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Glycaemic variability in patients with type 2 diabetes mellitus treated with dulaglutide, with and without concomitant insulin: Post hoc analyses of randomized clinical trials

Esteban Jódar PhD[1] 🔾 | Irene Romera PhD[2] | Qianqian Wang PhD[3] |
Sarah Louise Roche PhD[4] | Luis-Emilio García-Pérez PhD[2] 🔾

[1]Hospital Universitario Quirón Madrid, Universidad Europea, Madrid, Spain

[2]Lilly SA, Alcobendas, Spain

[3]Eli Lilly and Company, Indianapolis, Indiana, USA

[4]Eli Lilly and Company, Cork, Ireland

Correspondence
Dr. Luis-Emilio García-Pérez, PhD, Lilly S.A., Alcobendas, Madrid, Spain.
Email: garcia_luis-emilio@lilly.com

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Eli Lilly and Company

Abstract

Aim: To investigate the association between treatment with dulaglutide and glycaemic variability (GV) in adult patients with type 2 diabetes mellitus (T2D).

Materials and Methods: Post hoc analyses of six randomized, phase 3 studies were conducted to investigate the association between treatment with dulaglutide 1.5 mg once weekly and GV in adult patients with T2D. Using data from seven- and eight-point self-monitored plasma glucose (SMPG) profiles over up to 28 weeks of treatment, GV in within- and between-day SMPG, and between-day fasting glucose from SMPG (FSMPG) was assessed according to standard deviation and coefficient of variation.

Results: Pooled data from five studies with dulaglutide as monotherapy or added to oral glucose-lowering medication, without concomitant insulin treatment, revealed clinically meaningful reductions in within- and between-day SMPG, and between-day FSMPG variability from baseline in the dulaglutide group. Comparisons between treatment groups in two studies demonstrated that reductions from baseline in within-day and between-day SMPG, and between-day FSMPG variability were greater for treatment with dulaglutide compared with insulin glargine, as well as for treatment with dulaglutide when added to insulin glargine compared with insulin glargine alone.

Conclusions: In patients with T2D, treatment with dulaglutide as monotherapy or added to oral glucose-lowering medication, without concomitant insulin treatment, was potentially associated with a reduction in GV. Treatment with dulaglutide was associated with a reduction in GV to a greater degree than insulin glargine. When added to insulin glargine, treatment with dulaglutide was associated with greater decreases in GV compared with insulin glargine alone. As reduced GV may be associated with better outcomes, these findings may have clinical relevance.

KEYWORDS
antidiabetic drug, basal insulin, dulaglutide, glycaemic control, phase III study, type 2 diabetes

1 | INTRODUCTION

The "gold standard" for assessing glycaemic control in patients with type 2 diabetes mellitus (T2D) is centred on glycated haemoglobin (HbA1c), a clinical readout also proposed as a diagnostic criterion.[1] As noted by the American Diabetes Association (ADA), a limitation of HbA1c assessment is that it does not provide a measure of glycaemic variability (GV).[2] For example, two patients might record the same HbA1c level at a given point in time, but one might experience a far greater degree of blood glucose fluctuations than the other, which may have resulted in one or several hypoglycaemic events that would have gone unnoticed in an assessment of HbA1c.

Hypoglycaemia is a limiting factor in the effective glycaemic control of diabetes due to the nature of treatment strategies to lower blood glucose levels.[3] This matter is complicated further by GV, which prompts the concern that the risk of hypoglycaemia as blood glucose lowers with treatment is greater for patients who experience significant GV compared with those who do not,[4,5] irrespective of the actual HbA1c level.[6] Thus, the ADA recommends that clinicians exercise judgment when HbA1c is used as the only determinant in assessing glycaemic control, especially if the HbA1c reading is bordering a threshold that might warrant a change in medication.[2] GV is also implicated in microvascular and macrovascular complications[5,7,8] and is an independent determinant of coronary plaque instability.[9] A previous post hoc analysis of data from five phase 3 studies found that reductions in within-day GV were significantly associated with improvements in daily mean glucose and HbA1c.[10] A lowering of GV is therefore a desirable and perhaps critical treatment outcome.[4,11]

Studies on GV with injectable treatments have largely been focused on insulin, with fewer investigating the newer class of glucagon-like peptide-1 receptor agonists (GLP-1RAs).[12-26] A substudy of the Assessment of Weekly AdministRation of LY2189265 in Diabetes (AWARD)-4 Phase 3 trial demonstrated that treatment with dulaglutide compared with insulin glargine, in adult patients on concomitant insulin lispro, resulted in similar proportions of glucose values in the normoglycaemic range, but dulaglutide provided an improved balance between the proportion of values within the near normoglycaemic range and values within the hypoglycaemic range.[26] The substudy used continuous glucose monitoring (CGM) to assess GV, allowing for repeated glucose estimates at very short intervals and thus calculation of multiple metrics to provide a comprehensive assessment of GV.[26,27] Along with findings of reduced GV with other GLP-1RAs,[12,23] this prompts the hypothesis that dulaglutide may reduce GV in various patient populations and treatment scenarios.

The objective of this post hoc analysis was to investigate the association between treatment with dulaglutide and GV in adult patients with T2D. Specifically, we wished to first assess GV when dulaglutide is used in monotherapy or when added to oral glucose-lowering medications. Secondly and thirdly, we sought to determine GV following dulaglutide treatment, compared with insulin glargine, and when added to insulin glargine.

