

ORIGINAL ARTICLE

Exenatide once weekly improved 24-hour glucose control and reduced glycaemic variability in metformin-treated participants with type 2 diabetes: a randomized, placebo-controlled trial

Juan P. Frías MD¹ | Samer Nakhle MD² | James A. Ruggles PhD³ |
Sergey Zhuplatov MD, PhD³ | Eric Klein MD⁴ | Rong Zhou PhD⁵ | Poul Strange MD, PhD⁶

¹National Research Institute, Los Angeles, California, USA

²Palm Medical Research, Las Vegas, Nevada, USA

³Medical Affairs, AstraZeneca, Wilmington, Delaware, USA

⁴Capital Clinical Research Center, Olympia, Washington, USA

⁵Department of Biostatistics, Medpace, Cincinnati, Ohio, USA

⁶Integrated Medical Development, Princeton Junction, New Jersey, USA

Corresponding Author: Juan P. Frías, MD, National Research Institute, 2010 Wilshire Blvd., Suite 302, Los Angeles, CA 90057, USA (jfrías@clinical-studies.com).

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Aim: To assess the effects of once-weekly exenatide on 24-hour glucose control and variability.

Materials and methods: This double-blind, placebo-controlled trial randomized metformin-treated adults with type 2 diabetes to once-weekly exenatide 2.0 mg or placebo. Continuous glucose monitoring (CGM) was performed at baseline and weeks 4 and 10. The primary outcome was change in CGM-measured 24-hour mean glucose level.

Results: In the once-weekly exenatide (n = 60) and placebo (n = 56) groups (modified intention-to-treat population), the baseline glycated haemoglobin (HbA1c) concentrations were 8.2% and 8.0%, respectively, and the fasting plasma glucose (FPG) concentration was 9.86 and 9.32 mmol/L, respectively. Once-weekly exenatide significantly (p < 0.001) reduced 24-hour mean glucose level versus placebo (week 4, -1.44 vs -0.29 mmol/L; week 10, -1.71 vs -0.17 mmol/L), with consistent control throughout the week. Once-weekly exenatide significantly reduced FPG and 2-hour postprandial glucose (PPG) levels versus placebo at week 4 (FPG, -1.65 vs -0.11 mmol/L; PPG, -1.79 vs -0.11 mmol/L) and week 10 (FPG, -2.32 vs -0.28 mmol/L; PPG, -2.46 vs -0.33 mmol/L). At week 10, once-weekly exenatide reduced the mean amplitude of glucose excursions (MAGE; -0.84 vs 0.16 mmol/L) and standard deviation (s.d.) of mean glucose (-0.35 vs 0.04 mmol/L). By week 10, once-weekly exenatide-treated participants spent more time in euglycaemia (once-weekly exenatide, 77% vs placebo, 58%), less time in hyperglycaemia (22% vs 42%), and a similar time in hypoglycaemia (0.7% vs 0.3%). Common adverse events were injection-site nodule (once-weekly exenatide, 10.0% vs placebo, 0.0%), urinary tract infection (6.7% vs 8.9%) and nausea (6.7% vs 0.0%).

Conclusions: In metformin-treated participants with type 2 diabetes, once-weekly exenatide significantly improved daily glucose control and reduced glycaemic variability at weeks 4 and 10, as shown by reductions in 24-hour glucose, FPG and PPG levels, MAGE and s.d., and increased time spent in euglycaemia.

KEYWORDS

24-hour glucose profile, continuous glucose monitoring, exenatide once weekly, glycaemic variability, type 2 diabetes

1 | INTRODUCTION

Glycated haemoglobin (HbA1c), which reflects average blood glucose concentrations over 2-3 months, has long been considered the

benchmark for assessing glycaemic control and the associated risk of long-term complications in people with diabetes. Landmark clinical trials have shown that lowering HbA1c reduces the risk of development and progression of diabetes complications,^{1,2} which has led to a

treatment focus on achieving the generally recommended target HbA1c of <7.0%.³ Although controversial,^{4,5} in the past decade, a body of evidence has implicated glycaemic variability in the pathogenesis of diabetes complications, suggesting that glycaemic variability should also be considered a target for glucose-lowering therapies.^{6,7} Glycaemic variability refers to acute excursions in blood glucose levels, including hypoglycaemic events and postprandial hyperglycaemia, and may be known by some patients and physicians as daily glucose fluctuations.⁸ As HbA1c is a measure of overall blood glucose concentrations over 2-3 months, it does not directly reflect the degree of glycaemic variability.⁹ Ideally, management of type 2 diabetes should strive for control of HbA1c levels and close approximation of normal diurnal glycaemic variability.

The glucagon-like peptide-1 (GLP-1) receptor agonist exenatide once weekly provides continuous exenatide exposure via gradual release of exenatide from microspheres, thus minimizing peaks and troughs in exenatide concentrations. Once-weekly exenatide has been shown to improve glycaemic control in a glucose-dependent manner, with a low risk of hypoglycaemia, in people with type 2 diabetes.¹⁰ The extended-release delivery method, glucose-dependent effects on insulin and glucagon,¹¹ and improved postprandial glucose (PPG) control observed with once-weekly exenatide¹² are proposed to lead to less glycaemic variability, although studies specifically designed to evaluate glycaemic variability with once-weekly exenatide treatment have been limited.

