or more hypoglycaemic events (based on

ADA definitions¹⁹) at night (00:00–05:59 hours) or at any time of day (24 hour), the rate of such hypoglycaemic events, and body weight during the 12-month period.

2.3 | Data analysis and statistics

Data were grouped by reported concomitant use of sulphonylurea and/or glinide (yes or no). Relative risks of hypoglycaemia were analysed using Cochran–Mantel–Haenszel methodology stratified by screening HbA1c (<8.0% or ≥8.0%). Rate ratios were estimated using an overdispersed Poisson regression model with treatment and randomization strata of screening HbA1c (<8.0% or ≥8.0%) as fixed effects, and logarithm of the treatment period as offset.

Between-treatment differences in HbA1c change from baseline and FPG change from baseline were analysed using the least squares (LS) mean difference, by a mixed model for repeated measurements (MMRM). The MMRM for between-treatment differences in HbA1c used treatment groups, randomization stratum (screening HbA1c [<8.0% or ≥8.0%]), concomitant sulphonylurea or glinide (yes or no), visit (week 12, 6, 9, month 12), treatment-by-visit interaction, concomitant sulphonylurea and/or glinide-by-treatment group interaction, and concomitant sulphonylurea and/or glinide-by-treatment group-by-visit interaction as fixed effects; baseline HbA1c-by-visit interaction, and baseline HbA1c were covariates. Between-treatment differences in change from baseline FPG were analysed by MMRM using a similar model as for HbA1c.

The between-treatment difference in insulin dose and body weight change from baseline to month 12 was analysed in each subgroup using the LS mean difference, by an analysis of covariance (ANCOVA) model with treatment groups, and randomization stratum (screening HbA1c [<8.0% or ≥8.0%]) as fixed effects; baseline basal insulin dose was a covariate in the insulin dose analysis, and baseline body weight was a covariate in the body weight analysis.

3 | RESULTS

3.1 | Participants

Of the 241 participants randomized in the EDITION JP 2 trial, 152 (63%) received concomitant sulphonylurea and/or glinide (+SU/G) during the study and 89 (37%) did not receive either sulphonylurea or glinide (-SU/G; Table 1). The proportion of participants receiving biguanide at baseline was 63% and 53% in the +SU/G subgroup and the -SU/G subgroup, respectively (Table 1). Differences were also observed in the use of α -glucosidase inhibitors (21% vs. 42%); however, use of dipeptidyl peptidase (DPP4) inhibitors (41% vs. 47%) and thiazolidinedione (8% vs. 7%) was comparable for both subgroups (Table 1). In both the +SU/G subgroup and the -SU/G subgroup, the proportion of participants who had been randomized to Gla-300 versus Gla-100 was comparable.

During the 12-month treatment period, 25 (16%) participants in the +SU/G subgroup received sulphonylurea and 5 (3%) received glinide as their only OAD; the remaining participants received either sulphonylurea or glinide in combination with other OADs (104 [68%] and

TABLE 1 Baseline demographics of the randomized population

	Participants receiving concomitant sulphonylurea and/or glinide (+SU/G)			Participants not receiving sulphonylurea or glinide (-SU/G)		
	Gla-300 (N = 75)	Gla-100 (N = 77)	All (N = 152)	Gla-300 (N = 46)	Gla-100 (N = 43)	All (N = 89)
Age, mean (SD) y	61.3 (10.4)	58.9 (12.4)	60.1 (11.5)	60.9 (11.5)	63.2 (10.9)	62.0 (11.2)
Male, n (%)	45 (60.0)	44 (57.1)	89 (58.6)	32 (69.6)	26 (60.5)	58 (65.2)
Body weight, mean (SD) kg	67.3 (13.7)	66.6 (11.8)	66.9 (12.7)	67.7 (13.7)	64.8 (14.4)	66.3 (14.0)
BMI, mean (SD) kg/m ²	25.7 (3.9)	25.1 (3.5)	25.4 (3.7)	25.7 (4.0)	24.4 (3.8)	25.1 (4.0)
Duration of diabetes, mean (SD) y	14.2 (7.3)	13.7 (7.8)	13.9 (7.5)	13.8 (9.2)	14.4 (10.2)	14.1 (9.6)
Fasting C-peptide, mean (SD), ng/mL	1.18 (0.85)	1.03 (0.60)	1.10 (0.74)	1.06 (0.82)	0.85 (0.59)	0.96 (0.72)
Duration of basal insulin treatment, mean (SD) y	2.25 (2.11)	2.43 (2.43)	2.34 (2.27)	2.62 (2.65)	2.67 (2.47)	2.64 (2.55)
HbA1c, mean (SD)						
%	8.07 (0.74)	8.18 (0.78)	8.12 (0.76)	7.86 (0.66)	7.85 (0.71)	7.85 (0.68)
Mmol/Mol	64.7 (8.1)	65.9 (8.5)	65.2 (8.3)	62.4 (7.2)	62.3 (7.8)	62.3 (7.4)
FPG, mean (SD)						
Mmol/L	7.8 (2.2)	7.5 (1.8)	7.7 (2.0)	7.5 (1.9)	7.2 (2.1)	7.4 (2.0)
Mg/dL	140.7 (39.9)	135.5 (33.0)	138.1 (36.5)	135.0 (34.3)	130.3 (37.6)	132.7 (35.8)
Basal insulin and analogues	75 (100)	77 (100)	152 (100)	46 (100)	43 (100)	89 (100)
Previous basal insulin type, n (%)						
Insulin glargine	73 (97.3)	70 (90.9)	143 (94.1)	46 (100)	40 (93.0)	86 (96.6)
NPH	0	0	0	0	0	0
Insulin detemir	2 (2.7)	8 (10.4)	10 (6.6)	0	3 (7.0)	3 (3.4)
Previous basal insulin daily injection number, n (%)						
Once daily	73 (97.3)	75 (97.4)	148 (97.4)	45 (100) ^a	41 (95.3)	86 (97.7)
Twice daily	2 (2.7)	2 (2.6)	4 (2.6)	0	2 (4.7)	2 (2.3)
Previous daily basal insulin dose, mean (SD)						
U/kg/d	0.25 (0.15)	0.25 (0.13) ^b	0.25 (0.14) ^b	0.24 (0.12) ^c	0.23 (0.11)	0.24 (0.11) ^c
U/d	17.0 (11.1)	16.7 (9.1) ^b	16.8 (10.1) ^b	16.4 (9.3) ^c	15.0 (8.2)	15.7 (8.8) ^c
Previous OAD treatment, n (%)						
Sulphonylureas						
Glimepiride	64 (85.3)	65 (84.4)	129 (84.9)	1 (2.2)	1 (2.3)	2 (2.2)
Glibenclamide	55 (73.3)	60 (77.9)	115 (75.7)	0	1 (2.3)	1 (1.1)
Gliclazide	7 (9.3)	3 (3.9)	10 (6.6)	1 (2.2)	0	1 (1.1)
Gliclazide	2 (2.7)	2 (2.6)	4 (2.6)	0	0	0
Glinides						
Repaglinide	11 (14.7)	12 (15.6)	23 (15.1)	0	1 (2.3)	1 (1.1)
Repaglinide	5 (6.7)	4 (5.2)	9 (5.9)	0	0	0
Mitiglinide calcium/voglibose combination	4 (5.3)	2 (2.6)	6 (3.9)	0	0	0
Mitiglinide calcium	2 (2.7)	3 (3.9)	5 (3.3)	0	0	0
Nateglinide	0	3 (3.9)	3 (2.0)	0	0	0
Metformin/pioglitazone combination	0	0	0	0	1 (2.3)	1 (1.1)
Biguanides						
Biguanides	46 (61.3)	49 (63.6)	95 (62.5)	25 (54.3)	22 (51.2)	47 (52.8)
DPP4 inhibitor						
DPP4 inhibitor	31 (41.3)	31 (40.3)	62 (40.8)	20 (43.5)	22 (51.2)	42 (47.2)
α-Glucosidase inhibitors						
α-Glucosidase inhibitors	20 (26.7)	12 (15.6)	32 (21.1)	23 (50.0)	14 (32.6)	37 (41.6)
Thiazolidinedione	7 (9.3)	5 (6.5)	12 (7.9)	3 (6.5)	3 (7.0)	6 (6.7)
Other drugs used in diabetes	0	1 (1.3)	1 (0.7)	1 (2.2)	1 (2.3)	2 (2.2)