2 | MATERIALS AND METHODS

2.1 | Study designs and patients

AWARD-1, -2, -3, -6 and -8 were randomized, parallel-arm, double-blinded phase 3 studies assessing the efficacy of dulaglutide 1.5 mg once weekly (and also 0.75 mg in AWARD-1, -2 and -3) versus: placebo or exenatide twice daily (+ metformin and pioglitazone, AWARD-1); insulin glargine (+ metformin and glimepiride, AWARD-2); metformin (AWARD-3); liraglutide (+ metformin, AWARD-6); and placebo (+ glimepiride, AWARD-8), with regard to glycaemic control in patients with T2D. AWARD-9 was a randomized, open-label, parallel-arm comparison of the effects of dulaglutide 1.5 mg versus placebo on glycaemic control in patients with T2D receiving basal insulin glargine, with or without metformin. Detailed study designs and inclusion and exclusion criteria for the trials have been previously reported.[28-33]

In AWARD-2 (dulaglutide vs. insulin glargine), patients were instructed to adjust the dose of insulin according to a dosing algorithm and targeting a fasting plasma glucose (FPG) level <5.6 mmol/L.[29] At 26 weeks, the daily dose of glargine (mean ± standard deviation [SD]) was (last observation carried forward [LOCF]) 26 ± 24 units (0.29 ± 0.21 units/kg). AWARD-9 (dulaglutide + insulin glargine vs. placebo + insulin glargine) employed intensive insulin dose titration in both arms using the treat-to-target algorithm. At 28 weeks, least squares (LS) mean ± standard error (SE) increases from baseline in the daily dose of glargine were 13 ± 2 U (0.1 ± 0.02 U/kg) and 26 ± 2 U (0.3 ± 0.02 U/kg) for dulaglutide/glargine and placebo/glargine groups, respectively.[33]

2.2 | Ethics approval and consent to participate

Study protocols were reviewed and approved by appropriate institutional review boards for each of the study sites. The clinical trials were conducted according to Good Clinical Practice and the Declaration of Helsinki guidelines. All patients provided written informed consent before undergoing the study procedure. The studies are registered at ClinicalTrials.gov (NCT01064687, NCT01075282, NCT01126580, NCT01624259, NCT01769378 and NCT02152371).

2.3 | Post hoc analyses of GV

Included in the objectives of the clinical trials was measurement of blood glucose values from seven-point (AWARD-6, -8 and -9) or eight-point (AWARD-1, -2 and -3) self-monitored plasma glucose (SMPG) profiles. Patients were provided with commercially available blood glucose meters and asked to collect two SMPG profiles, each over a 24-hour period and on two separate days, within a period of up to 14 days (depending on the study) prior to baseline, and two SMPG profiles, each over a 24-hour period and on two separate days, within a period of up to 14 days (depending on the study) prior to

endpoint. The SMPG profile collection day was not prespecified in relation to the day of dulaglutide administration. These seven- or eight-point SMPG profiles were both pre-meal and 2-hours post-meal for morning, midday and evening, along with nighttime measurements at bedtime (not included in AWARD-8 and -9) and 3:00 AM (or 5 hours after bedtime; not included in AWARD-6). Post hoc analyses used these data to assess within-day GV from SMPG, between-day GV from SMPG, and between-day GV from fasting SMPG (FSMPG), as measured by SD and coefficient of variation (CV), similarly to a previous study that relied on two SMPG profiles.[10] Within-day GV measures variability across several time points within the same day. Between-day GV measures variability across days and can be shown for either a specific daily time point (morning pre-meal for example) or for daily average (inclusive of all daily time points assessed). We performed pooled post hoc analyses of clinical trial data from AWARD-1, -2, -3, -6 and -8 (dulaglutide as monotherapy or when added to oral glucose-lowering medication), as well as on individual group results from AWARD-2 and -9 studies (dulaglutide compared with or added to insulin glargine, respectively).

The within-day GV from SMPG was calculated by first calculating the SD and CV ([SD divided by the mean] $\times$ 100) for a single day using seven SMPG time points (3:00 AM/5 hours post bedtime time point excluded from eight-point profiles) and then averaging the SD and CV separately over two SMPG profiles for baseline and two SMPG profiles for endpoint.

The between-day GV from SMPG was calculated in two steps: first, for each SMPG time point during the day (morning pre-meal, morning post-meal, midday pre-meal, midday post-meal, evening pre-meal, evening post-meal, bedtime, 3:00 AM or 5 hours post bedtime) by calculating the SD and CV for each SMPG time point from two SMPG profiles; second, for the full SMPG profile by averaging the SD and CV separately over seven SMPG time points (3:00 AM/5 hours post bedtime time point in eight-point profiles excluded in this calculation). This was performed for both baseline and endpoint.

The between-day GV from FSMPG was assessed by calculating the morning pre-meal SD and CV values separately from two SMPG profiles for baseline and two SMPG profiles for endpoint. A visual representation of these calculations is presented in Supplementary Figure S5.

Analyses were based on an efficacy evaluable analysis set, defined as the intention-to-treat population with non-missing two profiles of SMPG at baseline and evaluable endpoint without post-rescue visits. Missing values of SMPG profiles at endpoint were imputed using LOCF. The endpoint was Week 26 for AWARD-1, -2, -3, -6 and -8 and Week 28 for AWARD-9.

