

ORIGINAL ARTICLE

Efficacy and safety of autoinjected exenatide once-weekly suspension versus sitagliptin or placebo with metformin in patients with type 2 diabetes: The DURATION-NEO-2 randomized clinical study

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Aims: Glucagon-like peptide-1 receptor agonists and dipeptidyl peptidase-4 inhibitors treat type 2 diabetes through incretin-signaling pathways. This study compared the efficacy and safety of the glucagon-like peptide-1 receptor agonist exenatide once-weekly (Miglyol) suspension for autoinjection (QWS-AI) with the dipeptidyl peptidase-4 inhibitor sitagliptin or placebo.

Materials and methods: In this open-label, multicentre study of patients with type 2 diabetes who had suboptimal glycaemic control on metformin monotherapy, 365 patients were randomized to receive exenatide 2.0 mg QWS-AI, sitagliptin 100 mg once daily or oral placebo (3:2:1 ratio). The primary endpoint was change in glycated hemoglobin (HbA1c) from baseline to 28 weeks.

Results: At 28 weeks, exenatide QWS-AI significantly reduced HbA1c from baseline compared to sitagliptin (−1.13% vs −0.75% [baseline values, 8.42% and 8.50%, respectively]; $P = .02$) and placebo (−0.40% [baseline value, 8.50%]; $P = .001$). More exenatide QWS-AI-treated patients achieved HbA1c <7.0% than did sitagliptin- or placebo-treated patients (43.1% vs 32.0% and 24.6%; both $P < .05$). Exenatide QWS-AI and sitagliptin reduced fasting plasma glucose from baseline to 28 weeks (−21.3 and −11.3 mg/dL) vs placebo (+9.6 mg/dL), with no significant difference between the 2 active treatments. Body weight decreased with both active treatments (−1.12 and −1.19 kg), but not with placebo (+0.15 kg). No improvement in blood pressure was observed in any group. The most common adverse events with exenatide QWS-AI were gastrointestinal events and injection-site reactions.

Conclusions: This study demonstrated that exenatide QWS-AI reduced HbA1c more than sitagliptin or placebo and was well tolerated.

KEYWORDS

autoinjector, exenatide, once weekly, sitagliptin, suspension, type 2 diabetes

1 | INTRODUCTION

Glucagon-like peptide-1 receptor agonists (GLP-1RAs) and dipeptidyl peptidase-4 inhibitors (DPP-4is) are 2 classes of incretin-based glucose-lowering medications recommended for patients with type 2 diabetes

(T2D).¹ Both GLP-1RAs and DPP-4is act through the glucagon-like peptide-1 (GLP-1) receptor; GLP-1RAs directly activate the receptor, whereas DPP-4is prevent degradation of endogenous GLP-1.

Administration frequency and ease of use can both influence long-term use of a therapy, particularly injectable therapies.² The

GLP-1RA exenatide was initially developed as a twice-daily (BID) injection.³ A once-weekly (QW) formulation was later developed,⁴ containing the active ingredient of exenatide BID encapsulated into biodegradable poly(D,L-lactide-coglycolide) microspheres.⁵ Exenatide QW is administered using a single-dose tray, with some assembly required,⁶ or as a pre-assembled single-dose dual-chamber pen.⁷ For both devices, patients need to mix exenatide-containing microspheres and aqueous diluent before injection.^{4,7}

Exenatide delivery has been further simplified by the development of a QW suspension for autoinjection (QWS-AI), in which the microspheres are suspended in a mixture of nonaqueous triglycerides (Miglyol 812). The autoinjector delivers a single 2.0-mg exenatide dose (as do all QW delivery systems) in a premeasured volume (0.85 mL), eliminating the need for reconstitution and improving mixing speed. Pharmacokinetic data demonstrated that exenatide 2.0 mg QWS-AI achieved steady-state exenatide concentrations within the range observed with exenatide 2.0 mg QW;⁸ thus, the dosage was considered appropriate for future investigation.

Previous studies compared the efficacy and safety of GLP-1RAs with DPP-4is.^{9–18} The DURATION-2 and DURATION-4 studies demonstrated that exenatide QW achieved better glycaemic control than sitagliptin, both as monotherapy and in combination with metformin.^{9,10} This study compared the efficacy and safety of the exenatide QWS-AI formulation vs the maximum approved dose of sitagliptin and vs placebo among patients receiving suboptimal glycaemic control with metformin monotherapy.

2 | MATERIALS AND METHODS

This phase 3, randomized, open-label, multicentre, active- and placebo-controlled study (DURATION-NEO-2; NCT01652729), conducted at 81 centres in the USA between February 2013 and April 2014, comprised a screening period (screening visit followed by second visit within 14 days) and a 28-week treatment period. Study drug was initiated at randomization (baseline), 1 week after the second screening visit. Visits were conducted at 2-week intervals to week 4 and at 4-week intervals thereafter.

Eligible patients were aged ≥ 18 years with T2D on a stable regimen of metformin ≥ 1500 mg/d for ≥ 2 months before screening. Additional inclusion criteria were glycated hemoglobin (HbA1c) of 7.1% to 11.0% at screening, fasting plasma glucose (FPG) < 280 mg/dL at screening and at visit 2, body mass index ≤ 45 kg/m² and stable body weight ($\leq 3\%$ variation for ≥ 3 months before screening). Exclusion criteria included any clinically significant medical condition that could affect study participation; an estimated glomerular filtration rate < 30 mL/min/1.73 m²; exposure to exenatide or any GLP-1RA; use of any DPP-4i, sulfonyleurea or thiazolidinedione, or weight-loss medications within 3 months before screening; or ≥ 2 episodes of severe hypoglycaemia within 6 months of screening.

Patients provided written informed consent before enrollment. The study protocol was approved by institutional review boards at each study site and was conducted in accordance with the Declaration of Helsinki and Good Clinical Practice guidelines.