Abbreviations: BMI, body mass index; DPP, dipeptidyl peptidase; NPH, neutral protamine Hagedorn; OAD, oral antihyperglycaemic drug; SD, standard deviation; +SU/G, participants receiving concomitant sulphonylurea and/or glinide; -SU/G, participants not receiving sulphonylurea or glinide.

^a Data for one participant in the -SU/G subgroup not included as they were randomised but not treated.

^b Data not available for one participant.

^c Data not available for two participants.

18 [12%], respectively). The other OADs were: α-glucosidase inhibitors, biguanides, dipeptidyl peptidase-4 (DPP-4) inhibitors, and thiazolidinediones. The proportion of participants that received one, two or more than two OADs was 20%, 33% and 47% in the +SU/G subgroup,

and 56%, 34% and 10% in the -SU/G group, respectively (Table S1, see the supporting information for this article in File S1). Alpha-glucosidase inhibitors were used by 32 (21%) participants in the +SU/G subgroup and 37 (42%) in the -SU/G subgroup.

Of those participants who received sulphonylurea and/or glinide, 129 (85%) participants had previously received sulphonylurea and 23 (15%) had previously received glinide (Table 1). Of those participants who did not receive either sulphonylurea or glinide during the study, two (2%) had previously received sulphonylurea and one (1%) had previously received glinide (Table 1). In the +SU/G subgroup, three participants had their treatment withdrawn. All participants remained in the +SU/G subgroup. None of the participants in the -SU/G subgroup started receiving sulphonylurea or glinide during the study.

The previous basal insulin dose was comparable between the +SU/G and -SU/G subgroups (Table 1). The most common type of basal insulin used prior to entry into the EDITION JP 2 trial was insulin glargine (94% and 97% of participants in the +SU/G subgroup and -SU/G subgroup, respectively; Table 1). No participants had previously received neutral protamine Hagedorn (NPH) (Table 1). Other than differences in prior glucose-lowering therapies, baseline characteristics were comparable between the +SU/G and -SU/G subgroups, including fasting C-peptide ($p > 0.05$; Table 1).

3.2 | Glycaemic control

3.2.1 | HbA1c

The reduction in HbA1c from baseline to month 12 was comparable with Gla-300 and Gla-100, irrespective of concomitant sulphonylurea and/or glinide use; LS mean difference (95% confidence interval [CI]) between the insulin treatment groups was -0.0 (-0.3 to 0.2)% and 0.1 (-0.2 to 0.4)% in the +SU/G and -SU/G subgroups, respectively. For participants in the +SU/G subgroup, mean (standard deviation [SD]) HbA1c reduced from 8.1 (0.7)% at baseline to 7.6 (0.7)% at month 12 with Gla-300, and 8.2 (0.8)% to 7.8 (1.0)% with Gla-100 (Figure 1A). In the -SU/G subgroup, HbA1c reduced from 7.8 (0.7)% at baseline to 7.4 (0.8)% at month 12 with Gla-300, and 7.9 (0.7)% to 7.5 (0.8)% with Gla-100 (Figure 1A).

3.2.2 | Laboratory-measured FPG

LS mean difference (95% CI) in FPG from baseline to month 12 between the insulin treatment groups was 0.3 (-0.3 to 0.9) mmol/L (5.4 [-6.1 to 16.8] mg/dL) and 0.7 (-0.1 to 1.5) mmol/L (12.1 [-2.6 to 26.7] mg/dL) in the +SU/G and -SU/G subgroups, respectively. For participants in the +SU/G group, mean (SD) FPG decreased from baseline such that at month 12 it was 6.7 (1.7) mmol/L (120.2 [30.2] mg/dL) in the Gla-300 group and 6.4 (1.7) mmol/L (115.2 [30.8] mg/dL) in the Gla-100 group (Figure S1A, see the supporting information for this article in File S1). In the -SU/G subgroup, mean (SD) FPG also decreased from baseline such that at month 12 it was 6.9 (2.5) mmol/L (124.9 [44.5] mg/dL) in the Gla-300 group, and 6.2 (1.9) mmol/L (111.2 [34.0] mg/dL) in the Gla-100 group (Figure S1B in File S1).