In the present study, we investigated the effect of once-weekly exenatide compared with placebo on 24-hour glucose control and glycaemic variability [using data obtained from continuous glucose monitoring (CGM)], and assessed changes in fasting plasma glucose (FPG) and PPG levels in participants with type 2 diabetes on background metformin therapy.

2 | MATERIALS AND METHODS

2.1 | Study design

This was a randomized, double-blind, parallel-group clinical trial conducted from December 2014 to August 2015 across 30 sites in the USA (ClinicalTrials.gov identifier: NCT02288273). The study consisted of a 4-week lead-in period, a 10-week treatment period and a 4-week follow-up for standard safety assessments.

Glucose concentrations were measured every 5 minutes (288 times per day) over 7 days during the final week (baseline) of the 4-week lead-in period and during weeks 4 and 10 using a CGM system (Dexcom G4; Dexcom, San Diego, CA, USA). Glucose values were blinded to both participants and investigators. The CGM sensor was inserted on day -8, day 21 and day 63 at evening time with on-site calibration using an Accu-Chek Aviva Plus glucose meter (Roche, Basel, Switzerland). Participants were instructed to calibrate the CGM system device according to the manufacturer's instructions every 12 hours. Changes from baseline in CGM measures were assessed on day 6 (± 1 day) of weeks 4 and 10, which was the last full day before administration of the next dose of study drug (day 7 of each week).

Thus, CGM assessments aligned with any potential trough in exenatide concentration, if one were to occur.

We measured FPG and HbA1c levels at screening, on day -7 (week -1 during lead-in; FPG only), at randomization (day 1; week 1), and on days 15 (week 3), 22 (week 4), 57 (week 9), 64 (week 10) and 70 (week 10).

Standardized meal tests were conducted on day -7 (week -1), day 22 (week 4) and day 64 (week 10). Participants consumed (within 30 minutes) a standardized breakfast meal accounting for ~35% of the daily calorie intake (620-700 kcal; Table S1, File S1). Blood samples for glucose and insulin were collected before the breakfast meal and at 30, 60, 120 and 180 minutes after the breakfast meal.

Exenatide concentration was measured on days 1 (week 1), 15 (week 3), 22 (week 4; prior to the meal), 57 (week 9), 64 (week 10; prior to the meal) and 70 (week 10).

2.2 | Participants

The study included people with type 2 diabetes aged 18-75 years with HbA1c levels between 7.0% and 10.0% (53 and 86 mmol/mol) and a body mass index of ≤ 45 kg/m². Participants were on a stable dose of metformin (≥ 1500 mg/d) for at least 8 weeks before study start, and no other glucose-lowering medications were permitted (File S1). Participants who felt that they were unable to use the CGM device during the lead-in period were encouraged to withdraw before randomization, as CGM was the primary tool used to measure glycaemic variability. Participants provided written informed consent, and the protocol was approved by the institutional review board at each site. The trial was conducted in accordance with the International Conference on Harmonisation guidelines.

2.3 | Treatment

At the lead-in visit, the participant's current dietary and exercise behaviour were reviewed. Participants were instructed on medical nutrition in accordance with the American Diabetes Association guidelines or locally accepted guidelines. During the 4-week lead-in period, participants were treated with metformin extended release 1500 or 2000 mg (depending on their dose at screening) once daily with their evening meal. After the lead-in period, participants were randomized with a computer-generated random sequence using an interactive voice/web response system. Participants were randomized 1:1 using a blocked randomization schedule to receive either once-weekly exenatide 2.0 mg plus open-label metformin extended release 1500 or 2000 mg once daily, or placebo while continuing open-label metformin extended release 1500 or 2000 mg for 10 weeks. Double-blind study medication was self-administered subcutaneously once weekly (first dose on day 1, then on day 7 of each treatment week). To ensure blinding, the placebo powder for injection consisted of microspheres that were indistinguishable from microspheres used for incorporation of exenatide and was packaged to match the single-dose trays used for once-weekly exenatide.

2.4 | Hypotheses and outcome measures

The primary hypothesis was that once-weekly exenatide on a background of metformin and diet/exercise would lead to significant reductions in 24-hour mean glucose level from baseline to weeks 4 and 10 (primary outcome) compared with placebo on a background of metformin and diet/exercise.

Secondary hypotheses were that once-weekly exenatide on a background of metformin and diet/exercise would significantly increase the proportion of time spent in the euglycaemic range, and reduce PPG and FPG levels, 24-hour mean amplitude of glucose excursions (MAGE), and standard deviation (s.d.) of 24-hour mean glucose level compared with placebo on a background of metformin and diet/exercise at weeks 4 and 10.