2.1 | Randomization and blinding

Randomization was achieved centrally through an interactive web system and stratified by screening HbA1c $< 9.0\%$ or $\geq 9.0\%$. Patients were randomized in a 3:2:1 ratio to exenatide 2.0 mg QWS-AI, sitagliptin 100 mg or placebo, thereby maximizing the amount of safety data for exenatide QWS-AI while minimizing the number of patients receiving placebo. Patients, investigators, study-site staff and the sponsor were blinded to the identity of sitagliptin or placebo, which were administered in capsules of identical appearance. Exenatide QWS-AI administration was not blinded, and no placebo injection was provided. Personnel involved with data review and analysis were blinded to key efficacy data throughout the 28-week assessment period.

2.2 | Treatments and procedures

Sitagliptin and placebo were administered orally once daily in the morning, and exenatide QWS-AI was administered QW by subcutaneous injection in the abdomen, thigh or upper arm via prefilled, single-dose autoinjector with an integrated needle on the same day of the week at any time of day. Before the first exenatide QWS-AI dose, a medically qualified staff member trained patients or caregivers concerning autoinjection methodology. Proportion of medication use was determined by comparison of study drug dispensed vs drug returned.

Stable doses of metformin (≥ 1500 mg/d) and antihypertensive and lipid-lowering agents (if applicable) were continued throughout the study. In the event of loss of glucose control (FPG > 270 mg/dL at 2 consecutive visits from weeks 4–16 or > 240 mg/dL at 2 consecutive visits from weeks 16–28), rescue therapy with glucose-lowering treatment was initiated at the investigator's discretion.

Patients were instructed to record 6-point self-monitored blood glucose (SMBG) profiles (3 measurements 15 minutes before each of 3 main meals and 3 measurements 1.5–2 hours after each meal) on any 3 days before baseline and during weeks 16 and 28.

A subset of patients in each treatment group participated in a standardized meal test at baseline and week 16. For the meal test, patients were provided a standardized c. 660 kcal breakfast (60% carbohydrates, 15% protein, 25% fat) and this was consumed within 15 minutes.

2.3 | Efficacy measures

2.3.1 | Glycaemic control

The primary efficacy endpoint was change from baseline in HbA1c at week 28. Secondary endpoints, assessed at week 28, included the proportion of patients achieving HbA1c $< 7.0\%$ and change in FPG from baseline. For patients in the meal test cohort, change from baseline in 2-hour postprandial glucose (PPG) at week 16 was a secondary endpoint.

Tertiary glycaemic endpoints included the proportion of patients achieving HbA1c $\leq 6.5\%$ at week 28, evaluation of 6-point SMBG profiles, changes from baseline in fasting insulin and homeostatic model assessment of pancreatic β -cell function (HOMA-B) and insulin sensitivity (HOMA-S).

2.3.2 | Cardiovascular risk markers

Change from baseline to week 28 in body weight was a secondary endpoint. Tertiary endpoints related to cardiovascular risk included changes from baseline in systolic and diastolic blood pressure, fasting lipid concentrations, B-type natriuretic peptide, urinary albumin-to-creatinine ratio, high-sensitivity C-reactive protein, heart rate and waist circumference, as well as the proportion of patients achieving a reduction in both HbA1c and body weight at week 28. Blood pressure and heart rate were assessed twice in the sitting position after the patient had rested for 5 minutes. Averages of the 2 readings were recorded.

2.3.3 | Patient-reported outcomes

Patient-reported endpoints (Diabetes Medication Satisfaction Tool, Impact of Weight on Quality of Life-Lite) are described and reported in File S1.

2.4 | Exenatide pharmacokinetics

Exenatide pharmacokinetics were evaluated in exenatide QWS-AI-treated patients who had ≥ 1 exenatide concentration above the lower limit of quantification at week 16 or 28. Methods for exenatide pharmacokinetics analysis are provided in File S1.

2.5 | Safety and tolerability

The primary safety endpoint was incidence of adverse events (AEs). Methods for AE analysis are provided in File S1. Anti-exenatide antibodies detected at 1/625 dilution (high dilution) were termed "high-positive"; antibodies detected at lower dilutions were termed "low-positive."

Any reported or suspected cardiovascular events, pancreatitis, malignancies or deaths were adjudicated using prespecified criteria by a clinical events classification (CEC) committee blinded to study treatment.

Hypoglycaemia AEs were categorized as major, minor or symptoms of hypoglycaemia. Major hypoglycaemia was defined as an event that resulted in loss of consciousness, seizure or coma that resolved after administration of glucagon or glucose, or any event that required third-party assistance to resolve because of severe impairment in consciousness or behavior and was associated with a glucose concentration of <54 mg/dL. Minor hypoglycaemia was defined as a non-major hypoglycaemia event with symptoms of hypoglycaemia and a glucose concentration of <54 mg/dL. If a hypoglycaemia event did not meet symptomatic or blood glucose criteria for a major or minor event, it was classified as symptoms of hypoglycaemia (this could include events for which no blood glucose measure was available).

2.6 | Statistical analysis

Efficacy and pharmacodynamic variables were analysed using the modified intent-to-treat (mITT) population, defined as all randomized patients who received ≥ 1 dose of study drug. Pharmacokinetic variables were analysed in the pharmacokinetic-evaluable population, consisting of all mITT patients who received exenatide QWS-AI and

had adequate/reliable pharmacokinetic data. Postprandial data analyses were performed for the meal test-evaluable population, defined as all mITT patients who participated in the meal test, consumed $\geq 75\%$ of the standardized meal and had no missing 2-hour PPG measurements at baseline and week 16. Safety data analysis was performed for the as-treated population.

