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BRIEF REPORT

Glycaemic control and hypoglycaemia in people with type 2 diabetes switching from twice-daily basal insulin to once-daily insulin glargine 300 U/mL or insulin glargine 100 U/mL (EDITION 1 and EDITION 2 subgroup analysis)

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In this *post hoc* analysis we compared glycaemic control and hypoglycaemia between insulin glargine 300 U/mL (Gla-300) and glargine 100 U/mL (Gla-100) administered once daily in people with type 2 diabetes (T2DM) from the EDITION 1 (basal plus mealtime insulin) and EDITION 2 (basal insulin plus oral antihyperglycaemic drugs) trials who were previously receiving twice-daily insulin. At randomization, 16.9% and 20.0% of people in EDITION 1 and 2, respectively, were receiving twice-daily basal insulin. Glycated haemoglobin change from baseline to Month 6 was similar over 6 months with Gla-300 or Gla-100 (least squares mean difference −0.01%; 95% confidence interval [CI] −0.27 to 0.24] in EDITION 1 and 0.16%; 95% CI −0.25 to 0.57, in EDITION 2). Participants previously receiving twice-daily insulin in EDITION 1 had a lower risk of confirmed (≤3.9 mmol/L [≤70 mg/dL]) or severe hypoglycaemia with Gla-300 vs Gla-100 at night (00:00–05:59 hours), but not at any time (24 hours); in EDITION 2 the risk was reduced at night and any time (24 hours). In conclusion, Gla-300 provided similar glycaemic control with less hypoglycaemia compared with Gla-100 in people with T2DM switching from twice-daily to once-daily basal insulin.

KEYWORDS

basal insulin, glycaemic control, hypoglycaemia, insulin analogues, phase III study, type 2 diabetes

1 | INTRODUCTION

Reducing the number of daily basal insulin injections for people with type 2 diabetes (T2DM) can lower the burden of disease management, potentially leading to improved treatment adherence and persistence,[1] which may be associated with better long-term blood glucose control, improved health resource utilization, and reduced costs.[2,3] Long-acting basal insulin analogues, such as insulin glargine 100 U/mL (Gla-100; Lantus; Sanofi, Paris, France) or detemir, have improved pharmacokinetic and pharmacodynamic profiles, with longer duration of action than neutral protamine Hagedorn (NPH) insulin,[3,4] allowing many people with T2DM to adopt a once-daily

regimen[3,4]; however, a substantial proportion of individuals using basal insulin still inject at least twice daily.[3,5] Potential reasons for this may include a perceived, or real, risk of hypoglycaemia with shorter-acting basal insulins,[2,6,7] the desire to adjust daytime and night-time basal insulin doses, and reducing the injection site discomfort associated with higher volume injections.[8]

Insulin glargine 300 U/mL (Gla-300; Toujeo; Sanofi) has a prolonged pharmacokinetic/pharmacodynamic profile compared with Gla-100, with low variability and high reproducibility, resulting in more predictable and evenly distributed glucose-lowering activity beyond 24 hours.[9,10] This extended and more stable coverage may enable more people currently administering multiple daily basal insulin injections to minimize the number of basal injections. The EDITION 1 to 3 trial programme assessed the efficacy and safety of Gla-300 in T2DM, and demonstrated similar glycaemic control vs Gla-100 with less hypoglycaemia.[11] This *post hoc* analysis of EDITION 1 and 2 has explored the effect of switching to once-daily therapy on outcomes with Gla-300 and Gla-100 in the subgroup of participants previously receiving twice-daily basal insulin injections.

2 | MATERIALS AND METHODS

2.1 | Study design and participants

EDITION 1 (NCT01499082) and 2 (NCT01499095) were multicentre, randomized, open-label, two-arm, parallel-group, 6-month, phase IIIa trials in people aged ≥18 years with T2DM receiving basal and prandial insulin (EDITION 1), or basal insulin with oral antihyperglycaemic drugs (EDITION 2) at baseline; results from these studies have been previously reported.[12,13] Participants in both trials were randomized (1:1) to receive once-daily evening injections of either Gla-300 or Gla-100 titrated to a fasting self-monitored plasma glucose (SMPG) target of 4.4 to 5.6 mmol/L (80-100 mg/dL). Full titration protocols are provided in File S1.