2.4 | Statistical analysis

For AWARD-1, -2, -3, -6 and -8, descriptive statistics were calculated for baseline and endpoint GV measurements for patients taking dulaglutide 1.5 mg. A paired t-test with LOCF imputation was conducted to compare baseline and Week 26 endpoint GV measurements for the pooled AWARD studies and for each individual AWARD study. As the individual trials included in the pooled analysis showed consistent results, adjustment for trial heterogeneity was deemed unnecessary. For AWARD-2 (dulaglutide vs. insulin glargine) and AWARD-9 (dulaglutide added to insulin glargine vs. placebo added to insulin glargine), change of GV measurements at study endpoint with LOCF imputation was analysed by analysis of covariance, with fixed effect treatment, country and baseline GV measurements as covariates.

3 | RESULTS

3.1 | Patient baseline demographics and characteristics

The baseline demographics and characteristics for patients in the AWARD-1, -2, -3, -6, -8 and -9 trials are shown in Supplementary Table S1. The dulaglutide groups in AWARD-1, -2, -3, -6 and -8 were generally similar with regard to percentage of female patients, age, body mass index, HbA1c and FPG, although mean HbA1c ranged from 7.6% in AWARD-3 to 8.4% in AWARD-8. Mean weight was variable between dulaglutide groups from these studies, ranging from 84.8 kg in AWARD-8 to 96.8 kg in AWARD-1. Dulaglutide and insulin glargine groups in AWARD-2 were similar across all baseline characteristics, as were the treatment groups of dulaglutide added to insulin glargine and insulin glargine alone in AWARD-9.

3.2 | Potential association between dulaglutide and GV as monotherapy or when added to oral glucose-lowering medications

Data from AWARD-1, -2, -3, -6 and -8 showed that treatment with dulaglutide was potentially associated with reductions in within- and between-day SMPG variability by CV from baseline to endpoint, for each of the trials as well as for pooled data (Figure 1). These reductions were statistically significant except for between-day SMPG variability in AWARD-2. Closer inspection of between-day SMPG variability revealed that numerical reductions in variability from baseline to endpoint, were potentially associated with dulaglutide at all eight daily time points (Figure 2). Treatment with dulaglutide was potentially associated with statistically significant reductions from baseline to endpoint in between-day FSMPG variability in the pooled group, and with numerical reductions for such in each of the trials except AWARD-1, where a negligible increase (CV mean change from baseline 0.15, 95% confidence interval [CI] −0.98 to 1.29) was observed. For AWARD-6, this reduction from baseline to endpoint was statistically significant (Supplementary Figure S6). SD data were largely consistent with these results and are shown in Supplementary Tables S2 and S3. There was a strong correlation between baseline FSMPG values from the two SMPG profiles and FPG values from the central laboratory ($r = 0.67$, 0.65).

(A)

Within-day SMPG variability

(B)

Between-day SMPG variability
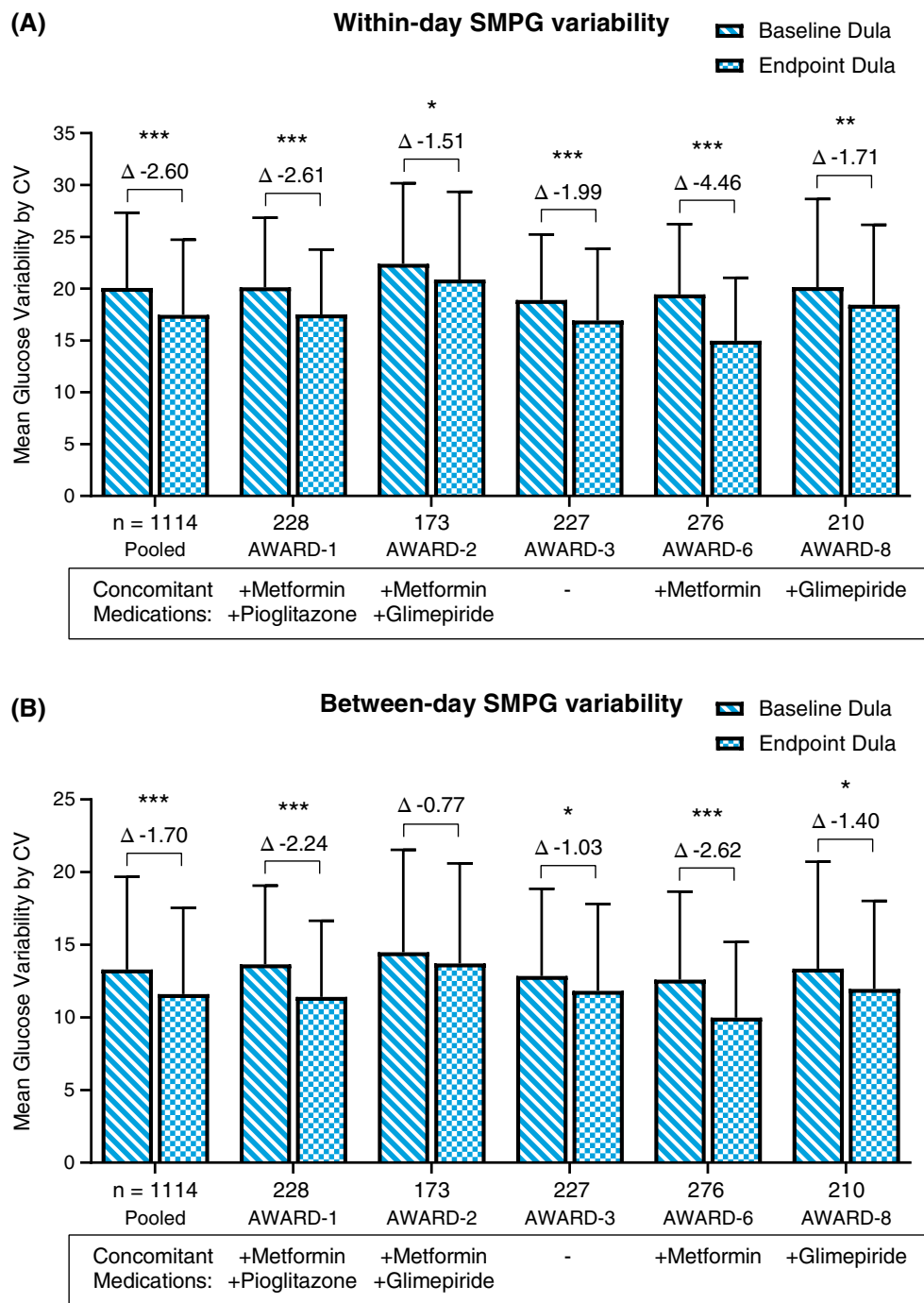
FIGURE 1 Within-day and between-day self-monitored plasma glucose (SMPG) variability at baseline and endpoint for dulaglutide as monotherapy or when added to oral glucose-lowering medications. Mean (A) within-day and (B) between-day SMPG variability according to coefficient of variation (CV) at baseline and endpoint in patients treated with dulaglutide 1.5 mg. Endpoint was Week 26. Δ, difference in means; Dula, dulaglutide; n, number of patients in the analysis. *$P < 0.05$, **$P < 0.01$, ***$P < 0.001$. Error bars indicate standard deviation