In addition to the primary outcome of change in 24-hour mean glucose level at weeks 4 and 10, CGM data were analysed for the following secondary outcomes: 24-hour glucose profile, change in 24-hour mean glucose between days 1 and 6 of week 10, MAGE (defined as the mean absolute difference from peak to trough for those differences that exceeded the s.d. of CGM assessments over 24 hours),¹³ s.d. of 24-hour mean glucose, and the proportion of time participants had plasma glucose measurements <3.9 mmol/L (low glucose/hypoglycaemic range), ≥ 3.9 to ≤ 10.0 mmol/L (euglycaemic range) and >10.0 mmol/L (high glucose/hyperglycaemic range). An exploratory outcome compared 24-hour CGM profiles at each time point between treatments at week 10. CGM data were analysed retrospectively for the coefficient of variation (CV).

Secondary outcomes measured at a central laboratory included the change from baseline at weeks 4 and 10 in FPG level, 2-hour mean PPG level from the standardized meal test, and HbA1c level. The 3-hour postprandial insulin area under the curve (AUC) from the meal test was designated an exploratory outcome.

2.5 | Exenatide pharmacokinetic measurements

Pharmacokinetic samples were analysed by Covance (West Trenton, NJ, USA) using a bioanalytical method, and exenatide concentrations were summarized descriptively.

2.6 | Safety

Safety was assessed throughout the trial and after 4 weeks of follow-up. Standard laboratory safety variables, including vital signs, body weight, ECGs and clinical laboratory values, and physical examinations were performed for each participant. The frequency and severity of adverse events (AEs) and serious AEs and the rate of discontinuations attributable to AEs were recorded. AEs were classified according to the Medical Dictionary for Regulatory Activities (version 17.1).

2.7 | Statistical analysis

A modified intention-to-treat (ITT) model was used to analyse all outcomes. The modified ITT population consisted of all randomized participants who received at least one dose of study drug. Categorical

variables were summarized by frequency and percentages; continuous variables were summarized by descriptive statistics.

The sample size of 110 participants (55 per treatment group), with an assumed dropout rate of 30%, gave a minimum of 39 participants per treatment. This number provided 90% power to detect a difference in the change in 24-hour mean glucose of 1.00 mmol/L, assuming an s.d. of 1.33 mmol/L, at week 4 between once-weekly exenatide and placebo, and >90% power for the week 10 treatment comparison.

A sequential testing procedure was implemented to control the family-wise type I error. Endpoints were assessed for superiority of once-weekly exenatide versus placebo. In the hierarchical testing order, the primary endpoint of 24-hour mean glucose level at week 10 was tested first, followed by 24-hour mean glucose level at week 4, then the secondary endpoints: FPG level at week 10, 2-hour mean PPG level at week 10, then FPG level at week 4, and 2-hour mean PPG level at week 4. Each test was performed at a 5% significance level. For other secondary and exploratory endpoints, nominal *p* values are presented.

For CGM-derived variables, 24-hour glucose profiles with <260 of 288 measurements were censored, as an incomplete profile could lead to bias. For profiles with >260 but <288 measurements, missing values were imputed by cubic spine interpolation, or linear interpolation when the number of data points around the missing data was inadequate to support a cubic spine.

2.7.1 | Analysis of the primary outcome

The 24-hour mean glucose concentration was calculated as the AUC from the 24-hour glucose profile, divided by 24 hours. The change from baseline in 24-hour mean glucose was analysed on day 6 of week 4 and day 6 of week 10 using a maximum likelihood-based mixed-model repeated measures (MMRM) method, with treatment, baseline HbA1c, baseline 24-hour mean glucose, week of visit and treatment-by-week interaction as fixed effects and participant and error as random effects. An unstructured covariance matrix was used in the MMRM analysis. Least-squares (LS) means and standard error (s.e.) values for the change within each treatment group and the difference between treatment groups are presented. *p* values were calculated for between-treatment comparisons.

2.7.2 | Analysis of secondary and exploratory outcomes

Changes from baseline in CGM measures were analysed on day 6 of weeks 4 and 10, with profiles censored as noted above. A similar MMRM model was used to analyse secondary outcomes of FPG, PPG, MAGE, s.d. of 24-hour mean glucose, and the proportion of time spent within glycaemic ranges, as well as the exploratory outcome of 3-hour postprandial insulin, with the baseline level of the dependent variable as the fixed effect. Insulin AUC and changes in CV were summarized descriptively. The per cent reduction in 2-hour incremental mean PPG level was also assessed, with treatment, baseline HbA1c, baseline 2-hour incremental mean PPG, visit and treatment by visit as fixed effects, and participant and error as random effects. Change in 24-hour mean glucose level between days 1 and

6 of week 10 was analysed using a mixed model, with baseline HbA1c as a covariate. An analysis of covariance model was used to analyse change in HbA1c with treatment as a factor and baseline HbA1c as a covariate. LS means \pm s.e. for the change within each treatment group and the difference between treatment groups are presented. *p* values were calculated for between-treatment comparisons.

An exploratory outcome was the comparison between the adjusted mean 24-hour glucose curves using CGM profiles at week 10, based on maximum amplitude of deviation from zero (MADz). Fourier coefficients for individual participant CGM data from each 24-hour period were derived using 24 hours as the longest cycle and aggregated for each protocol period.¹⁴ The data were then aggregated across the whole treatment group for that period, resulting in a defined group function for each period by treatment, from which changes from baseline and treatment difference functions were derived. To control for multiplicity, a bootstrap was performed to define the 95% confidence bounds of the MADz by time point.