This *post hoc* analysis was performed in participants who had received twice-daily injections of Gla-100 or NPH insulin at 2 different times of day during the last 7 days before randomization. Participants receiving twice-daily Gla-100 before randomization were switched to Gla-300 or remained on Gla-100 using an equivalent starting dose. For those previously receiving NPH insulin twice daily, the starting dose of Gla-300 or Gla-100 was 20% lower than the previous NPH insulin dose. The subpopulations from each study were analysed separately; participants injecting basal insulin more frequently than twice a day were excluded from the analysis.

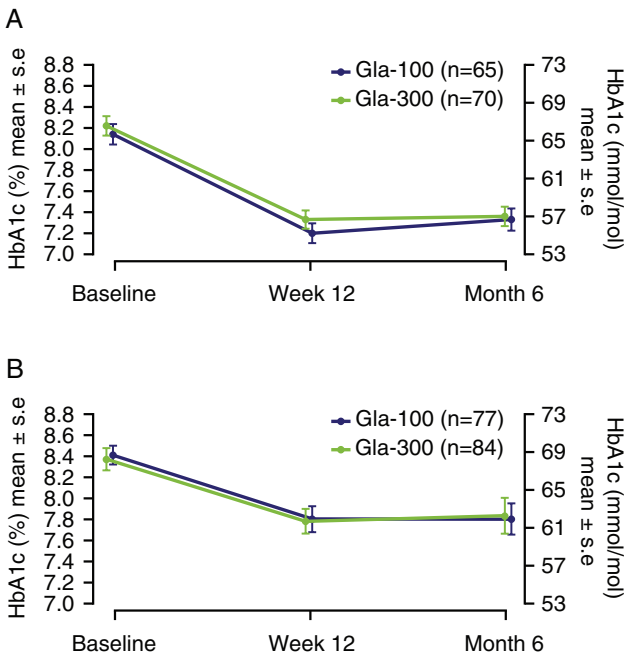

FIGURE 1 HbA1c over 6 months in participants previously treated with twice-daily basal insulin in A, the EDITION 1 study and B, the EDITION 2 study (modified intention-to-treat population). Abbreviation: s.e., standard error

2.2 | Outcomes

The efficacy endpoints were change in glycated haemoglobin (HbA1c), SMPG and insulin dose from baseline to Month 6. Safety endpoints included: participants with ≥1 confirmed or severe hypoglycaemic event (nocturnal [00:00–05:59 hours] and at any time of day [24 hours]); annualized rates of hypoglycaemia; and change in body weight from baseline to Month 6. All hypoglycaemic events were defined based on American Diabetes Association categories[14] and thresholds[15] (File S1). Details of analyses and statistics performed are provided in File S1.

3 | RESULTS

3.1 | Study population

In total, 296 participants had previously received twice-daily insulin, 135/801 (16.9%) from EDITION 1, and 161/804 (20.0%) from EDITION 2. Baseline characteristics were similar in both treatment groups overall and within each study for these participants (File S1 Results; Table S1).

3.2 | Glycaemic control

Overall, a greater decrease in HbA1c from baseline to Month 6 for participants previously receiving twice-daily insulin was observed in EDITION 1 than EDITION 2; however, similar improvements were observed for Gla-300 and Gla-100 (Figure 1). The least squares (LS) mean (standard error) change from baseline to Month 6 was −0.77 (0.09)% (−8.4 [1.0] mmol/mol) with Gla-300 and −0.76 (0.10)% (−8.3 [1.0] mmol/mol) with Gla-100 in EDITION 1, and −0.40 (0.16)% (−4.4 [1.8] mmol/mol) and −0.55 (0.17)% (−6.0 [1.8 mmol/mol), respectively, in EDITION 2. The LS mean difference in change from baseline to Month 6 between groups was −0.01% (95% confidence interval [CI] −0.27 to 0.24) or −0.1 mmol/mol (95% CI −2.9 to 2.6) in EDITION 1 and 0.16% (95% CI −0.25 to 0.57) or 1.7 mmol/mol (95% CI −2.8 to 6.2) in EDITION 2. Reductions in HbA1c were consistent with those previously reported for the overall study population,[12,13] and with those observed in participants previously receiving once-daily dosing (Figure S1, File S1).