3.3 | Effect of dulaglutide on GV compared with insulin glargine

The analysis from AWARD-2 showed that the change from baseline to endpoint in within-day SMPG variability by CV was statistically significantly greater for dulaglutide, compared with insulin glargine (Figure 3). Greater numerical reductions from baseline to endpoint in between-day SMPG (Figure 3) and FSMPG (Supplementary Figure S7) variability by CV were observed for dulaglutide, compared with insulin glargine, although there was no statistical significance between groups (LS mean group difference dulaglutide vs. insulin glargine: between-day

SMPG −0.60, 95% CI −2.12 to 0.91; between-day FSMPG −1.51, 95% CI −3.73 to 0.71). Analyses of GV by SD were consistent with these results (Supplementary Table S4).

3.4 | Effect of dulaglutide added to insulin glargine on GV compared with insulin glargine alone

Data from AWARD-9 showed greater numerical, but not statistically significant, reductions from baseline to endpoint in within-day and between-day SMPG variability by CV for dulaglutide added to insulin
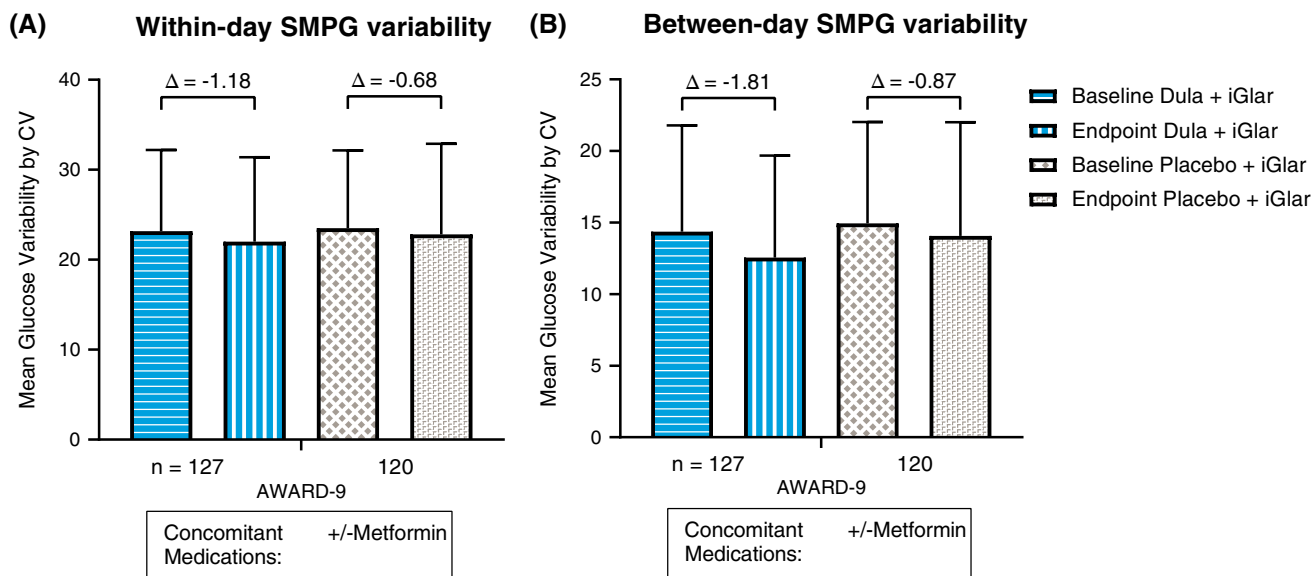
Between-day SMPG variability
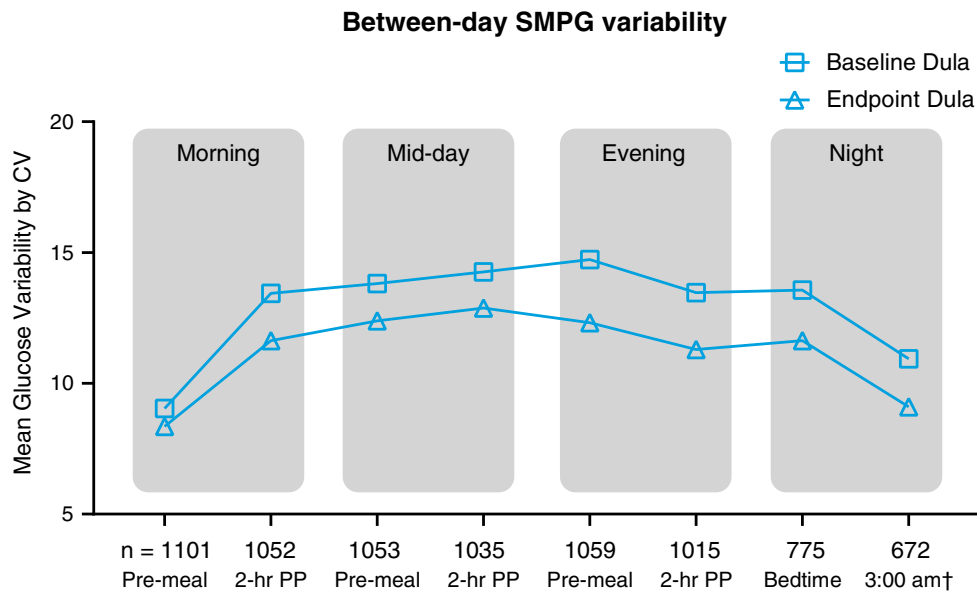