3 | RESULTS

3.1 | Participants

A total of 150 participants were screened and entered the lead-in period, and 117 participants were randomized [once-weekly

exenatide + metformin (*n* = 61); placebo + metformin (*n* = 56); Figure S1, File S1]. One participant randomized in the once-weekly exenatide group was not treated or analysed because of pregnancy, so the modified ITT population included 116 participants. In the once-weekly exenatide and placebo groups, 8/61 (13.1%) and 8/56 (14.3%) participants, respectively, discontinued the study, and 53/61 (86.9%) and 48/56 (85.7%) completed the trial. Baseline characteristics and demographics of the modified ITT population were generally well matched between groups (Table 1).

3.2 | Outcome measures

3.2.1 | Primary outcome

Once-weekly exenatide significantly reduced 24-hour mean glucose level compared with placebo at week 4 (LS mean \pm s.e. reduction from baseline: -1.44 ± 0.20 vs -0.29 ± 0.21 mmol/L; difference, -1.15 ± 0.29 mmol/L; *p* < 0.001 .001) and week 10 (-1.71 ± 0.25 vs -0.17 ± 0.27 mmol/L; difference: -1.54 ± 0.37 mmol/L; *p* < 0.001 .001; Figure 1A).

3.2.2 | Secondary and exploratory outcomes

Once-weekly exenatide reduced mean glucose over 24 hours compared with placebo at weeks 4 and 10 (Figure S2, File S1). At week 10, treatment differences in changes from baseline in 24-hour glucose cycles were significant beginning at approximately 09:00 hours

TABLE 1 Demographics and baseline characteristics of the modified intention-to-treat population

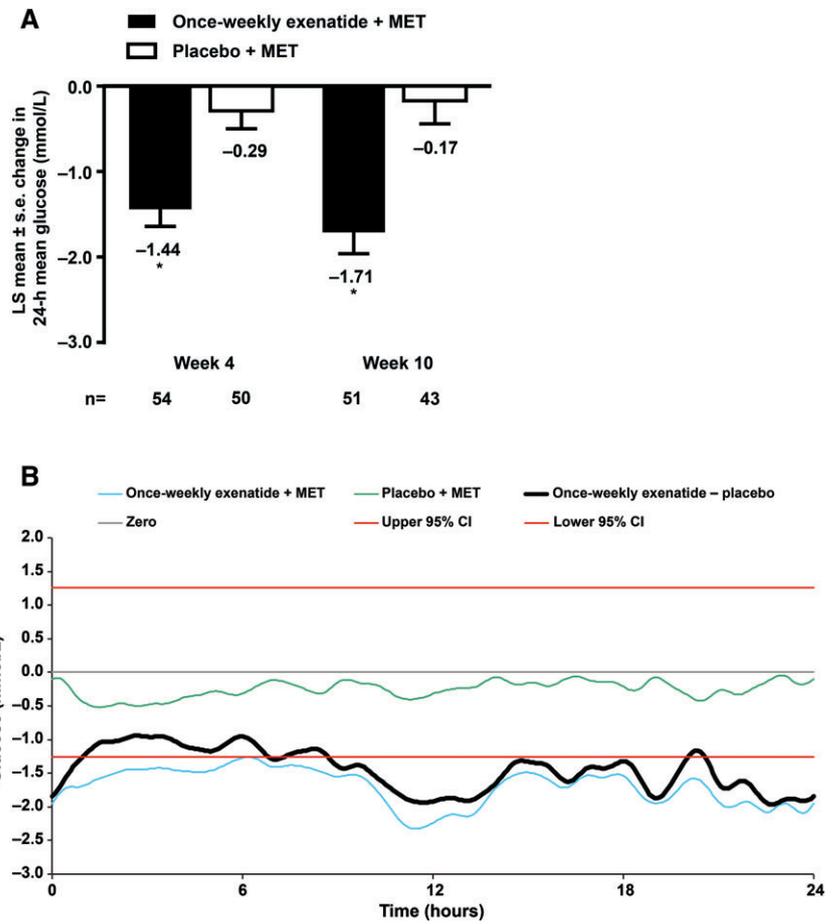
Characteristic	Once-weekly exenatide + metformin <i>n</i> = 60	Placebo + metformin <i>n</i> = 56	Overall <i>N</i> = 116
Age, years	55 \pm 11	56 \pm 10	56 \pm 10
Male sex, <i>n</i> (%)	33 (55.0)	32 (57.1)	65 (56.0)
Race, <i>n</i> (%)			
White	52 (86.7)	46 (82.1)	98 (84.5)
Black or African-American	3 (5.0)	5 (8.9)	8 (6.9)
Asian	3 (5.0)	4 (7.1)	7 (6.0)
Native Hawaiian or Pacific Islander	1 (1.7)	0 (0.0)	1 (0.9)
Other	1 (1.7)	1 (1.8)	2 (1.7)
Ethnicity, <i>n</i> (%)			
Hispanic or Latino	32 (53.3)	26 (46.4)	58 (50.0)
Not Hispanic or Latino	28 (46.7)	30 (53.6)	58 (50.0)
Duration of diabetes ¹ , years	9 \pm 6	10 \pm 8	9 \pm 7
Metformin dose, mg	1925.0 \pm 180.0	1875.0 \pm 218.5	1900.9 \pm 200.2
Body weight, kg	90.5 \pm 19.3	90.0 \pm 19.1	90.2 \pm 19.1
Body mass index, kg/m ²	32.0 \pm 6.2	31.6 \pm 5.4	31.8 \pm 5.8
HbA1c, %	8.2 \pm 1.1	8.0 \pm 0.9	8.1 \pm 1.0
HbA1c, mmol/mol	66 \pm 12	64 \pm 10	65 \pm 11
FPG, mmol/L	9.86 \pm 2.77	9.32 \pm 3.02	9.60 \pm 2.90
2-h PPG, mmol/L	12.28 \pm 3.00	12.29 \pm 2.81	12.28 \pm 2.90
24-h mean glucose, mmol/L	10.31 \pm 2.33	10.20 \pm 2.36	N/A
MAGE, mmol/L	5.05 \pm 1.56	5.02 \pm 1.48	
s.d. of 24-h mean glucose, mmol/L	2.10 \pm 0.66	2.07 \pm 0.60	N/A