The primary endpoint was assessed using a mixed-effects model repeated measures (MMRM) with change in HbA1c as the dependent variable; treatment, week of visit, treatment-by-week interaction, baseline HbA1c stratum and baseline HbA1c stratum-by-week interaction as fixed factors; and patient as random effect. Covariates included baseline HbA1c and baseline HbA1c-by-week interaction. Changes in continuous endpoints were tested using MMRM analyses. A general linear model evaluated change from baseline for parameters assessed only at baseline and 1 post-baseline visit. Proportions of patients achieving HbA1c targets were summarized and compared between treatment groups using Cochran-Mantel-Haenszel tests, stratified by baseline HbA1c stratum, using last-observation-carried-forward data.

Hypothesis testing on primary and secondary efficacy endpoints followed a serial-gated procedure, with all tests carried out at a 2-sided significance level of $P < .05$. Three primary efficacy endpoint hypotheses were tested sequentially: superiority of exenatide QWS-AI to placebo; noninferiority of exenatide QWS-AI to sitagliptin; and superiority of exenatide QWS-AI to sitagliptin. Four secondary efficacy endpoint hypotheses were then tested sequentially: superiority for HbA1c goal of exenatide QWS-AI to sitagliptin; superiority for FPG of exenatide QWS-AI to sitagliptin; superiority for body weight of exenatide QWS-AI to sitagliptin; and superiority for 2-hour PPG of exenatide QWS-AI to sitagliptin. Once a hypothesis test failed, nominal P -values were calculated for subsequent endpoints.

2.7 | Sample size

The protocol specified randomization of a total of 360 patients (exenatide QWS-AI, $n = 180$; sitagliptin, $n = 120$; placebo, $n = 60$), with an expected 15% withdrawal rate. A subset of c. 100 patients was proposed to participate in the standardized meal test assessment (exenatide QWS-AI, $n = 50$; sitagliptin, $n = 33$; placebo, $n = 16$). Further details of sample size calculation are provided online in File S1.

3 | RESULTS

3.1 | Patients

The study was completed by 311 patients (85% of those randomized) (Figure 1). More placebo-treated patients (23%) discontinued than did exenatide QWS-AI- (15%) or sitagliptin-treated patients (11%). Compliance, determined by study drug received vs that planned, was between 97% and 98% among all groups. Twenty-nine patients received rescue therapy (File S1).

Demographic and baseline characteristics were similar across treatment groups, except for a larger proportion of men and a smaller proportion of Hispanic patients in the placebo group (Table 1).

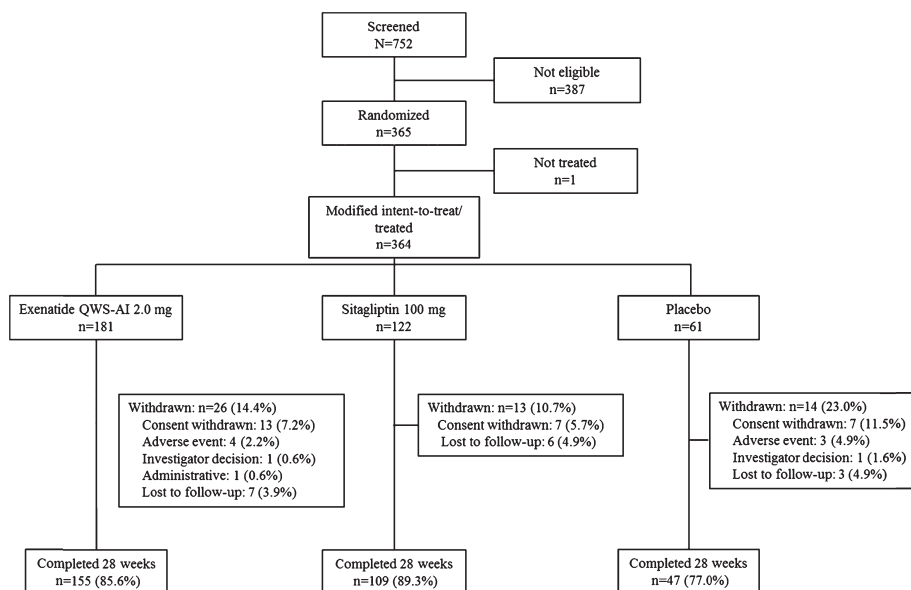


FIGURE 1 Study enrollment and outcomes. QWS-AI, once-weekly suspension for autoinjection

TABLE 1 Demographic and baseline characteristics in the modified intent-to-treat population

Characteristic	Exenatide QWS-AI (n = 181)	Sitagliptin (n = 122)	Placebo (n = 61)
Male, n (%)	89 (49.2)	66 (54.1)	37 (60.7)
Age, years	53.4 (9.8)	54.3 (9.0)	53.4 (9.5)
Race, n (%)			
White	148 (81.8)	98 (80.3)	50 (82.0)
Black	24 (13.3)	18 (14.8)	7 (11.5)
Asian	9 (5.0)	2 (1.6)	3 (4.9)
Other	0 (0.0)	4 (3.3)	1 (1.6)
Hispanic ethnicity, n (%)	111 (61.3)	77 (63.1)	32 (52.5)
HbA1c, %	8.4 (1.0)	8.5 (1.0)	8.5 (1.0)
FPG, mg/dL	178.0 (46.6)	176.9 (42.5)	172.8 (44.3)
Body weight, kg	89.2 (21.4)	88.1 (20.3)	89.0 (20.1)
Body mass index, kg/m ²	32.1 (5.4)	31.6 (5.8)	31.5 (5.1)
Duration of type 2 diabetes, years	8.5 (6.3)	7.9 (4.6)	8.7 (5.8)
Other medications, n (%)			
Agents acting on the renin-angiotensin system	81 (44.8)	55 (45.1)	29 (47.5)
Lipid-modifying agents	52 (28.7)	40 (32.8)	19 (31.1)
β-Blocking agents	15 (8.3)	9 (7.4)	6 (9.8)
Calcium channel blockers	10 (5.5)	4 (3.3)	8 (13.1)
Other antihypertensive	2 (1.1)	3 (2.5)	0 (0.0)

Abbreviations: FPG, fasting plasma glucose; HbA1c, glycated hemoglobin; QWS-AI, once-weekly suspension for autoinjection.