3.2.3 | SMPG

For participants in the +SU/G subgroup, mean (SD) change in 24-hour average plasma glucose (based on 7-point SMPG profiles; Figure S2A in File S1) from baseline to month 12 was -0.67 (2.41) mmol/L (-12.1 [43.4] mg/dL) in the Gla-300 group, and -0.50 (2.41) mmol/L (-9.0 [43.4] mg/dL) in the Gla-100 group. In the -SU/G subgroup,

change in 24-hour average plasma glucose (based on 7-point SMPG profiles; Figure S2B in File S1) from baseline to month 12 was -1.18 (2.77) mmol/L (-21.2 [50.0] mg/dL) in the Gla-300 group, and -0.16 (2.58) mmol/L (-2.9 [46.5] mg/dL) in the Gla-100 group.

For participants in the +SU/G subgroup, mean (SD) change in average pre-injection SMPG from baseline to month 12 was 1.54 (4.49) mmol/L (27.8 [80.9] mg/dL) in the Gla-300 group, and 0.68 (3.25) mmol/L (12.31 [58.47] mg/dL) in the Gla-100 group ($p = 0.181$). In the -SU/G subgroup, mean (SD) change in average pre-injection SMPG from baseline to month 12 was -0.13 (3.12) mmol/L (-2.4 [56.2] mg/dL) in the Gla-300 group, and 1.4 (3.3) mmol/L (26.0 [59.1] mg/dL) in the Gla-100 group ($p = 0.025$).

3.3 | Insulin dose

While the mean basal insulin dose increased from baseline to month 12 with both Gla-300 and Gla-100 (Figure 1B), the final daily dose for Gla-300 was higher than that for Gla-100, for both the +SU/G ($p < 0.002$) and -SU/G ($p < 0.003$) subgroups. LS mean difference (95% CI) in the change in daily basal insulin dose from baseline to month 12 between the insulin treatment groups was 3.3 (0.9 to 5.8) U (0.05 [0.02 to 0.08] U/kg) and 5.3 (0.9 to 9.6) U (0.08 [0.03 to 0.14] U/kg) in +SU/G and -SU/G subgroups, respectively.

3.4 | Body weight

For participants in the safety population for the +SU/G subgroup, mean (SE) change in body weight from baseline to month 12 was -0.4 (0.3) kg and 0.3 (0.3) kg in the Gla-300 and Gla-100 treatment groups, respectively (Figure 1C); mean (SD) body weight at baseline was 67.3 (13.7) kg for Gla-300 and 66.6 (11.8) kg for Gla-100, while at month 12 it was 66.9 (13.9) kg for Gla-300 and 66.9 (13.0) kg for Gla-100. In the -SU/G subgroup, mean (SE) change in body weight from baseline to month 12 was -1.2 (0.4) kg and 0.9 (0.4) kg in the Gla-300 and Gla-100 groups, respectively (Figure 1C); mean (SD) body weight at baseline was 67.6 (13.9) kg for Gla-300 and 64.8 (14.4) kg for Gla-100, while at month 12 it was 66.4 (13.7) kg for Gla-300 and 65.7 (15.6) kg for Gla-100. The between-treatment difference in the change in weight from baseline to month 12 was smaller for participants receiving concomitant sulphonylurea and/or glinide (LS mean difference: -0.7 ; 95% CI: -1.5 to 0.1 kg, $p = 0.0687$) compared with those not receiving either sulphonylurea or glinide (LS mean difference: -2.1 ; 95% CI: -3.2 to -1.1 kg, $p < 0.0001$).

3.5 | Hypoglycaemia

The cumulative mean number of confirmed (≤ 3.9 mmol/L [≤ 70 mg/dL]) or severe hypoglycaemic events at night (00:00–05:59 hours) and any time of day increased steadily over the 12 months (Figure 2). A post hoc exploratory analysis using a negative binomial regression model performed for the annualized rate of confirmed (≤ 3.9 mmol/L [≤ 70 mg/dL]) or severe hypoglycaemic events indicated that these were significantly reduced for Gla-300 versus Gla-100, both during the night [00:00–05:59 hours] ($p = 0.0001$), and at any time of day (24 hour) ($p = 0.0015$). For nocturnal events, Gla-300 was associated with a