N/A, not available.

Data are mean \pm s.d., unless otherwise noted.

¹Data not available for all participants: once-weekly exenatide + metformin, *n* = 58; placebo + metformin, *n* = 55.

FIGURE 1 A, Least-squares (LS) mean \pm s.e. change from baseline in 24-hour mean glucose at week 4 and week 10. Modified intention-to-treat population [once-weekly exenatide + metformin (MET), $n = 60$; placebo + MET, $n = 56$]. B, Comparison of change from baseline in the mean 24-hour glucose profile at week 10, as shown by MADz. Fourier coefficients for individual participant continuous glucose monitoring data from each 24-hour period were derived using 24 hours as the longest cycle and aggregated for each protocol period.¹⁴ The data were then aggregated across the whole treatment group for that period, resulting in a defined group function for each period by treatment from which changes from baseline and treatment difference functions were derived. To control for multiplicity, a bootstrap was performed to define the 95% confidence bounds of the MADz by time point. Solid blue line = once-weekly exenatide + MET; solid green line = placebo + MET; solid black line = treatment difference (once-weekly exenatide – placebo) of the change from baseline at each time point; a significant difference between treatments is designated when this black line is outside the range of the 95% confidence interval (red lines). * $p < 0.001$, treatment difference (once-weekly exenatide – placebo) in LS mean changes.



and remained significant throughout most of the day and early evening, as shown by MADz (Figure 1B).

Once-weekly exenatide significantly reduced FPG level compared with placebo at week 4 (placebo-adjusted difference: -1.54 ± 0.39 mmol/L; $p < 0.001$.001) and week 10 (difference: -2.04 ± 0.42 mmol/L; $p < 0.001$.001; Figure 2A). Once-weekly exenatide also reduced PPG concentrations after the standardized breakfast meal (Figure 2B), resulting in significantly greater reductions from baseline in 2-hour mean PPG level compared with placebo at week 4 (difference: -1.68 ± 0.43 mmol/L; $p < 0.001$.001) and week 10 (difference: -2.13 ± 0.46 mmol/L; $p < 0.001$.001; Figure 2C). At week 10, once-weekly exenatide reduced the baseline-adjusted AUC for PPG versus placebo by 13.5% ($p =$ non-significant), indicating that once-weekly exenatide reduced the decrement in PPG rise. Once-weekly exenatide numerically, but not significantly, increased the 3-hour postprandial insulin AUC compared with placebo at week 4 (mean \pm s.d.: 1231 ± 993 vs 1133 ± 849 pmol/L; $p =$ non-significant) and week 10 (1084 ± 729 vs 1036 ± 737 pmol/L; $p =$ non-significant) from baseline (1070 ± 605 vs 1136 ± 701 pmol/L).

Participants treated with once-weekly exenatide had reductions in MAGE at week 4, and reductions with once-weekly exenatide were significant versus placebo at week 10 (difference: -1.00 ± 0.28 mmol/L; nominal $p < 0.001$.001; Figure 2D). Once-weekly exenatide also significantly reduced the s.d. of 24-hour mean glucose versus placebo at week 10 (-0.35 ± 0.07 vs 0.04 ± 0.08 mmol/L; difference: -0.39 ± 0.10 mmol/L; nominal $p < 0.001$.001). Changes in s.d. were not significantly

different from placebo at week 4 (-0.25 ± 0.06 vs -0.10 ± 0.06 mmol/L; difference: -0.16 ± 0.09 mmol/L; nominal $p = .082$). CV values were similar between treatments (Table S2, File S1).