Data are given as mean (standard deviation) unless otherwise stated.

3.2 | Efficacy

3.2.1 | Glycaemic control

Exenatide QWS-AI led to significantly greater HbA1c reduction from baseline to week 28 vs sitagliptin (least-squares mean [LSM] difference, -0.38% ; 95% confidence interval [CI], -0.70% to -0.06% ;

$P = .021$) or placebo (-0.72% ; 95% CI, -1.15% to -0.30% ; $P = .001$) (Table 2). Greater HbA1c reductions with exenatide QWS-AI vs sitagliptin were observed from week 16 onward (Figure 2A). At week 28, a higher proportion of exenatide QWS-AI-treated patients (43.1%) achieved HbA1c $< 7.0\%$ than did sitagliptin- (32.0%) or placebo-treated patients (24.6%) (Figure 2B).

Exenatide QWS-AI resulted in numerically greater FPG reductions than sitagliptin and greater FPG reductions than placebo ($P < .001$) (Table 2). The difference in FPG reduction for exenatide QWS-AI vs sitagliptin was not statistically significant; thus, the hierarchical testing sequence ended at this point and all subsequent analyses are presented as nominal P -values. FPG reductions with exenatide QWS-AI and sitagliptin were evident from week 4 - (Figure 2C) and were greater with exenatide QWS-AI vs sitagliptin from weeks 8-24 (nominal $P < .01$).

The meal test cohort consisted of 121 patients (exenatide QWS-AI, $n = 60$; sitagliptin, $n = 41$; placebo, $n = 20$), with 44, 31 and 15 evaluable patients, respectively. LSM (standard error) changes in 2-hour PPG concentrations from baseline to week 16 were -59.6 (10.5), -23.6 (13.0) and -38.7 (17.0) mg/dL, respectively. LSM difference for exenatide QWS-AI was -36.0 mg/dL (95% CI, -67.2 to -4.7 mg/dL; nominal $P = .025$) vs sitagliptin and -20.9 mg/dL (-60.0 to $+18.3$ mg/dL; nominal $P = .291$) vs placebo.

The mean 6-point SMBG concentration in the mITT population decreased from baseline to week 28 in all groups (Table 2; Figure 2D), with a numerically greater reduction observed among exenatide QWS-AI-treated patients (nominal $P = .145$ vs sitagliptin; nominal $P = .001$ vs placebo).

Fasting insulin concentrations were modestly increased with exenatide QWS-AI, reduced with sitagliptin (nominal $P = .014$ vs exenatide QWS-AI) and increased with placebo (nominal $P = .838$ vs exenatide QWS-AI) (Table 2). Pancreatic β -cell function (HOMA-B) improved more with QWS-AI than with sitagliptin or placebo (nominal $P = .002$ and $P = .001$, respectively). Insulin sensitivity (HOMA-S) differed between exenatide QWS-AI and sitagliptin, decreasing with exenatide QWS-AI and increasing with sitagliptin (nominal $P = .044$).