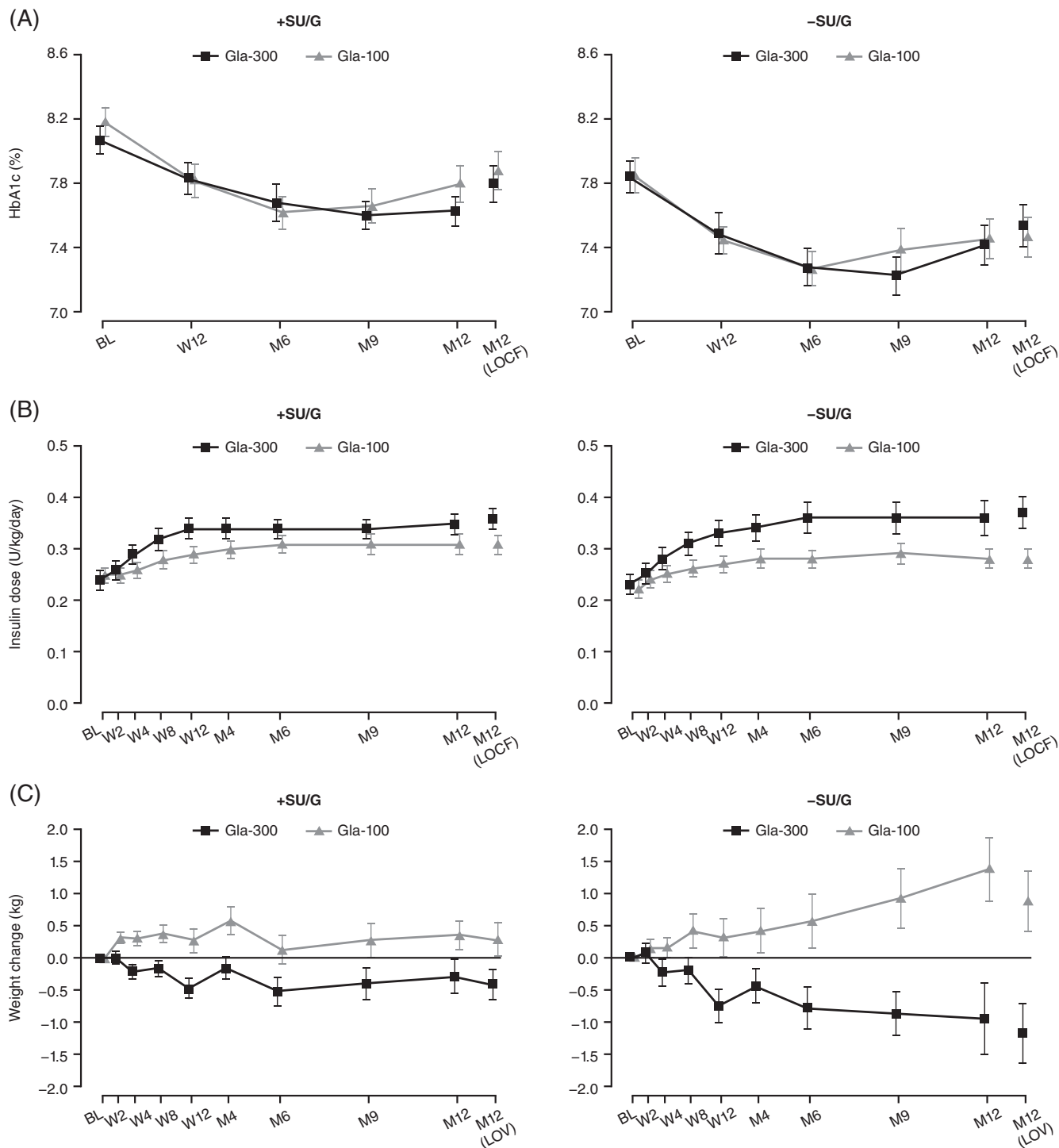


FIGURE 1 Glycaemic control, insulin dose, and change in body weight across the 12-month treatment period, for participants with or without concomitant sulphonylurea and/or glinide. A, mean (\pm SE) HbA1c (mITT population), B, mean (\pm SE) insulin dose (mITT population), C, mean (\pm SE) change in body weight (safety population). BL, baseline; CI, confidence interval; LOCF, last observation carried forward; LOV, last on-treatment value; LS, least squares; mITT, modified intent-to-treat; SE, standard error; +SU/G, participants receiving concomitant sulphonylurea or glinide; -SU/G, participants not receiving sulphonylurea or glinide

significantly reduced annualized rate of events versus Gla-100, in both the +SU/G ($p = 0.0032$) and -SU/G ($p = 0.0133$) subgroup. For the annualized rate of confirmed (≤ 3.9 mmol/L [≤ 70 mg/dL]) or severe hypoglycaemic events at any time of day (24 hour), these were significantly reduced with Gla-300 versus Gla-100 in the +SU/G subgroup ($p = 0.0137$), but not in the -SU/G subgroup ($p = 0.0530$) (Figure 2).

Pooled Gla-300 and Gla-100 data demonstrated a statistically significant reduction in the number of participants experiencing ≥ 1 confirmed (≤ 3.9 mmol/L [≤ 70 mg/dL]) or severe hypoglycaemia events, at night (00:00–05:59 hours) over the 12-month treatment period in the -SU/G versus the +SU/G subgroup (relative risk: 1.39 [95% CI: 1.001 to 1.920]) (Figure 3A). There was also a trend towards fewer