Once-weekly exenatide increased the proportion of time spent in the euglycaemic range (3.9–10.0 mmol/L) at weeks 4 and 10 through reductions in the hyperglycaemic range (>10.0 mmol/L), with no increase in time spent in the hypoglycaemic range (<3.9 mmol/L; Figure 2E). Treatment differences in LS mean \pm s.e. changes from baseline for once-weekly exenatide compared with placebo were significant for reductions in time spent in the hyperglycaemic range (week 4 difference: $-12.0\% \pm 3.4\%$; $p < 0.001$.001; week 10 difference: $-20.6\% \pm 4.4\%$; nominal $p < 0.001$.001) and for increases in time spent in the euglycaemic range (week 4 difference: $11.6\% \pm 3.4\%$; nominal $p < 0.001$.001; week 10 difference: $20.1\% \pm 4.3\%$; nominal $p < 0.001$.001). Once-weekly exenatide did not increase time spent in the hypoglycaemic range, as the change in time spent with blood glucose <3.9 mmol/L was similar with once-weekly exenatide and placebo (week 4: nominal $p = .266$; week 10: nominal $p = .180$).

Daily glycaemic control with once-weekly exenatide appeared consistent throughout the week based on CGM measures taken near the beginning and end of week 10. The change in 24-hour mean glucose from day 1 to day 6 of week 10 was 0.29 ± 0.19 mmol/L with once-weekly exenatide and -0.38 ± 0.20 mmol/L with placebo.

At week 10, once-weekly exenatide significantly reduced HbA1c compared with placebo [$-0.92\% \pm 0.10\%$ vs $-0.20\% \pm 0.11\%$ (-10.1 ± 1.1 vs -2.2 ± 1.2 mmol/mol); difference: $-0.73\% \pm 0.15\%$ (-8.0 ± 1.6 mmol/mol); nominal $p < 0.001$.001].