TABLE 2 Efficacy endpoints

Endpoint	Exenatide QWS-AI (n = 181)	Sitagliptin (n = 122)	Placebo (n = 61)	LSM between-group difference (95% CI)	
				Exenatide QWS-AI vs sitagliptin	Exenatide QWS-AI vs placebo
Glycaemic control					
HbA1c, %					
Baseline, mean (SD)	8.42 (1.00)	8.50 (1.04)	8.50 (1.04)		
Endpoint, mean (SD)	7.28 (1.31)	7.56 (1.31)	7.74 (1.44)		
Change from baseline, LSM (SE)	-1.13 (0.11)	-0.75 (0.13)	-0.40 (0.19)	-0.38 (-0.70 to -0.06); P = .021	-0.72 (-1.15 to -0.30); P = .001
FPG, mg/dL					
Baseline, mean (SD)	178.0 (46.6)	176.9 (42.5)	172.8 (44.3)		
Endpoint, mean (SD)	148.7 (48.0)	155.1 (42.6)	165.5 (46.2)		
Change from baseline, LSM (SE)	-21.3 (3.9)	-11.3 (4.6)	+9.6 (7.1)	-10.1 (-21.8 to 1.7); P = .092	-30.9 (-46.7 to -15.1); P < .001
Mean daily SMBG, mg/dL					
Baseline, mean (SD)	188.1 (39.9)	184.6 (36.2)	181.4 (34.8)		
Endpoint, mean (SD)	150.5 (29.7)	153.2 (26.5)	167.4 (33.7)		
Change from baseline, LSM (SE)	-31.9 (2.3)	-26.9 (2.7)	-13.1 (4.3)	-5.1 (-11.8 to +1.75); P = .145 ^a	-18.8 (-28.3 to -9.3); P = .001 ^a
Fasting insulin, mU/L					
Baseline, mean (SD)	20.7 (19.1)	20.9 (34.9)	19.7 (13.5)		
Endpoint, mean (SD)	22.3 (18.5)	17.4 (10.3)	23.5 (25.3)		
Change from baseline, LSM (SE)	+1.5 (1.4)	-4.0 (1.7)	+2.1 (2.8)	+5.5 (+1.1 to +9.8); P = .014 ^a	-0.6 (-6.6 to +5.4); P = .838 ^a
HOMA-B, %^b					
Baseline, geometric mean (SE)	45.3 (2.4)	45.8 (2.8)	47.8 (4.8)		
Endpoint, geometric mean (SE)	69.0 (4.0)	56.6 (3.5)	54.7 (6.8)		
Ratio of week 28 to baseline, geometric LSM (SE)	1.5 (0.07)	1.1 (0.07)	1.0 (0.10)	1.3 (1.1-1.5); P = .002 ^a	1.4 (1.2-1.8); P = .001 ^a
HOMA-S, %^b					
Baseline, geometric mean (SE)	44.7 (2.1)	44.8 (2.6)	43.9 (3.8)		
Endpoint, geometric mean (SE)	42.1 (2.1)	47.5 (2.8)	43.8 (4.5)		
Ratio of week 28 to baseline, geometric LSM (SE)	0.9 (0.04)	1.1 (0.05)	1.0 (0.08)	0.9 (0.8-1.0); P = .044 ^a	0.9 (0.8-1.1); P = .329 ^a
Cardiovascular risk markers					
Body weight, kg					
Baseline, mean (SD)	89.2 (21.4)	88.1 (20.3)	89.0 (20.1)		
Endpoint, mean (SD)	86.9 (21.4)	86.4 (18.6)	88.0 (20.6)		
Change from baseline, LSM (SE)	-1.1 (0.3)	-1.2 (0.3)	+0.2 (0.5)	+0.1 (-0.7 to +0.9); P = .863 ^a	-1.3 (-2.3 to -0.2); P = .020 ^a
Heart rate, beats/min					
Baseline, mean (SD)	73.1 (9.6)	74.4 (8.7)	73.2 (7.9)		
Endpoint, mean (SD)	75.5 (9.7)	74.8 (7.7)	73.1 (8.2)		
Change from baseline, LSM (SE)	+2.7 (0.7)	+0.5 (0.7)	-0.3 (0.9)	Not calculated	Not calculated
SBP, mm Hg					
Baseline, mean (SD)	127.6 (12.8)	128.9 (12.4)	127.7 (15.5)		
Endpoint, mean (SD)	129.1 (12.8)	128.9 (12.0)	130.4 (15.9)		
Change from baseline, LSM (SE)	+1.2 (0.9)	+0.8 (1.1)	+2.4 (1.7)	+0.5 (-2.3 to +3.2); P = .736 ^a	-1.2 (-4.9 to +2.6); P = .531 ^a
DBP, mm Hg					
Baseline, mean (SD)	77.4 (8.9)	79.0 (7.8)	77.0 (8.1)		
Endpoint, mean (SD)	78.8 (8.9)	78.4 (7.7)	76.1 (7.9)		
Change from baseline, LSM (SE)	+1.0 (0.6)	+0.2 (0.7)	-1.0 (1.1)	+0.8 (-1.0 to +2.6); P = .363 ^a	+2.0 (-0.4 to +4.4); P = .108 ^a

Abbreviations: CI, confidence interval; DBP, diastolic blood pressure; FPG, fasting plasma glucose; HbA1c, glycated hemoglobin; HOMA-B, homeostatic model assessment of pancreatic β -cell function; HOMA-S, homeostatic model assessment of insulin sensitivity; LSM, least-squares mean; QWS-AI, once-weekly suspension for autoinjection; SBP, systolic blood pressure; SD, standard deviation; SE, standard error; SMBG, self-monitored blood glucose.

LSM between-group differences are shown for parameters analysed by formal hypothesis testing.

^aNominal P-value; formal hypothesis testing was stopped after FPG analysis.

^bFor variables for which change from baseline is calculated as a ratio and reported as geometric LSM (SE), baseline and endpoint values are reported as geometric mean (SE). SE is reported as the measure of variance for the geometric mean for the following reasons: geometric mean is the exponential of the mean obtained on the logarithm scale. The geometric SE is a symmetric parameter that shows the precision of the geometric mean, whereas geometric SD is not a symmetric parameter and is difficult to present in a tabulation format for interpretation.