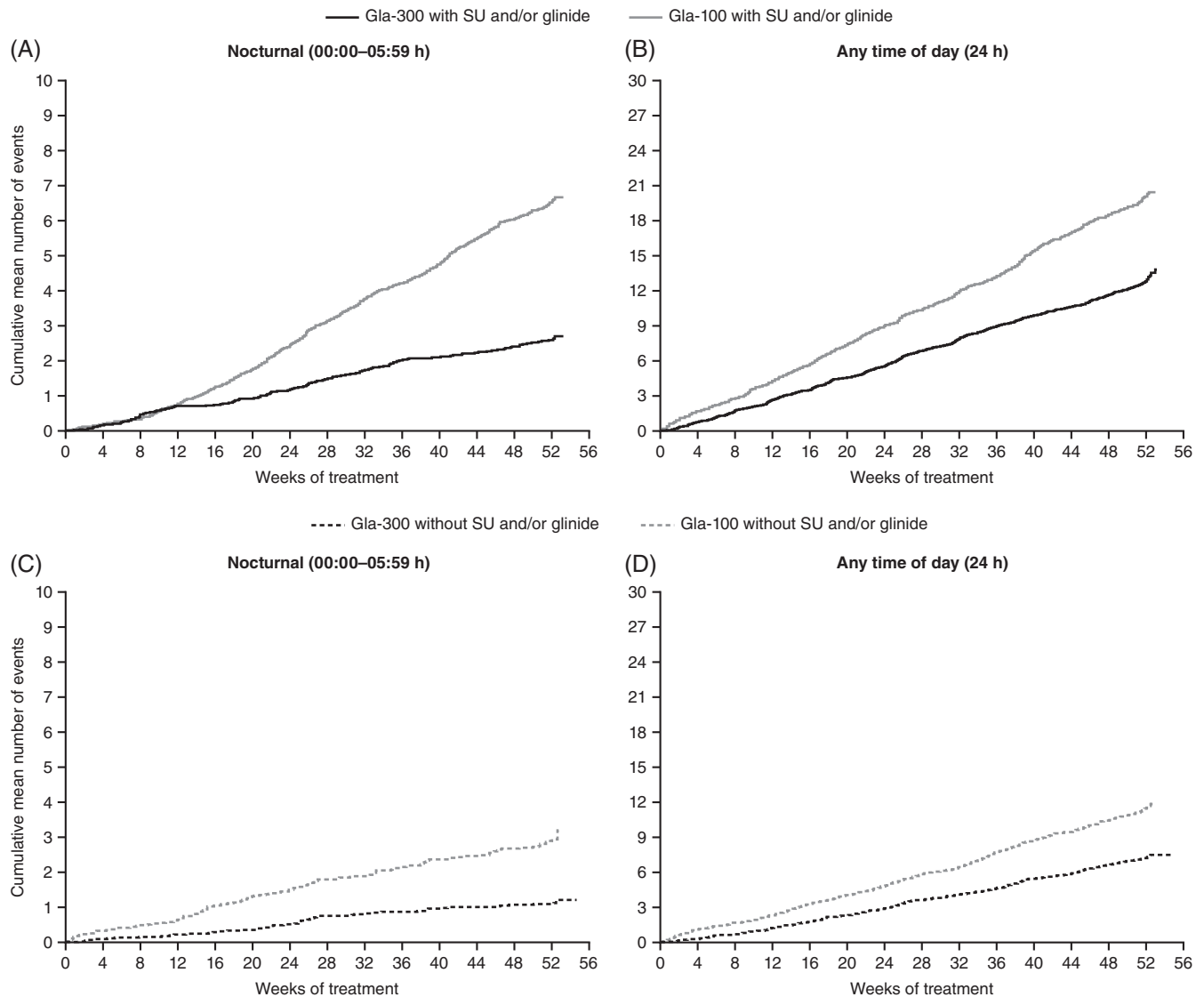


FIGURE 2 Cumulative mean number of confirmed (≤ 3.9 mmol/L [≤ 70 mg/dL]) or severe hypoglycaemic events per participant for participants with or without concomitant sulphonylurea and/or glinide during the 12-month treatment period (safety population). A, during the night (00:00–05:59 h) and B, at any time of day (24 h). G, glinide; +SU/G, participants receiving concomitant sulphonylurea or glinide; -SU/G, participants not receiving sulphonylurea or glinide; SU, sulphonylurea

participants experiencing any time of day (24 hour) confirmed (≤ 3.9 mmol/L [≤ 70 mg/dL]) or severe hypoglycaemia over the 12-month treatment period in the -SU/G versus the +SU/G subgroup (relative risk: 1.17 [95% CI: 0.997 to 1.377]) (Figure 3A). For the annualized rates of these hypoglycaemia events, there was also a trend towards lower annualized rates of nocturnal confirmed (≤ 3.9 mmol/L [≤ 70 mg/dL]) or severe hypoglycaemia for participants in the -SU/G versus +SU/G subgroups; rates were similar irrespective of Gla-300 and Gla-100 use (rate ratio: 1.91 [95% CI: 0.695 to 5.27]) (Figure 3B). In the pooled Gla-300 and Gla-100 group, rates of any time of day (24 hour) confirmed (≤ 3.9 mmol/L [≤ 70 mg/dL]) or severe hypoglycaemia were statistically significantly lower in the -SU/G versus +SU/G subgroups (rate ratio: 1.72 [95% CI: 1.103 to 2.697]) (Figure 3B). In the +SU/G subgroup, the annualized rates of any time (24 hour) confirmed (≤ 3.9 mmol/L [≤ 70 mg/dL]) or severe hypoglycaemia were 13.15 and 20.33 events/participant-year in the Gla-300

and Gla-100 subgroups, respectively; in the -SU/G group, the rates were 7.38 and 11.69 events/participant-year, respectively (Figure 3B).

Few severe hypoglycaemic events were reported (2 vs. 3 in the +SU/G and -SU/G subgroups, respectively).

4 | DISCUSSION

In the EDITION JP 2 trial conducted in Japanese people with T2DM, participants receiving Gla-300 achieved sustained glycaemic control and experienced less hypoglycaemia versus those receiving Gla-100.⁷ The current post hoc analysis demonstrates that these results were observed similarly for the +SU/G and -SU/G subgroups.

The +SU/G subgroup, overall, was associated with a higher risk for hypoglycaemia compared with the -SU/G subgroup. There was a statistically significant reduction in the risk of nocturnal (00:00–05:59 hours) or any time (24 hour) confirmed (≤ 3.9 mmol/L