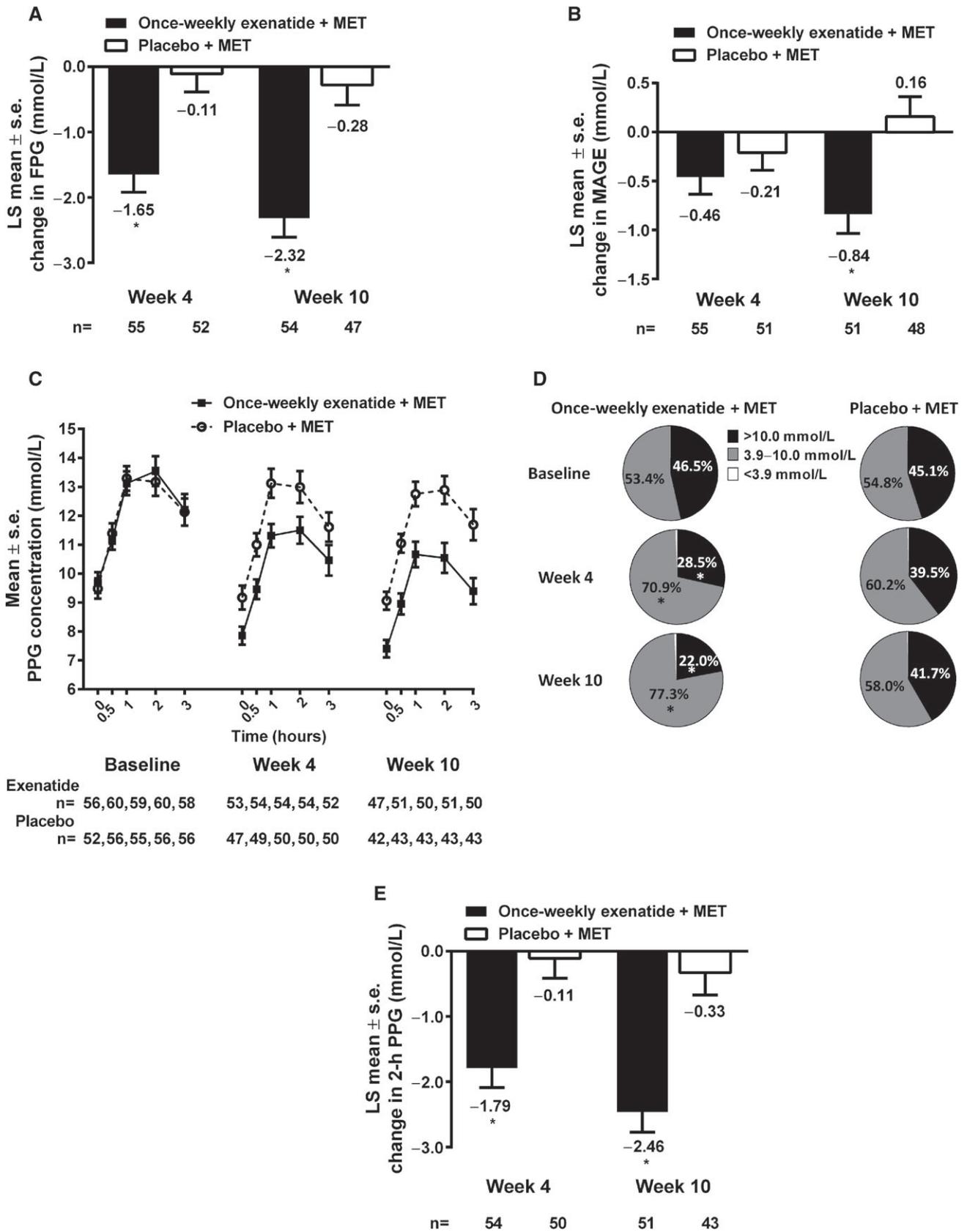


FIGURE 2 A, Least-squares (LS) mean ± s.e. change from baseline in fasting plasma glucose (FPG). B, Mean ± s.e. Postprandial glucose (PPG) concentrations after the standardized breakfast meal. Black squares = once-weekly exenatide + metformin (MET); white circles = placebo + MET. C, LS mean ± s.e. change from baseline in 2-hour mean PPG. D, LS mean ± s.e. change from baseline in mean amplitude of glucose excursions (MAGE). E, Mean proportions of time spent in glycaemic ranges. Modified intention-to-treat population (once-weekly exenatide + MET, n = 60; placebo + MET, n = 56). *p < 0.001, treatment difference (once-weekly exenatide - placebo) in LS mean changes.

3.3 | Exenatide pharmacokinetics

In participants treated with once-weekly exenatide, the mean \pm s.d. exenatide concentration was 62 ± 70 ng/L at the start of week 4, and a steady-state concentration was reached at approximately week 8 (Figure S3, File S1). At study end, the mean \pm s.d. exenatide concentration was 255 ± 155 ng/L.

3.4 | Safety

There were no clinically meaningful changes in clinical laboratory variables, vital signs, ECG results or physical examination findings. Participants had reductions in body weight in both groups over 10 weeks (mean \pm s.d. reduction: -1.1 ± 2.1 kg and -0.5 ± 1.9 kg in the once-weekly exenatide and placebo groups, respectively).

The most common AEs reported were injection-site nodule (once-weekly exenatide, 10.0% and placebo, 0.0%), urinary tract infection (6.7% and 8.9%), and nausea (6.7% and 0.0%; Table 2). Most AEs were mild to moderate in nature. All serious AEs were considered by the investigator to be unrelated to treatment. These were observed in four participants in the once-weekly exenatide group (one participant each with acute pancreatitis, non-cardiac chest pain, chest pain and nephrolithiasis) and one participant in the placebo group (upper respiratory tract infection). There were no deaths. AEs leading to study discontinuation occurred in 3/60 participants (5.0%) who received once-weekly exenatide [acute pancreatitis (same participant as above), urticaria and nephrotic syndrome] and 2/56 participants (3.6%) who received placebo (constipation and increased blood creatinine). The participant with acute pancreatitis also had a history of hypertension, hypercholesterolaemia and *Klebsiella pneumoniae*-positive blood samples.

4 | DISCUSSION

The management of type 2 diabetes is based largely on achieving HbA1c goals, which has been shown to reduce the risk of microvascular and possibly macrovascular complications;^{1,2} however, when

managing patients, daily glycaemic variability may provide important data to consider in addition to HbA1c, with the goal of better approximating the glucose profile of individuals without diabetes. This was the first prospective study designed and statistically powered to evaluate the effect of the GLP-1 receptor agonist once-weekly exenatide on glycaemic variability, using CGM, in people with type 2 diabetes on background metformin therapy. Once-weekly exenatide significantly improved measures of glycaemic variability and glycaemic control compared with placebo within 4 weeks of treatment, and the effect on glucose-lowering was consistent, with similar control observed throughout week 10. Once-weekly exenatide was generally well tolerated.

Multiple measures of glycaemic variability and glycaemic control improved during treatment with once-weekly exenatide compared with placebo, including significantly greater reductions in 24-hour mean glucose at the first assessment at week 4 and at week 10, and MAGE and s.d. at week 10. CV values were similar between treatments at weeks 4 and 10, which may suggest that the reduction in s.d. was related to the reduction in average glycaemic load but does not subtract from the importance of reducing variability as shown. Glycaemic control was consistent throughout the week once steady state was attained, as shown by similar 24-hour mean glucose between days 1 and 6 of week 10. Comparison of 24-hour glucose curves at week 10 using MADz showed significant improvement during the typical waking hours, which would be consistent with the glucose-dependent mechanism of exenatide. Significant treatment differences between once-weekly exenatide and placebo groups for FPG and PPG excursions at weeks 4 and 10 were also observed. The reduction in PPG level was largely accounted for by the reduction in FPG level; however, there was also a non-significant reduction in the decrement of postprandial rise with once-weekly exenatide, independent of changes in FPG. Once-weekly exenatide numerically increased postprandial insulin AUC versus placebo, although this difference was not statistically significant, nor was it large enough to fully account for the change in PPG level. The rate of gastric emptying contributes in large part to changes in PPG; however, gastric emptying was not measured in this study. Another effect of GLP-1 receptor agonists, such as once-weekly exenatide, is their impact on satiety. Increased satiety may lead to a reduction in food intake, which may in turn contribute to reduced glucose variability. Furthermore, once-weekly exenatide increased the amount of time spent in the target glycaemic range of 3.9–10.0 mmol/L as early as week 4 of treatment, without increasing time spent in the hypoglycaemic range.