FIGURE 2 Between-day SMPG variability at eight distinct daily time points at baseline and endpoint for dulaglutide as monotherapy or when added to oral glucose-lowering medications. Pooled analysis of AWARD-1, -2, -3, -6 and -8 presenting the mean between-day self-monitored plasma glucose (SMPG) variability according to coefficient of variation (CV) at baseline and endpoint for eight daily time points, in patients treated with dulaglutide 1.5 mg. Endpoint was Week 26. † or 5 hours (hrs) after bedtime. There was no bedtime profile in AWARD-8, and no 3:00 AM profile in AWARD-6. Dula, dulaglutide; n, number of patients in the analysis; PP, postprandial
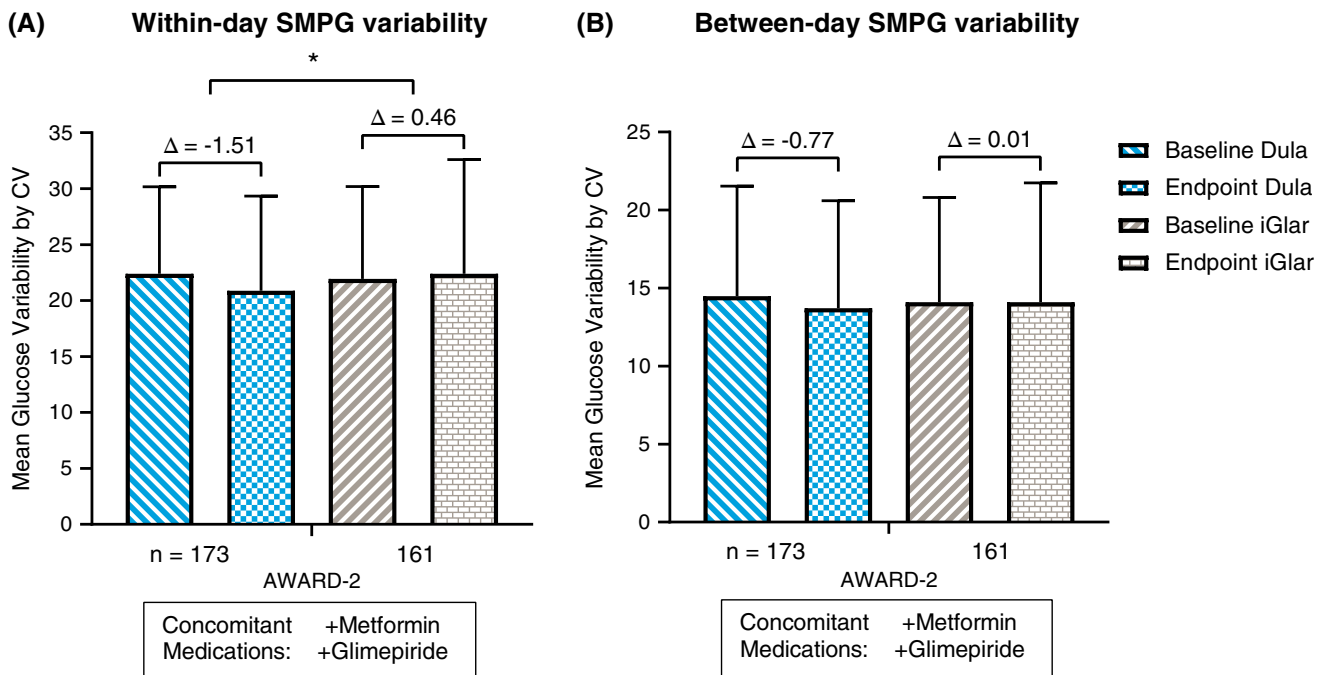
FIGURE 3 Within-day and between-day self-monitored plasma glucose (SMPG) variability at baseline and endpoint for dulaglutide versus insulin glargine. Mean (A) within-day and (B) between-day SMPG variability according to coefficient of variation (CV) at baseline and endpoint in patients treated with dulaglutide 1.5 mg or insulin glargine. Endpoint was Week 26. Δ, difference in means; Dula, dulaglutide; iGlar, insulin glargine; n, number of patients in the analysis. *P < 0.05. Error bars indicate standard deviation