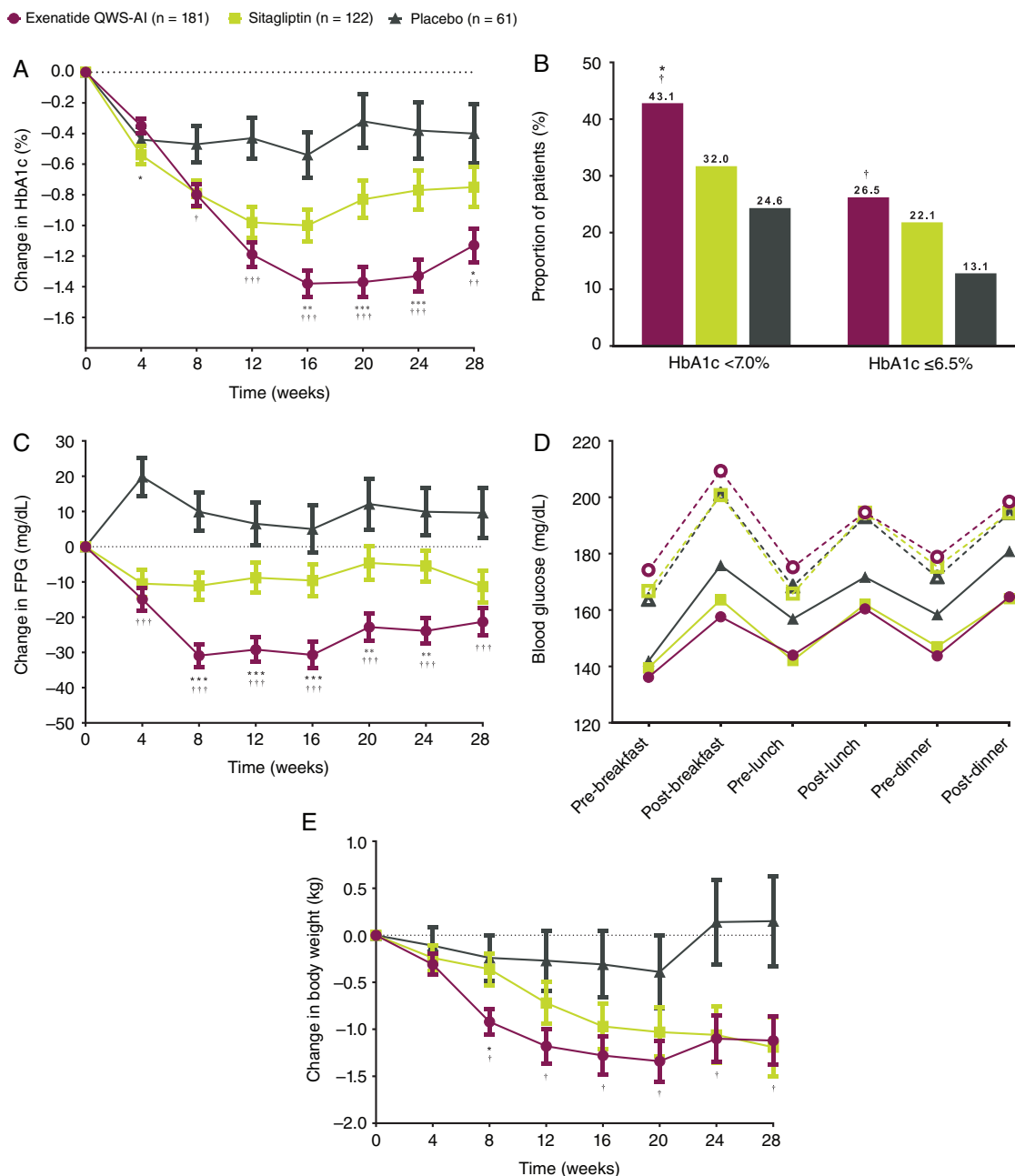


FIGURE 2 Primary and secondary efficacy outcomes. A, Least-squares mean (standard error) (LSM [SE]) change in glycated hemoglobin (HbA1c) from baseline to 28 weeks. B, Proportion of patients achieving HbA1c <7.0% and ≤6.5% at week 28. C, LSM (SE) change in fasting plasma glucose (FPG) from baseline to 28 weeks. D, Mean self-monitored blood glucose values at baseline (open symbols, dashed lines) and 28 weeks (closed symbols, solid line). E, LSM (SE) change in body weight from baseline to 28 weeks. QWS-AI, once-weekly suspension for autoinjection. **P* < .05, ***P* < .01, ****P* < .001 exenatide QWS-AI vs sitagliptin; †*P* < .05, ††*P* < .01, †††*P* < .001 exenatide QWS-AI vs placebo. All *P*-values are nominal, with the exception of HbA1c and FPG

3.2.2 | Cardiovascular risk markers

Body weight decreased over the 28-week treatment period with exenatide QWS-AI and sitagliptin, with no difference observed between groups (nominal *P* = .8625) (Table 2; Figure 2E). Most other cardiovascular risk markers (eg, blood pressure, lipids) were unchanged from baseline and did not differ between groups, although heart rate increased by +2.7 beats/min from baseline among exenatide QWS-AI-treated patients (Table 2; Table S1).

3.2.3 | Patient-reported outcomes

Results of patient-reported outcome surveys (Diabetes Medication Satisfaction Tool, Impact of Weight on Quality of Life-Lite), which demonstrated improvements from baseline, are provided in Table S1.

3.3 | Exenatide pharmacokinetics

For the 134 patients in the pharmacokinetic-evaluable population, plasma exenatide concentrations were similar at weeks 8, 16 and

28, indicating steady-state attainment. The geometric mean (10th, 90th percentiles) steady-state exenatide concentration between weeks 16 and 28 was 153 (50, 354) pg/mL.

3.4 | Safety and tolerability

AEs were reported by 55.8%, 32.8% and 47.5% of exenatide QWS-AI, sitagliptin and placebo recipients, respectively, during the 28-week treatment period (Table 3).

Five exenatide QWS-AI-treated patients (2.8%) had a serious AE (SAE; obstructive abdominal hernia, diarrhea, rheumatoid arthritis, breast cancer, brain stem infarction). No SAEs occurred with sitagliptin, and 3 SAEs (acute myocardial infarction [AMI], coronary artery disease, injury resulting from a fall) were reported in 2 placebo recipients (3.3%) (Table 3).

AEs resulting in withdrawal before week 28 occurred in 3 exenatide QWS-AI recipients (obstructive abdominal hernia, lower gastrointestinal hemorrhage, breast cancer), in no sitagliptin recipients and in 3 placebo recipients (AMI, "feeling abnormal," hypoesthesia, angioedema) (Table 3).

Of 24 suspected events submitted to the CEC committee for adjudication, 4 were confirmed (brain stem infarction, breast cancer and benign fibroadenoma of the breast with exenatide QWS-AI, and

AMI with placebo). No thyroid neoplasm, pancreatic cancer, renal failure or pancreatitis events were reported in any group (Table 3).

No major hypoglycaemia episodes were reported. One sitagliptin recipient had a minor hypoglycaemic event, and symptoms of hypoglycaemia occurred in 4 exenatide QWS-AI recipients, in 7 sitagliptin recipients and in 2 placebo recipients (Table 3). Among patients with symptoms of hypoglycaemia, 4 had no blood glucose value reported, 6 had glucose values between 56 and 70 mg/dL and 3 had values >70 mg/dL.

The most common AEs ($\geq 5\%$ of patients) were nausea (exenatide QWS-AI, 8.8%; sitagliptin, 1.6%; placebo, 0.0%), injection-site nodules (7.7% of exenatide QWS-AI recipients) and nasopharyngitis (exenatide QWS-AI, 0.6%; sitagliptin, 0.0%; placebo, 6.6%). More exenatide QWS-AI-treated patients than sitagliptin-treated patients experienced gastrointestinal AEs (nausea, vomiting, diarrhea, dyspepsia). Injection-site-related AEs were reported only among exenatide QWS-AI recipients and included nodules, induration, bruising and pruritus (Table 3). Most injection-site nodules were mild, and none led to treatment cessation.