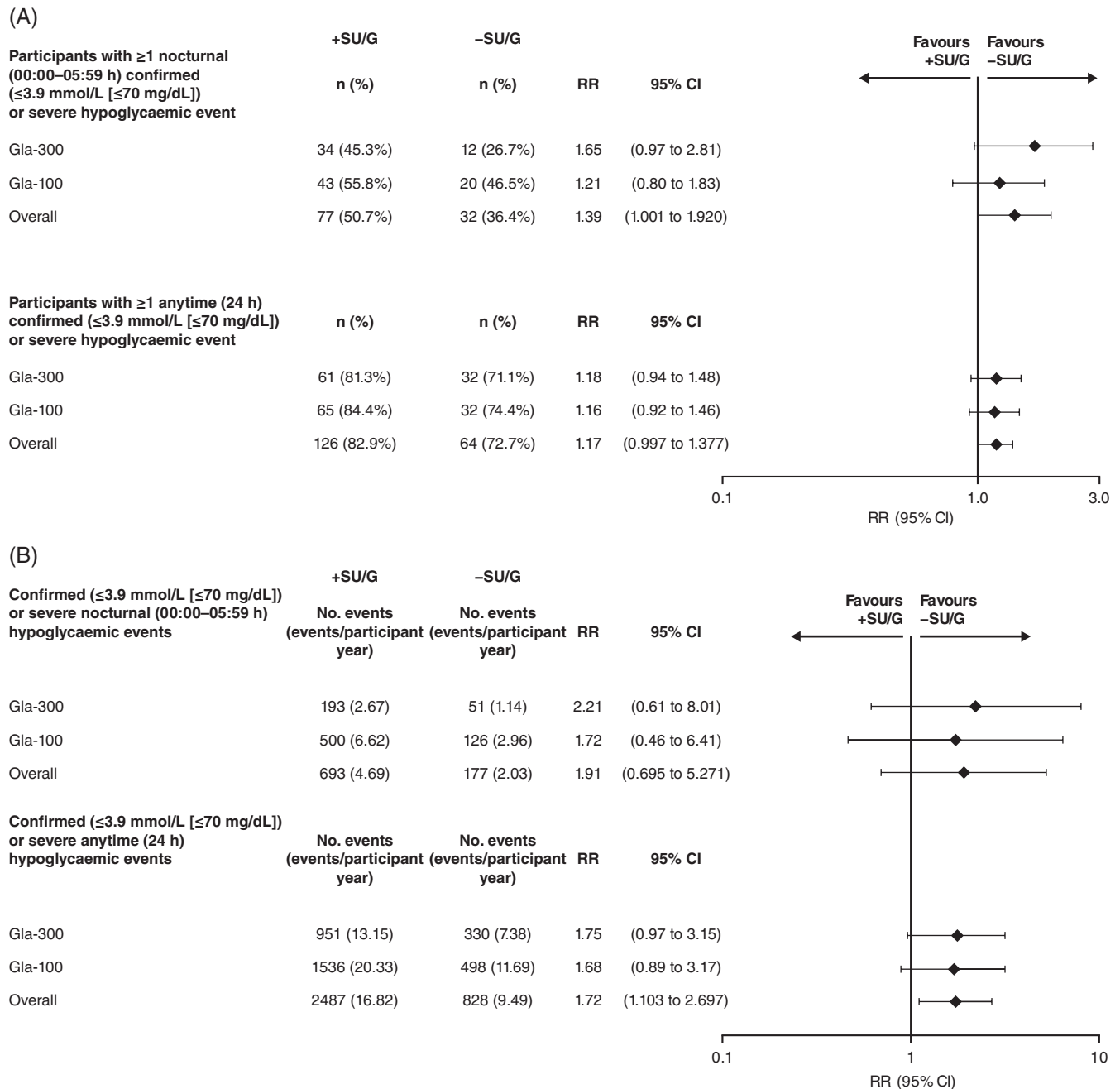


FIGURE 3 Confirmed (≤ 3.9 mmol/L [≤ 70 mg/dL]) or severe hypoglycaemia, during the night (00:00–05:59 hours) and at any time of day (24 hour) over the 12-month treatment period, for participants with or without concomitant sulphonylurea and/or glinide (safety population). A, relative risk of experiencing ≥ 1 hypoglycaemic event and B, rate ratio of hypoglycaemic events. A, based on RR stratified by randomization strata of screening HbA1c ($< 8.0\%$ or $\geq 8.0\%$), using a Cochran–Mantel–Haenszel (CMH) methodology. n (%) = number and percentage of patients with at least one hypoglycaemia event. CI, confidence interval; G, glinide; RR, relative risk; +SU/G, participants receiving concomitant sulphonylurea or glinide; -SU/G, participants not receiving sulphonylurea or glinide; SU, sulphonylurea. B, based on overdispersed Poisson regression model with treatment and randomization strata of screening HbA1c ($< 8.0\%$, $\geq 8.0\%$) as fixed effects, and logarithm of the treatment-emergent period as offset. CI, confidence interval; G, glinide; RR, rate ratio; +SU/G, participants receiving concomitant sulphonylurea or glinide; -SU/G, participants not receiving sulphonylurea or glinide; SU, sulphonylurea

≤ 70 mg/dL]) or severe hypoglycaemia in the -SU/G versus +SU/G subgroup, irrespective of whether Gla-300 or Gla-100 was used. This higher risk for hypoglycaemia with sulphonylurea is presumably related to their effects on insulin secretion,²⁰ as has been reported previously in the literature, both when used as a monotherapy,²¹ and when used concomitantly with basal insulin.²² However, it remains

possible that differences in the subgroups studied also contributed to higher risk in the +SU/G participants. Although there were no more than modest differences in baseline HbA1c, FPG, duration of diabetes and of insulin use, and basal insulin dose, clear differences in the numbers of oral agents used were apparent. Whereas 56% of -SU/G participants were taking only one and 10% were taking more than two

OADs at randomization, the corresponding percentages were 20% and 47% in the +SU/G subgroup.

Given the similar HbA1c levels and basal insulin doses at entry in the +SU/G and -SU/G subgroups, the clearly greater need for glucose-lowering therapies in the +SU/G subgroup suggests that insulin secretion and/or action was more impaired in these participants. With the caveat of an ongoing SU/G effect on insulin secretion in the +SU/G subgroup, the similarity in baseline C-peptide would suggest comparable residual basal insulin secretion between the two groups. However, the greater increases in plasma glucose after meals (shown by SMPG) in the +SU/G subgroup versus the -SU/G subgroup indicate a greater compromise in meal-related insulin secretion and insulin-stimulated muscle glucose uptake. Thus, it seems likely that the higher risk of hypoglycaemia in the +SU/G subgroup was influenced directly by the effects of sulphonylurea, and also by underlying metabolic differences in the population requiring different pharmacological treatments at study entry. Nevertheless, regardless of the mechanisms underlying greater risk of hypoglycaemia in the +SU/G subgroup, the advantage of Gla-300 relative to Gla-100 in limiting risk of hypoglycaemia was found to be present to approximately the same degree in both subgroups.

This analysis indicates that Gla-300 was associated with a significantly reduced annualized rate of nocturnal confirmed (≤ 3.9 mmol/L [≤ 70 mg/dL]) or severe hypoglycaemic events versus Gla-100, in both the +SU/G and -SU/G subgroups. For any time of day (24 hour) confirmed (≤ 3.9 mmol/L [≤ 70 mg/dL]) or severe hypoglycaemia rates were significantly reduced in the +SU/G but not the -SU/G subgroup. The type and dose of background OADs remained unchanged during the study, unless identified safety concerns necessitated a reduction in dose or discontinuation of OAD. Therefore, it is possible that there were differences in the dosage of background OADs between groups, or other factors, that could have contributed to the differing hypoglycaemic risks.

Consistent with the EDITION JP 2 overall trial results,⁷ a greater relative dose of Gla-300 than Gla-100 was required; this was observed in both the +SU/G and -SU/G subgroups. There appeared to be a greater treatment difference in the -SU/G subgroup compared with the +SU/G; however, this difference was not significant. As in the other EDITION studies in T2DM populations,^{8,12} less body weight gain was observed with Gla-300 versus Gla-100. This was observed in both the +SU/G and -SU/G subgroups. However, the difference in body weight change observed between participants treated with Gla-300 and those receiving Gla-100 achieved statistical significance in the -SU/G subgroup, with those treated with Gla-300, on average, losing body weight, while those on Gla-100 gained body weight. The treatment difference was constant throughout the treatment period in the Gla-300 + SU/G subgroup. By contrast, for participants in the Gla-300 -SU/G subgroup, the treatment difference in body weight increased steadily from month 4 to month 12, at which time it was greater compared with that in the Gla-100 -SU/G subgroup. Although the reason for this finding is unknown, the observation is of potential clinical relevance for patients and physicians. Fear of body weight gain is a common barrier to continuing insulin treatment.²³ In the current study, no body weight gain was observed with Gla-300 in either the

+SU/G or -SU/G subgroup, which may encourage individuals to continue their insulin regimen.