Similar changes in pre-breakfast SMPG and 8-point SMPG profiles were found between Gla-300 and Gla-100 in both studies (File S1 Results; Table S2). These changes were consistent with those observed in the overall population.[12,13] Low variability (~20%-30%) in 8-point SMPG profiles was consistently observed across all study visits for both treatment groups in EDITION 1 and 2 (File S1, Table S2).

3.3 | Insulin dose

Mean daily basal insulin dose increased from baseline to Month 6 in both treatment groups, with the greatest increase during the initial 12 weeks of treatment and a higher dose increase observed with Gla-300 (File S1, Table S3). A greater relative difference in insulin dose between treatment groups was observed in EDITION 1 than EDITION 2 (13.2% vs 8.6%).

3.4 | Hypoglycaemia

The risk of confirmed (≤3.9 mmol/L [≤70 mg/dL]) or severe nocturnal hypoglycaemia was lower with Gla-300 than Gla-100 in both EDITION 1 and 2 (Figure 2A and Table S4, File S1). In EDITION 2, participants previously receiving twice-daily insulin also had a reduced risk of confirmed or severe hypoglycaemia at any time of day (24 hours) with Gla-300 vs Gla-100, regardless of the glycaemic threshold.

Annualized rates of confirmed or severe hypoglycaemia in participants previously receiving twice-daily insulin were similar for Gla-300 and Gla-100 in EDITION 1 (Figure 2B and Table S5, File S1). In EDITION 2, the annualized rate of nocturnal confirmed or severe hypoglycaemia was lower with Gla-300 vs Gla-100 at the ≤3.9 mmol/L (≤70 mg/dL) threshold, and similar with Gla-100 at the stricter threshold (<3.0 mmol/L [<54 mg/dL]). No significant between-group differences were noted for annualized rates of confirmed or severe hypoglycaemia at any time of day (24 hours).

Incidence and annualized rates of hypoglycaemia in participants previously receiving twice-daily insulin were generally consistent with those previously receiving once-daily insulin (Figures S2 and S3, File S1) and the overall population.[12,13]

For severe hypoglycaemia, the incidence and annualized rates in participants previously receiving twice-daily insulin was low and similar between treatment groups (Tables S4 and S5, File S1).