At the last visit, 105 (63.3%) exenatide QWS-AI recipients were positive (high-positive, $n = 26$ [15.7%]; low-positive, $n = 79$ [47.6%]) for anti-exenatide antibodies. High-positive patients achieved numerically lower HbA1c reduction (-0.6%) vs low-positive patients (-1.1%) or those negative for antibodies (-1.1%). Patients with anti-exenatide antibodies were more likely to experience injection-site reactions such as nodules, induration, pruritus or erythema than those negative for exenatide antibodies (14.5% of positive patients vs 1.8% of negative patients).

TABLE 3 Adverse events

Event, n (%)	Exenatide QWS-AI (n = 181)	Sitagliptin (n = 122)	Placebo (n = 61)
Any AE	101 (55.8)	40 (32.8)	29 (47.5)
Serious AEs	5 (2.8)	0 (0.0)	2 (3.3)
AEs leading to withdrawal	3 (1.7)	0 (0.0)	3 (4.9)
Specific AEs			
Thyroid neoplasms ^a	0 (0.0)	0 (0.0)	0 (0.0)
Pancreatic cancer ^a	0 (0.0)	0 (0.0)	0 (0.0)
Renal failure	0 (0.0)	0 (0.0)	0 (0.0)
Injection-site-related AEs	34 (18.8)	0 (0.0)	0 (0.0)
Nodules	14 (7.7)	0 (0.0)	0 (0.0)
Induration	7 (3.9)	0 (0.0)	0 (0.0)
Bruising	5 (2.8)	0 (0.0)	0 (0.0)
Pruritus	5 (2.8)	0 (0.0)	0 (0.0)
Gastrointestinal AEs	32 (17.7)	9 (7.4)	2 (3.3)
Nausea	16 (8.8)	2 (1.6)	0 (0.0)
Vomiting	6 (3.3)	0 (0.0)	0 (0.0)
Diarrhea	5 (2.8)	2 (1.6)	1 (1.6)
Dyspepsia	4 (2.2)	1 (0.8)	0 (0.0)
Hypoglycaemia			
Major	0 (0.0)	0 (0.0)	0 (0.0)
Minor	0 (0.0)	1 (0.8)	0 (0.0)
Symptoms of hypoglycaemia	4 (2.2)	7 (5.7)	2 (3.3)
Pancreatitis ^a	0 (0.0)	0 (0.0)	0 (0.0)
Cardiovascular events ^a	0 (0.0)	0 (0.0)	1 (1.6)

Abbreviations: AE, adverse event; QWS-AI, once-weekly suspension for autoinjection.

Data are shown as the number (%) of patients reporting an adverse event.

^aAdjudicated AEs.

4 | DISCUSSION

Administration frequency and ease of use may affect patients' ability to initiate and continue injectable therapies for long-term use. Exenatide QWS-AI is a new formulation that does not require reconstitution and can be administered via autoinjector pen, simplifying use. This study directly compared the efficacy and safety of exenatide QWS-AI with the oral DPP-4i sitagliptin or placebo over 28 weeks among patients with T2D who had insufficient glycaemic control on metformin monotherapy and found that exenatide QWS-AI was superior to sitagliptin and placebo for the primary endpoint of change from baseline in HbA1c at 28 weeks. Furthermore, more exenatide QWS-AI-treated patients achieved target HbA1c <7.0% at 28 weeks than did sitagliptin- or placebo-treated patients.

The effect of exenatide QWS-AI on HbA1c in this study is comparable to that observed with GLP-1RAs vs DPP-4is in previous studies. Of 8 randomized, head-to-head studies comparing the GLP-1RAs exenatide, liraglutide, albiglutide or dulaglutide with the DPP-4i sitagliptin as add-on therapy^{9,11-13,15-18} or monotherapy,¹⁰ 6 studies demonstrated significantly greater HbA1c reductions over 26 to 104 weeks with GLP-1RAs vs sitagliptin^{9,10,12,15,16,18}; 1 24-week study found no significantly different reductions with liraglutide 0.9 mg/d vs sitagliptin,¹⁷ and 1 26-week study found that sitagliptin was noninferior to liraglutide 1.2 mg/d.¹³ Additionally, a 24-week study found significantly greater HbA1c reductions with liraglutide vs

saxagliptin or vildagliptin.¹⁴ In 7 of the 9 earlier studies, proportions of patients achieving HbA1c levels <7.0% were greater with GLP-1RAs than DPP-4is.^{9,10,12,13,15,16,18}

FPG reductions in this trial were less robust than those with exenatide in previous trials. Based on nominal *P*-values, exenatide QWS-AI reduced FPG more than sitagliptin from weeks 8 to 24, but the difference was nonsignificant at week 28. Among previous studies comparing GLP-1RAs to DPP-4is, 8 (including 2 exenatide vs sitagliptin studies) found significantly greater FPG reductions with GLP-1RAs,^{9,10,12,14–18} and 1 study of liraglutide 1.2 mg/d found comparable reductions.¹³ The statistical power in this study was probably insufficient to detect a difference because of the high FPG variability.