The limitations previously described for the EDITION JP 2 trial⁷ also apply to this post hoc analysis. These include the open-label design owing to the different injection devices and volumes used. The number of patients in the -SU/G subgroup was smaller than that in the +SU/G subgroup; baseline glycaemic control was not similar between +SU/G and -SU/G, suggesting different population characteristics. Moreover, sulphonylurea and glinide were not the only concomitant OADs used in this study. However, of the concomitant OADs used, it is noted that α -glucosidase inhibitors, thiazolidinediones and biguanides (e.g. metformin) are known not to increase the risk of hypoglycaemia. Additionally, the intrinsic limitation of any post hoc analyses, that the analyses were not pre-planned, should also be considered in the interpretation of these findings.

The need for improved management strategies for T2DM in Japan is apparent from the considerable economic burden of the disease.⁶ The EDITION 1, 2, and 3 studies demonstrate sustained glycaemic control with less hypoglycaemia with Gla-300 versus Gla-100, thus providing an improved option for T2DM management. In Japan, guidelines for the management of T2DM recommend that OADs be initiated if diet and exercise do not achieve favourable glycaemic control.¹⁴ Considering that one of the most commonly used OAD classes in Japan is sulphonylureas,¹⁷ the results presented in this post hoc analysis suggest that regardless of sulphonylurea use, Gla-300 is an effective basal insulin therapy relevant to people in Japan, and may help reduce the burden of diabetes in Japan. The data also suggest, however, that to reduce the risk of hypoglycaemia, it may be preferable to withdraw sulphonylurea and start, for example, treatment with a DPP-4 inhibitor, when basal insulin is initiated.

In conclusion, this analysis of data from the EDITION JP 2 trial demonstrates that the comparable glycaemic control and reduced risk of hypoglycaemia reported for Gla-300 versus Gla-100 in the EDITION trials was observed regardless of individuals using or not using sulphonylurea and/or glinide. In both basal insulin treatment groups, a trend towards a higher risk of hypoglycaemia in the +SU/G subgroup versus the -SU/G subgroup was observed. Despite the limitation of post hoc analyses, these observations suggest that use of Gla-300 may be expected to have similarly favourable effects compared with Gla-100.

ACKNOWLEDGMENTS

This study was sponsored by Sanofi. The authors thank the study participants, trial staff and investigators for their participation. Rie Ichihashi, Sanofi Japan, performed statistical programming. Editorial assistance was provided by Sharon Eastwood (DPhil) of Fishawack Communications, UK, and was funded by Sanofi.

Conflict of interest

Y. Terauchi: research support – Astellas Pharma, AstraZeneca, Bayer Yakuhin, Boehringer Ingelheim, Daiichi-Sankyo, Dainippon-Sumitomo, Eli Lilly, Kissei, Kowa Pharmaceutical, Merck (MSD), Novartis, Novo Nordisk, Ono, Sanofi, Sanwa Kagaku Kenkyusho, Shionogi, Taishotoyama, Takeda, Tanabe-Mitsubishi; speakers

bureau – Astellas, AstraZeneca, Bayer Yakuhin, Boehringer Ingelheim, Daiichi-Sankyo, Dainippon-Sumitomo, Eli Lilly, Kissei, Kowa Pharmaceutical, Merck (MSD), Novartis, Novo Nordisk, Ono, Pfizer, Sanofi, Sanwa Kagaku Kenkyusho, Shionogi, Taishotoyama, Takeda, Tanabe-Mitsubishi, Teijin; other – advisor for EDITION JP studies.

M. C. R.: advisory panel – Sanofi; consultant – AstraZeneca, Biodel, Elcelyx, GlaxoSmithKline, Sanofi, Theracos, Valeritas; research support – AstraZeneca, Eli Lilly, Novo Nordisk. These dualities of interest have been reviewed and managed by Oregon Health & Science University.

T. H.: advisory panel – Eli Lilly, Novo Nordisk, Sanofi; research support – Astellas, AstraZeneca, Boehringer Ingelheim, Daiichi-Sankyo, Dainippon-Sumitomo, Eli Lilly, Merck (MSD), Novo Nordisk, Ono, Sanofi, Takeda, Tanabe-Mitsubishi, Bayer Yakuhin; speakers bureau – AstraZeneca, Boehringer Ingelheim, Daiichi-Sankyo, Eli Lilly, Kissei, Merck (MSD), Novo Nordisk, Ono, Sanofi, Takeda, Tanabe-Mitsubishi; other – Sanofi, Insulin-Dosing Supervision Committee.

M. K.: employee and stock/shareholder of Sanofi.

X. C.: employee of Sanofi.

Y. Takahashi: employee of Sanofi.

G. B. B.: advisory panel – Sanofi; consultant – Novartis; speakers bureau – Eli Lilly.

Author contributions

Sanofi was the sponsor of the study, and was responsible for the design and coordination of the trial, monitoring clinical sites, collecting and managing data, and performing all statistical analyses. Y. Terauchi collected the data and participated in reviewing and editing the manuscript as principal investigator. M. K. contributed to the design of the study protocol and reviewed the manuscript. X. C. operated the study and reviewed the manuscript as study director. Y. Takahashi participated in analysing the data and in writing, reviewing and editing the manuscript. M. C. R. and G. B. B. participated in analysing the findings and writing, reviewing and editing the manuscript. T. H. reviewed the data related to glycaemic control and dose titration as a member of the Insulin-Dosing Supervision Committee and reviewed the manuscript. All the authors had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