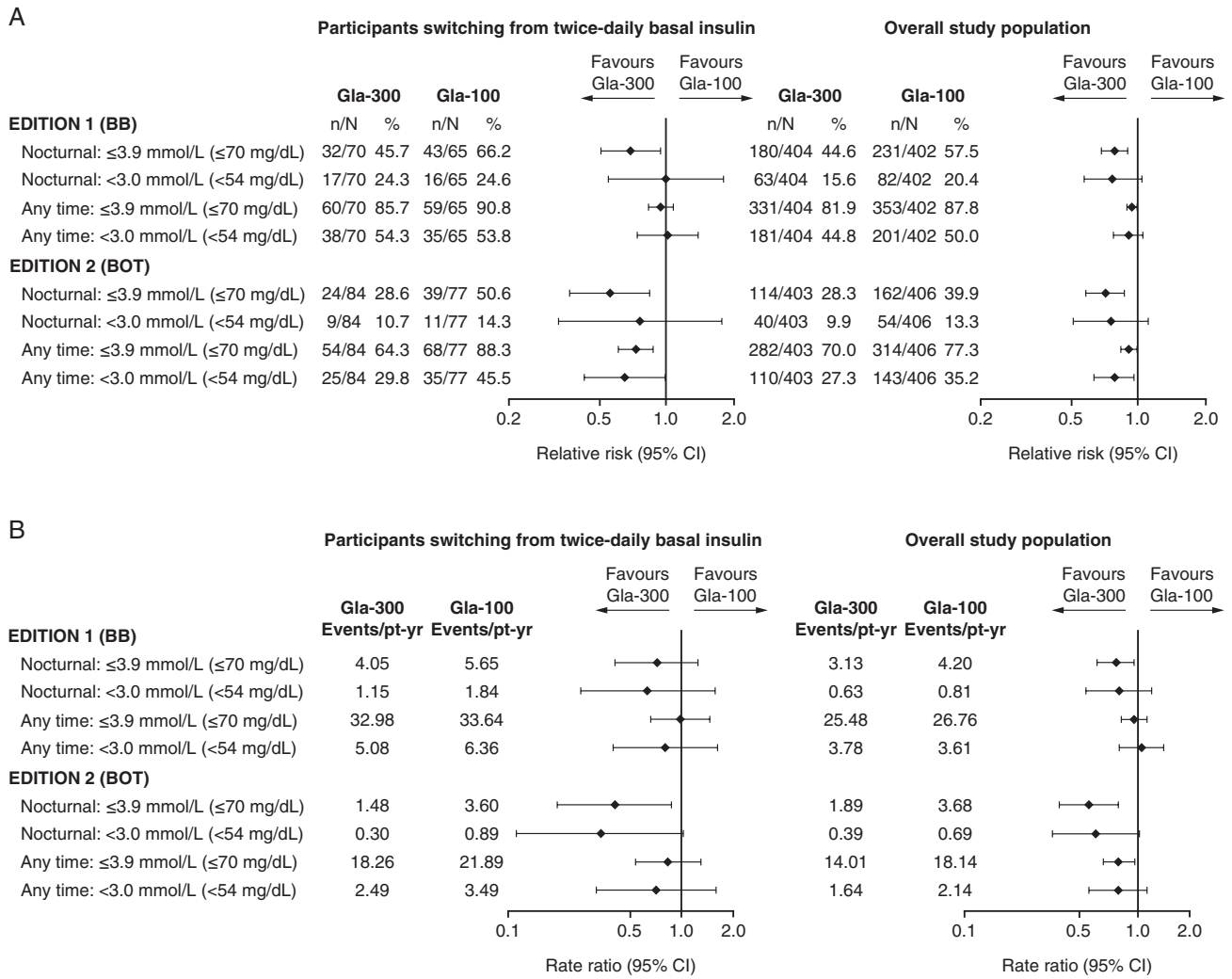

FIGURE 2 A, Percentage of participants experiencing ≥1 confirmed or severe hypoglycaemic event and B, annualized rates of confirmed or severe hypoglycaemic events at night (00:00–05:59 hours) or at any time (24 hours) and relative risk during the 6-month treatment periods (safety population). Abbreviations: BB, basal bolus; BOT, basal-supported oral therapy; CI, confidence interval; pt-yr, participant-year

3.5 | Body weight

The mean (standard deviation) weight gain from baseline to Month 6 was similar between treatment groups (Gla-300: 1.39 [3.50] kg; Gla-100: 1.32 [3.13] kg) in EDITION 1. In EDITION 2, a small decrease in body weight was seen in participants who switched to once-daily Gla-300 (−0.71 [5.11] kg); a slight increase in body weight was seen in the once-daily Gla-100 group (0.58 [2.59] kg).

4 | DISCUSSION

This *post hoc* analysis of participants from EDITION 1 and 2 who switched from a twice-daily to a once-daily insulin regimen demonstrated similar levels of glycaemic control, low glycaemic variability, and lower rates of hypoglycaemia with Gla-300 vs Gla-100. Differences in the occurrence of hypoglycaemia by treatment were observed within the trials: participants in EDITION 1 had a lower risk of confirmed (≤3.9 mmol/L [≤70 mg/dL]) or severe hypoglycaemia with Gla-300 vs Gla-100 at night (00:00–05:59 hours), while in EDITION 2, the risk was reduced both at night and at any time of day (24 hours).

Interestingly, participants in the Gla-100 subgroup experienced a reduction in HbA1c, despite several having already received Gla-100 prior to the study. This may reflect the rigorous titration algorithm used in these treat-to-target studies.[12,13] It is also possible that participants previously on a twice-daily regimen had previously found the management regimen complicated and had difficulty with self-titration; hence the improvement when switching to once-daily Gla-100.