In this study, body weight loss was greater with exenatide QWS-AI than with placebo but similar to body weight loss with sitagliptin. Among earlier studies comparing GLP-1RAs with DPP-4is,^{9,10,12–18} all but 2^{12,17} found significantly greater body weight reductions with GLP-1RAs over 24 to 104 weeks. The similar body weight loss seen with exenatide QWS-AI and sitagliptin in this study may be explained by body weight loss with exenatide QWS-AI being somewhat lower than expected. Previous exenatide QW studies report body weight loss of 2.0 to 4.0 kg over 26 to 30 weeks, compared with body weight loss of 1.1 kg with exenatide QWS-AI in this study.^{9,10,19,20} Similarly, the absence of blood pressure reduction observed in this study, which differs from previous studies of exenatide QW,^{9,10,19} may be associated with the lesser body weight loss observed with exenatide QWS-AI. A post-hoc analysis showed that patients in the lower quartiles of weight loss after treatment with exenatide QW had less reduction in systolic blood pressure.²¹

Although comparisons between studies and formulations are difficult, lower plasma exenatide concentrations in this study may have contributed to lower than expected weight reduction and, possibly, to less systolic blood pressure reduction.²² The exenatide concentration required to improve glycaemic control is significantly less than that provided by either exenatide QW (aqueous)²¹ or exenatide QWS-AI, but the concentration needed for body weight loss is close to the mean exenatide concentration measured in this study.²³ Further evaluation of the effects of exenatide QWS-AI on body weight is warranted.

This study also found that pancreatic β -cell function increased more with exenatide QWS-AI than with sitagliptin, consistent with previous findings for GLP-1RAs vs DPP-4is.^{10,15,16} A significant difference in insulin sensitivity between exenatide QWS-AI and sitagliptin was also observed, which is different from earlier studies that have reported no between-group differences for changes in insulin sensitivity.^{10,15–17} This effect may be driven by higher fasting insulin concentrations with exenatide QWS-AI than with sitagliptin. There were no differences between groups in mean daily glucose reductions observed in this study, whereas earlier studies consistently found greater improvements with GLP-1RAs vs DPP-4is.^{9,10,14,18} Finally, a greater increase in fasting insulin was observed in this study with exenatide vs sitagliptin, consistent with the DURATION-2 study;⁹ other studies did not find between-group differences in this measure.^{15–17} Overall, based on all comparative data, one may conclude that the profile of exenatide QWS-AI is similar to that of

exenatide QW and other GLP-1RAs, although some variability exists in results among different studies.

Interpretation of the data in this study is limited by several factors. One limitation of the study design was the lack of blinding for patients receiving exenatide QWS-AI, which may introduce observer or reporter bias, particularly for patient-reported outcomes. Although this approach avoided unnecessary injections for patients, it is possible that patient responses were biased by the knowledge that injected treatment was active. However, clinical trials with injectable therapies are often open label, to minimize the burden to patients in the trial. This approach is accepted by regulatory authorities for indication-seeking trials. The oral placebo group in this study provided a reasonable assessment of the study bias in itself. Other limitations of this study design include the imbalanced randomization ratio, which reduced the power of the study to detect differences between groups, because of the relatively small placebo group that was chosen to minimize the number of untreated patients. The meal test cohort was also small, and the study duration was less than 1 year.

The incidence of AEs in this study was generally similar to that observed in other studies comparing GLP-1RAs with the DPP-4is sitagliptin,^{12,13,15,18,24,25} saxagliptin or vildagliptin.¹⁴ Gastrointestinal events (nausea, diarrhea) were consistently more common with GLP-1RAs than with DPP-4is. In this study, the most common AEs reported with exenatide QWS-AI were gastrointestinal and injection-site-related events. Relatively modest rates of nausea with exenatide QWS-AI may be explained by the gradual release of exenatide from the microspheres and the lipid suspension formulation, which encapsulates exenatide bound to the surface of the microspheres. Occurrence of nodules is probably related to the microsphere formulation.⁵ These events were well tolerated, with no treatment withdrawals. There were 5 SAEs with exenatide QWS-AI and none with sitagliptin. There were no cases of major hypoglycaemia during the study, and 1 instance of minor hypoglycaemia with sitagliptin.

Consistent with observations concerning exenatide QW (aqueous),²⁶ the majority of exenatide QWS-AI recipients developed anti-exenatide antibodies. Patients with antibodies more often experienced injection-site reactions, and those with high-positive antibody levels had numerically lower HbA1c reduction (–0.6% vs –1.1% for those who were antibody-negative). Antibody effects on HbA1c reduction are not seen consistently in exenatide studies.²⁷

In this study, the exenatide QWS-AI formulation was compared with a DPP-4i. Another study (DURATION-NEO-1) compared the efficacy and safety of exenatide QWS-AI with exenatide BID in patients with T2D who were inadequately controlled with diet and exercise alone or with glucose-lowering therapies.²⁸ After 28 weeks, mean (standard error) reductions in HbA1c (–1.39 [0.09]%), FPG (–32.7 [3.9] mg/dL) and body weight (–1.49 [0.28] kg) with exenatide QWS-AI appeared larger than those in the current study. There are no obvious explanations for differences in efficacy data between the 2 studies, which may result from random variability in findings across studies or from undefined differences between patient populations.

In conclusion, this study demonstrated that exenatide QWS-AI was superior to sitagliptin in reducing HbA1c and in achieving the HbA1c target of <7.0%. While statistical superiority vs sitagliptin was

not demonstrated for some secondary endpoints, both treatments reduced FPG and body weight, with few SAEs in any group. Gastrointestinal events were more common with exenatide QWS-AI than with sitagliptin. Overall evidence suggests that an injectable therapy administered QW may be an alternative to daily oral therapy for patients with T2D.

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Conflict of interest

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Author contributions

All authors were involved in the writing, discussion and review of this manuscript. K. M. G. was the lead investigator, provided data acquisition and contributed to interpretation of the data. M. L. V. contributed to interpretation of the data. N. I. contributed to conception and design of the study, data acquisition and analysis and interpretation of the data. E. H. contributed to analysis and interpretation of the data. P. Ö. contributed to conception and design of the study and to analysis and interpretation of the data. All authors contributed to drafting and critical revision of the manuscript, and all authors approved the final version.

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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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