The pharmacokinetics of once-weekly exenatide are shaped by the long-acting formulation, in which exenatide is incorporated in biodegradable poly-(D,L-lactide-co-glycolide) polymer microspheres, allowing the continuous release of exenatide with once-weekly therapy.¹⁵ Weekly exenatide administration led to clinically significant improvements in glycaemic control that were evident by week 4, and steady-state concentration of exenatide at approximately week 8 was consistent with previous studies.^{16–19} Continuous exposure of exenatide translated into similar glucose-lowering effects at the beginning and end of the week. Further, continuous exenatide exposure has been associated with fewer gastrointestinal AEs compared with intermittent exenatide exposure provided by twice-daily exenatide.^{20–22}

TABLE 2 Summary of adverse events reported in $\geq 5\%$ of participants in either treatment group (modified ITT population)

Participants with AEs, n (%)	Once-weekly exenatide + metformin n = 60	Placebo + metformin n = 56
Injection-site nodule	6 (10.0)	0 (0.0)
Nausea	4 (6.7)	0 (0.0)
Urinary tract infection	4 (6.7)	5 (8.9)
Diarrhoea	3 (5.0)	2 (3.6)
Haematuria	3 (5.0)	0 (0.0)
Injection-site induration	3 (5.0)	3 (5.4)
Musculoskeletal pain	3 (5.0)	0 (0.0)
Proteinuria	3 (5.0)	1 (1.8)

In this study, AEs with once-weekly exenatide were consistent with the known safety and tolerability profile for once-weekly exenatide.

The improvements in glycaemic variability with once-weekly exenatide shown in the present study are consistent with a small subgroup analysis of seven participants with type 2 diabetes treated with once-weekly exenatide, who underwent CGM in the DURATION-1 trial.²³ Daily glucose exposure decreased significantly from baseline to week 30 (-17%; $p < 0.001$), and was sustained at week 52. After 52 weeks, there was a 47% decrease in the proportion of time that participants spent in the hyperglycaemic range (glucose >10.0 mmol/L), and a 67% increase in the proportion of time spent in the target glycaemic range of 3.9–7.8 mmol/L.

The FLAT-SUGAR (Fluctuation Reduction With Insulin and GLP-1 Added Together) trial recently examined the effects of twice-daily exenatide + insulin glargine + metformin versus rapid-acting insulin + insulin glargine + metformin on glycaemic variability measured using CGM in participants with type 2 diabetes.²⁴ Twice-daily exenatide significantly reduced the glucose CV and MAGE compared with prandial insulin, while HbA1c was similar in both groups at study end. Taken together with results from the present study, both short-acting twice-daily exenatide and long-acting once-weekly exenatide have been shown to reduce glycaemic variability, primarily by affecting postprandial excursions and fasting glucose, respectively.

Several trials have used CGM to examine the effects of other GLP-1 receptor agonists on glycaemic variability. Comparative trials with insulin showed that once-daily liraglutide significantly reduced MAGE, large amplitude of glycaemic excursions, and within-day s.d. of mean daily glucose.^{25,26} A small, uncontrolled study of Japanese people with type 2 diabetes also found that liraglutide significantly reduced MAGE from baseline and reduced the proportion of time spent in the hyperglycaemic range without any increase in time spent in the hypoglycaemic range.²⁷ The totality of data supports the efficacy of GLP-1 receptor agonists for reducing glycaemic variability; in addition, the present study showed consistent control of daily glucose throughout the week with once-weekly exenatide.

The 10-week study duration did not permit investigation of associations between long-term vascular complications of diabetes with improvements in glycaemic variability. Longer-term studies using CGM may be considered to examine the durability of changes in glycaemic variability with once-weekly exenatide.

In summary, in people with type 2 diabetes uncontrolled on metformin, once-weekly exenatide significantly improved daily glycaemic control and reduced glycaemic variability compared with placebo, as shown by reductions in 24-hour mean glucose, 24-hour glucose profile, MAGE and s.d., and increased time spent in the euglycaemic range, measured using CGM. Once-weekly exenatide exhibited meaningful reductions in FPG and PPG as early as week 4, which continued to improve at week 10, with values consistent with previous studies. At steady state, the exenatide concentration was consistent throughout the week, which led to steady and continuous glycaemic control throughout the week. The quality of this glycaemic control was particularly evident by the increased time spent in the euglycaemic range without increased time spent in the

hypoglycaemic range. These results are consistent with the glucose-dependent mechanism of action of exenatide and steady exenatide exposure as a result of continuous release of exenatide with once-weekly dosing.

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Conflict of interest

J. P. F. is an investigator and a consultant for AstraZeneca. J. A. R. and S. Z. are employees of AstraZeneca. E. K. is a speaker for AstraZeneca and Janssen, and an investigator for Antares, Asahi Kasei, AstraZeneca, Bristol-Myers Squibb, Catabasis, and Novo Nordisk. R. Z. is an employee of Medpace. P. S. is a consultant for AstraZeneca. S.N. has nothing to disclose.

Author contributions

J. P. F., J. A. R. and S. Z. participated in the conception and design of the study, data acquisition, analysis and interpretation, and critically revised the manuscript. S. N. and E. K. participated in data acquisition, analysis, and interpretation, and critically revised the manuscript. R. Z. and P. S. participated in the design of the study, data acquisition, analysis and interpretation, and critically revised the manuscript. J. P. F. is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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SUPPORTING INFORMATION

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

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