While 16.9% and 20.0% of participants in EDITION 1 and EDITION 2, respectively, were previously receiving twice-daily basal insulin, the possible reasons for this may differ. In EDITION 1, the mean daily basal insulin dose in those previously on a twice-daily regimen was >80 U at baseline. As the maximum dose delivered by injection devices used for Gla-100 and NPH insulin is 60 to 80 U/d, participants may have chosen a twice-daily regimen to avoid injecting twice at the same time. For these individuals, insulins that provide the same number of units in a lower injected volume may allow a return to a once-daily regimen. In EDITION 2, a high proportion of those previously on a twice-daily regimen (78%) were using NPH insulin, which has a shorter duration of action than Gla-100; this may have influenced the percentage of participants previously on twice-daily insulin.

The convenience of switching to once-daily dosing may improve quality of life,[1] adherence to therapy,[1] and, consequently, may lead to better glycaemic control.[2] Some people with diabetes, however, may still prefer a twice-daily regimen; this choice should be respected, as effective self-management is reliant on the patient being comfortable with their daily routine. Nevertheless, Gla-300 can be considered as an option for people with T2DM wishing to switch to a once-daily regimen.

Limitations of the present study include its *post hoc*, exploratory nature. As the EDITION studies were not designed to evaluate the effect of switching from twice-daily to once-daily dosing regimens, this analysis only included a small number of participants. As per the inclusion criteria of the studies,[12,13] participants were receiving relatively high doses of basal insulin, and may not be representative of the global T2DM population; however, this analysis offers clinical evidence on switching from twice-daily to once-daily basal insulin dosing. Further studies investigating switching to Gla-300 in different populations of people with T2DM, including those with lower body mass index and requiring lower doses of insulin, would be of interest.

In conclusion, in this *post hoc* analysis of 6-month data from EDITION 1 and 2, people with T2DM who switched from twice-daily basal insulin to once-daily evening injection of Gla-300 achieved similar glycaemic control with a lower risk of hypoglycaemia compared with those who switched to once-daily Gla-100. These findings suggest that people with T2DM currently on a twice-daily insulin regimen can choose to switch to once-daily Gla-300 while maintaining glycaemic control, without an increased risk of hypoglycaemia. Switching to once-daily Gla-300 is also likely to reduce the burden of self-management, which may improve adherence and potentially outcomes.[1,2] As the switching protocol used in the EDITION studies was similar to the guidance now provided in the Gla-300 product label,[16,17] these findings from the EDITION studies are likely to be relevant to real-life clinical practice. It will be interesting to see whether there are differences observed in glycaemic control between Gla-300 and Gla-100 in "real-life" clinical studies without centrally defined insulin titration algorithms.

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Conflict of interest

R. R. has received honoraria for advising and lecturing from Sanofi, MSD, Janssen, Eli Lilly, Kayentis, AstraZeneca and Boehringer Ingelheim, is a Board member for Novo Nordisk, and has received research support from Sanofi. M. C. d'E. has served on advisory panels for AstraZeneca, Eli Lilly and Takeda, and on the Speakers bureau for AstraZeneca, Eli Lilly, Takeda, Novo Nordisk and Boehringer Ingelheim. M. F. has received honoraria for advising, consulting and lecturing from Sanofi-Aventis, Boehringer Ingelheim, Eli Lilly, Janssen, MSD, Novo Nordisk, Takeda and AstraZeneca. F. J. A-B. has received honoraria for speaking/consulting for Abbott, AstraZeneca, Bristol-Myers Squibb, Eli Lilly, GlaxoSmithKline, LifeScan, Madaus, MannKind Corporation, Medtronic, Menarini, Merck Farma y Química, SA, MSD, Novartis, Novo Nordisk, Pfizer, Roche, Sanofi, Schering-Plough and Solvay. P. S. is employed by Sanofi. A. M. G. C. and F. B. are employees and stock/shareholders of Sanofi. C. H. W. has received honoraria for consulting/lecturing from AstraZeneca, Janssen, Sanofi, Boehringer Ingelheim, Eli Lilly and Novo Nordisk, and research support from AstraZeneca, Boehringer Ingelheim, Eli Lilly, Intarcia, Janssen, Merck, Novo Nordisk and Sanofi.

Author contributions

Sanofi was the sponsor of the EDITION studies, and was responsible for the design and coordination of the trials. Sanofi monitored the

clinical sites and collected and managed the data. All authors participated in the interpretation of the results, and in writing, reviewing and editing the manuscript.

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SUPPORTING INFORMATION

Additional Supporting Information may be found online in the supporting information tab for this article.

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