glargine, compared with insulin glargine alone (LS mean difference dulaglutide + insulin glargine vs. insulin glargine: within-day SMPG −0.46, 95% CI −2.68 to 1.76; between-day SMPG −1.51,

95% CI −3.31 to 0.30 [Figure 4]). Reductions from baseline to endpoint in between-day FSMPG variability by CV were statistically significantly greater for dulaglutide added to insulin glargine compared

FIGURE 4 Within-day and between-day self-monitored plasma glucose (SMPG) variability at baseline and endpoint for dulaglutide added to insulin glargine versus insulin glargine alone. Mean (A) within-day and (B) between-day SMPG variability according to coefficient of variation (CV) at baseline and endpoint in patients on insulin glargine and treated with dulaglutide 1.5 mg or placebo. Endpoint was Week 28. Δ, difference in means; Dula, dulaglutide; iGlar, insulin glargine; n, number of patients in the analysis. Error bars indicate standard deviation

with insulin glargine alone (Supplementary Figure S8). Analyses of GV by SD revealed statistically significantly greater reductions from baseline to endpoint in within-day and between-day SMPG, as well as between-day FSMPG variability, for dulaglutide added to insulin glargine compared with insulin glargine alone (Supplementary Table S4).

4 | DISCUSSION

This study investigated the association between GV and treatment with dulaglutide across various patient populations and treatment scenarios through post hoc analyses of six phase 3 clinical trials in adult patients with T2D. The findings suggest that treatment with dulaglutide was potentially associated with a reduction in GV when used in monotherapy or when added to oral glucose-lowering medications. Reductions in GV were numerically greater for dulaglutide, compared with insulin glargine, and for dulaglutide when added to insulin glargine, compared with insulin glargine alone.

Our analyses build on previous findings from the same clinical trials, which investigated efficacy of dulaglutide on patient clinical variables of HbA1c, SMPG, FPG or fasting serum glucose (FSG), and weight.[28-33] In patients not receiving concomitant insulin treatment in pooled AWARD-1, -2, -3, -6 and -8, treatment with dulaglutide was potentially associated with reductions from baseline in both within-day and between-day SMPG variability. This finding was consistent across all five individual trials. In fact, between-day SMPG variability was reduced at eight time points throughout the day. In the pooled group, treatment with dulaglutide was potentially associated with a reduction in between-day FSMPG variability from baseline also. Hence, treatment of adult patients with dulaglutide not only results in

significant reductions in HbA1c, SMPG, FPG or FSG, and weight from baseline when taken as a monotherapy[32] or when added to oral glucose-lowering medications[28-31] but, as shown in the present post hoc analysis, it was also potentially associated with reduced GV in those same groups. Interestingly, a previous study found that measures of long-term GV correlate with mean HbA1c in patients with type 1 diabetes mellitus (T1D),[34] which could partly explain our results. Although concomitant oral glucose-lowering medications may be partly driving the reductions in GV observed following treatment with dulaglutide, it is interesting to note that the reduction in GV observed with dulaglutide as a monotherapy (AWARD-3) was in line with these results. In addition, as discussed below in more detail, we observed a greater reduction in GV following treatment with dulaglutide, compared with insulin glargine, with concomitant metformin and glimepiride treatment in both groups (AWARD-2). These consistent effects on GV across studies with different background therapies suggest that treatment with dulaglutide is, at least in part, driving the observed reductions in GV.

Compared with insulin glargine in AWARD-2, treatment with dulaglutide resulted in greater reductions from baseline in within-day and between-day SMPG and in between-day FSMPG variability. In fact, treatment with insulin glargine resulted in minor increases from baseline in within- and between-day SMPG and somewhat greater increases in between-day FSMPG variability by CV (mean [SD] change from baseline: within-day SMPG 0.46 [10.41]; between-day SMPG 0.01 [8.82]; between-day FSMPG 2.55 [14.24]). These increases in SMPG variability were not presented with SD data, where decreases were observed (mean [SD] change from baseline: within-day SMPG −4.94 [17.32]; between-day SMPG −3.43 [14.78]). Interestingly, although similar reductions from baseline in SMPG and lesser reductions in FPG