ORCID

Yasuo Terauchi  <http://orcid.org/0000-0002-8872-3697>

Matthew C. Riddle  <http://orcid.org/0000-0003-1169-3036>

Geremia B. Bolli  <http://orcid.org/0000-0003-4966-4003>

REFERENCES

1. WHO. Global report on diabetes 2016. http://apps.who.int/iris/bitstream/10665/204871/1/9789241565257_eng.pdf?ua=1. Accessed January 27, 2016.
2. Mukai N, Doi Y, Ninomiya T, et al. Trends in the prevalence of type 2 diabetes and prediabetes in community-dwelling Japanese subjects: the Hisayama Study. *J Diabetes Investig*. 2014;5:162-169.
3. Chan JC, Malik V, Jia W, et al. Diabetes in Asia: epidemiology, risk factors, and pathophysiology. *JAMA*. 2009;301:2129-2140.
4. Saito E, Charvat H, Goto A, et al. Burden of cancer associated with type 2 diabetes mellitus in Japan, 2010–2030. *Cancer Sci*. 2016;107:521-527.
5. Tanaka S, Tanaka S, Imuro S, et al. Cohort profile: the Japan diabetes complications study: a long-term follow-up of a randomised lifestyle intervention study of type 2 diabetes. *Int J Epidemiol*. 2014;43:1054-1062.
6. International Diabetes Federation. *IDF Diabetes Atlas*. 7th ed. Brussels, Belgium: International Diabetes Federation; 2015. <http://www.diabetesatlas.org/>. Accessed January 27, 2016.
7. Terauchi Y, Koyama M, Cheng X, et al. Glycaemic control and hypoglycaemia with insulin glargine 300 U/mL compared with glargine 100 U/mL in Japanese adults with type 2 diabetes using basal insulin plus oral anti-hyperglycaemic drugs (EDITION JP 2 randomised 12-month trial including 6-month extension). *Diabetes Metab*. 2017;43:446-452.
8. Bolli GB, Riddle MC, Bergenstal RM, et al. New insulin glargine 300 U/mL compared with glargine 100 U/mL in insulin-naïve people with type 2 diabetes on oral glucose-lowering drugs: a randomized controlled trial (EDITION 3). *Diabetes Obes Metab*. 2015;17:386-394.
9. Riddle MC, Bolli GB, Ziemien M, et al. New insulin glargine 300 units/mL versus glargine 100 units/mL in people with type 2 diabetes using basal and mealtime insulin: glucose control and hypoglycaemia in a 6-month randomized controlled trial (EDITION 1). *Diabetes Care*. 2014;37:2755-2762.
10. Yki-Jarvinen H, Bergenstal R, Ziemien M, et al. New insulin glargine 300 units/mL versus glargine 100 units/mL in people with type 2 diabetes using oral agents and basal insulin: glucose control and hypoglycaemia in a 6-month randomized controlled trial (EDITION 2). *Diabetes Care*. 2014;37:3235-3243.
11. Riddle MC, Yki-Jarvinen H, Bolli GB, et al. One-year sustained glycaemic control and less hypoglycaemia with new insulin glargine 300 U/ml compared with 100 U/ml in people with type 2 diabetes using basal plus meal-time insulin: the EDITION 1 12-month randomized trial, including 6-month extension. *Diabetes Obes Metab*. 2015;17:835-842.
12. Yki-Jarvinen H, Bergenstal RM, Bolli GB, et al. Glycaemic control and hypoglycaemia with new insulin glargine 300 U/ml versus insulin glargine 100 U/ml in people with type 2 diabetes using basal insulin and oral antihyperglycaemic drugs: the EDITION 2 randomized 12-month trial including 6-month extension. *Diabetes Obes Metab*. 2015;17:1142-1149.
13. Terauchi Y, Koyama M, Cheng X, et al. 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). *Diabetes Obes Metab*. 2016;18:366-374.
14. Japan Diabetes Society. Evidence-based practice guideline for the treatment for diabetes in Japan 2013. http://www.jds.or.jp/modules/en/index.php?content_id=44. Accessed September 2, 2016.
15. Kostev K, Dippel FW, Rathmann W. Predictors of hypoglycaemia in insulin-treated type 2 diabetes patients in primary care: a retrospective database analysis. *Prim Care Diabetes*. 2014;8:127-131.
16. Arai K, Matoba K, Hirao K, et al. Present status of sulfonylurea treatment for type 2 diabetes in Japan: second report of a cross-sectional survey of 15,652 patients. *Endocrine*. 2010;57:499-507.
17. Tanabe M, Motonaga R, Terawaki Y, Nomiyama T, Yanase T. Prescription of oral hypoglycemic agents for patients with type 2 diabetes mellitus: a retrospective cohort study using a Japanese hospital database. *J Diabetes Investig*. 2017;8:227-234.
18. van Dalem J, Brouwers MC, Stehouwer CD, et al. Risk of hypoglycaemia in users of sulphonylureas compared with metformin in relation to renal function and sulphonylurea metabolite group: population based cohort study. *BMJ*. 2016;354:i3625.
19. ADA Workgroup on Hypoglycemia. Defining and reporting hypoglycemia in diabetes: a report from the American Diabetes Association Workgroup on Hypoglycemia. *Diabetes Care*. 2005;28:1245-1249.
20. Seino S. Cell signalling in insulin secretion: the molecular targets of ATP, cAMP and sulfonylurea. *Diabetologia*. 2012;55:2096-2108.
21. Palmer SC, Mavridis D, Nicolucci A, et al. Comparison of clinical outcomes and adverse events associated with glucose-lowering drugs in patients with type 2 diabetes: a meta-analysis. *JAMA*. 2016;316:313-324.
22. Vos RC, Rutten G. Oral hypoglycemic agents added to insulin monotherapy for type 2 diabetes. *JAMA*. 2017;318:1489-1490.

23. Peyrot M, Barnett AH, Meneghini LF, Schumm-Draeger PM. Insulin adherence behaviours and barriers in the multinational global attitudes of patients and physicians in insulin therapy study. *Diabet Med*. 2012; 29:682-689.

SUPPORTING INFORMATION

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

How to cite this article: Terauchi Y, Riddle MC, Hirose T, et al. Glycaemic control, hypoglycaemia, and weight change with insulin glargine 300 U/mL versus insulin glargine 100 U/mL in Japanese adults with type 2 diabetes: A 12-month comparison by concomitant sulphonylurea and/or gliinide use. *Diabetes Obes Metab*. 2018;20:2541-2550. <https://doi.org/10.1111/dom.13414>