were previously reported for dulaglutide, compared with insulin glargine,[29] our results suggest that SMPG and FSMPG variability are reduced to a greater extent with dulaglutide in those same patient groups. This is in support of a previous CGM subanalysis of the AWARD-4 study, where treatment with dulaglutide or insulin glargine resulted in similar proportions of glucose values in the normoglycaemic range, but dulaglutide provided an improved balance between the proportion of values within the near normoglycaemic range and values within the hypoglycaemic range, compared with insulin glargine, in adult patients on concomitant insulin lispro.[26] In addition, a previous post hoc analysis of the AWARD-2 study has shown that treatment with dulaglutide resulted in a higher probability of patients reaching FSG <7.2 mmol/L (<130 mg/dL) without hypoglycaemia in the initial weeks of treatment, compared with insulin glargine.[35] Interestingly, studies have found positive associations between hypoglycaemia and short-term GV in patients with T1D and T2D,[11] which could partly explain our results.

Treatment with dulaglutide added to insulin glargine resulted in greater reductions from baseline in both within-day and between-day SMPG variability, and between-day FSMPG variability, compared with insulin glargine alone in AWARD-9. Incidence of total hypoglycaemia, previously found to be positively associated with short-term GV,[11] was similar between treatment groups in AWARD-9.[33] This would suggest that these effects on GV are attributable to greater improved glycaemic control following the addition of dulaglutide to insulin glargine, compared with insulin glargine alone. These findings build on previous results in the same groups, which demonstrated that dulaglutide added to insulin glargine resulted in greater reductions in HbA1c, SMPG, FSG and weight compared with insulin glargine alone.[33] Similarly to results from AWARD-2, treatment with insulin glargine alone resulted in an increase from baseline in between-day FSMPG variability by CV (mean [SD] change from baseline: between-day FSMPG 2.01 [17.12]). However, a decrease from baseline was observed in the same variable by SD (mean [SD] change from baseline: between-day FSMPG −1.66 [24.05]).

The SMPG profile collection day was not prespecified in relation to the day of dulaglutide administration. Importantly, a previous post hoc analysis of AWARD-3 (dulaglutide vs. metformin as a monotherapy) showed that throughout the weekly dosing interval at steady state (attained between 2 and 4 weeks of dosing), dulaglutide 1.5 mg had a similar effect on blood glucose control during peak and trough plasma concentration days, as assessed by the change in mean daily SMPG concentrations.[36] As the endpoints for the current post hoc analysis were >20 weeks into the treatment periods, we believe that steady state would have been achieved by endpoint and that the day of administration relative to the day of SMPG profile collection is unlikely to have impacted the results of between-day SMPG variability.

As noted above, some of the GV results by CV were not presented by SD. Both CV and SD measure variability, but as CV presents the ratio of SD to the mean, it is independent of the unit being measured. As CV is the SD relative to the mean, CV will favour the arm with the highest mean among arms with similar SD. This explains the

instances where differences were observed between CV and SD data. As previous findings from the AWARD studies have shown significant differences in change from baseline to endpoint for mean SMPG and FPG or FSG after treatment with dulaglutide, as well as significant group differences in these measures at endpoint,[28-33] CV was the preferable primary measure for reporting variability in this study.

AWARD-4, -5, -7, -10 and -11 were not included in our post hoc analyses for various reasons. Patients in AWARD-4 and -7 were taking concomitant insulin lispro,[37,38] making interpretations of GV more difficult. The patient population in AWARD-7 also had moderate-to-severe chronic kidney disease,[38] so it would have added heterogeneity to the population analysed here. AWARD-5 and -10 did not include assessment of SMPG.[39,40] Higher doses of dulaglutide were investigated in AWARD-11, and the results were not published or added to the approved label at the time of our analyses.[41] In addition, dulaglutide 1.5 mg was the dose recommended as an add-on therapy by the European Medicines Agency[42] and the most commonly used dose[43] when the analysis was performed. For these reasons, it was the only dose included in our analyses.

Several studies on other GLP-1RAs have shown similar findings. Treatment of adult patients with lixisenatide in combination with insulin glargine (iGlarLixi) reduced GV to a greater extent than insulin glargine alone, as reported in both the LixiLan-O and LixiLan-L studies.[12] In the DUAL-II study, patients treated with a combination of insulin degludec and liraglutide (IDegLira) experienced a greater reduction in pre-breakfast between-day SMPG variability, compared with insulin degludec alone, although such differences were not observed in DUAL-I.[23] A meta-analysis of 16 studies suggests that patients with T2D treated with liraglutide are associated with lower GV.[25]

The risk of hypoglycaemia is an accompanying complication of reducing glucose levels following treatment in patients with T2D, and becomes even more of a concern with greater GV.[3-5] Studies have investigated and established associations between GV and microvascular and macrovascular outcomes,[5,7,8] although long-term direct evidence on macrovascular outcomes has not yet been shown.[5] Mounting evidence suggests that GV is a potential risk factor for the development of cardiac complications in patients with diabetes, potentially driven by vascular inflammation, oxidative stress, vasoconstriction and impaired angiogenesis, increased platelet activation and aggregation, and abnormal cardiovascular autonomic function.[8] Interestingly, one study found that GV, but not HbA1c, was associated with left ventricular mass in patients with T2D, possibly through activation of oxidative stress pathways.[7] GV is therefore gaining recognition as a critical focus of therapy, alongside the gold standard of HbA1c assessment.[4,11]

A limitation of our study is that the analyses were not prespecified and are thus post hoc in nature. Hence, conclusions are hypothesis-generating only. A second limitation is the use of SMPG to assess GV, as opposed to CGM. CGM has several advantages over conventional SMPG, such as repeated glucose estimates at very short intervals, which allows the calculation of multiple metrics, other than SD and CV, and thereby provides a more comprehensive assessment of GV.[27] Nonetheless, SMPG remains a well-recognized method for

assessing GV. For SMPG measurements, each patient was provided with a commercially available blood glucose meter. Previous studies assessing the analytical performance of several blood glucose meters have shown that results can vary between monitors.[44,45] As randomization is likely to have evenly distributed any variability associated with different glucometers across treatment groups within each study, we do not believe that interpretation of treatment effect would be limited. However, it is possible that the magnitude of the variability might be limited.

Although similar to a previous post hoc analysis of data from five phase 3 studies where assessment of between-day GV was based on two SMPG profiles per timepoint,[10] the contribution of two SMPG profiles only to the calculation of between-day GV, in contrast to seven time points to the calculation of within-day GV, may be regarded as a limitation. We did not evaluate long-term GV based on HbA1c levels. Although AWARD-1, -3 and -6 included the treatment groups exenatide twice daily, metformin and liraglutide, respectively, we did not perform comparative analyses of GV between dulaglutide and these groups. Interestingly, a prospective study in patients with T2D showed that treatment with dulaglutide was superior to that with liraglutide in terms of mean amplitude of glycaemic excursions (MAGE) following 24 weeks of treatment. Specifically, MAGE remained unchanged in the dulaglutide group, whereas increases were found in the liraglutide group.[46] Due to the non-comparative nature of the pooled analyses and related individual trial results, only a potential association between dulaglutide and GV can be concluded. This may be regarded as another limitation of the study.

Importantly, however, comparisons of dulaglutide with insulin glargine, as well as dulaglutide added to insulin glargine compared with insulin glargine alone might be considered major strengths of the study as GLP-1RAs and basal insulin are within the recommendations for first-line injectables.[47] Another strength is the addition of substantial information to the literature on GV following treatment with GLP-1RAs, although longer-term evaluations of GV are necessary.

In conclusion, based on these post hoc analyses of the AWARD dulaglutide development programme, treatment with dulaglutide in most instances was potentially associated with reduced GV in patients with T2D, when taken in monotherapy or added to oral glucose-lowering medication, without concomitant insulin treatment. In addition, treatment with dulaglutide was associated with a reduction in GV to a greater degree than insulin glargine. When added to insulin glargine, treatment with dulaglutide was associated with greater decreases in GV compared with insulin glargine alone. As reduced GV may be associated with better outcomes, these findings may have clinical relevance, although further studies are warranted.

CONFLICT OF INTEREST
E.J. reports being a clinical investigator for Amgen, Boehringer, AstraZeneca, FAES, Janssen, Lilly, MSD, Novo Nordisk, Pfizer, Sanofi, Shire and UCB. E.J. reports consultant/advisor fees for Amgen, AstraZeneca, FAES, Helios-Fresenius, Italfármaco, Lilly, MSD, Mundipharma, Novo Nordisk, UCB and Viatris. E.J. also reports speaker fees for Amgen, Asofarma, Astellas, AstraZeneca, Bayer, Boehringuer, BMS, FAES, Lilly, MSD, Mundipharma, Novo Nordisk, Technofarma, UCB and Viatris. I.R., Q.W. and L.E.G.P. are full-time employees and shareholders of Eli Lilly and Company. S.R. is a full-time employee of Eli Lilly and Company.

AUTHOR CONTRIBUTIONS
Esteban Jódar, Irene Romera, and Luis-Emilio García-Pérez contributed to the conception and/or design of the work. Esteban Jódar and Qianqian Wang contributed to the acquisition of data for the work. Qianqian Wang contributed to the analysis of data for the work. All authors contributed to the interpretation of data for the work. All authors contributed to drafting of the work and/or critical revision of the work for important intellectual content.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE
Study protocols were reviewed and approved by appropriate institutional review boards for each of the study sites. The clinical trials were conducted according to the Good Clinical Practice and the Declaration of Helsinki guidelines. All patients provided written informed consent before undergoing the study procedure. The studies are registered at ClinicalTrials.gov (NCT01064687, NCT01075282, NCT01126580, NCT01624259, NCT01769378 & NCT02152371).

DATA AVAILABILITY STATEMENT
Lilly provides access to all individual participant data collected during the trial, after anonymization, with the exception of pharmacokinetic or genetic data. Data are available to request 6 months after the indication studied has been approved in the US and EU and after primary publication acceptance, whichever is later. No expiration date of data requests is currently set once data are made available. Access is provided after a proposal has been approved by an independent review committee identified for this purpose and after receipt of a signed data sharing agreement. Data and documents, including the study protocol, statistical analysis plan, clinical study report, blank or annotated case report forms, will be provided in a secure data sharing environment. For details on submitting a request, see the instructions provided at https://www.vivli.org.

ORCID
Esteban Jódar https://orcid.org/0000-0002-1234-8560
Luis-Emilio García-Pérez https://orcid.org/0000-0003-3840-787X

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SUPPORTING INFORMATION

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