

Onset of Glycemic and Weight Outcomes in Patients Initiating Exenatide Once Weekly: The Relationship of Exenatide Exposure with Efficacy over the First 24 Weeks of Treatment

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ABSTRACT

Introduction: Exenatide is gradually released from exenatide once weekly (QW) microspheres, and at steady state, consistently controls glycated hemoglobin (HbA1c) in patients with type 2 diabetes (T2D). This post hoc analysis examined the timing to onset of clinical responses and their correlations with exenatide concentrations after initiation of exenatide QW in patients with T2D.

Methods: Trial data were retrospectively analyzed to explore the early clinical responses to exenatide QW, including the relationship of exenatide concentration with its effects on efficacy [fasting plasma glucose (FPG), HbA1c, and body weight] and tolerability (nausea and vomiting). Exenatide QW efficacy and

tolerability data were from DURATION-5, a 24-week, randomized, comparator-controlled trial [intent-to-treat (ITT) population]. Exenatide concentrations were measured in a patient subset (pharmacokinetic population).

Results: In the ITT ($n = 129$)/pharmacokinetic ($n = 72$) populations, baseline FPG, HbA1c, and body weight were 173/173 mg/dL, 8.5%/8.4%, and 97/98 kg, respectively. Exenatide concentrations gradually increased until reaching steady state at week 8. By week 4, the FPG reduction (-32.4 mg/dL) was 94% of the week 24 reduction (-34.6 mg/dL). Reductions in HbA1c began by week 4 (-0.6%) and stabilized by week 14 (week 24: -1.6%). Weight reduction at week 4 was -0.7 kg and decreased further (week 24: -2.3 kg). Peak nausea (7.2%) and vomiting (2.4%) occurred at weeks 6–8, declining thereafter.

Conclusion: Clinically relevant responses to exenatide QW were evident by week 4, after exenatide concentration passed the therapeutic threshold but before steady state was achieved.
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INTRODUCTION

Type 2 diabetes (T2D) is a chronic disease necessitating long-term, individualized treatment. Challenges associated with some treatments include weight gain, risk of hypoglycemia, gastrointestinal side effects, and rapid loss of glycemic control [1–3]. Other factors considered by physicians and patients may include mode of administration, frequency of dosing, and initial timing of therapeutic response, particularly for patients with symptomatic hyperglycemia.

The glucagon-like peptide-1 receptor agonist (GLP-1RA) exenatide improves glycemic control and reduces weight, with a low risk of hypoglycemia when taken without concomitant sulfonylureas or insulin, but an increased risk of gastrointestinal events [4]. The once weekly (QW) formulation has demonstrated sustained glycemic control and is dosed infrequently [5], but the initial rate of therapeutic response has been questioned. Exenatide acts through multiple mechanisms of action, including stimulating insulin secretion in a glucose-dependent manner, suppressing glucagon secretion in a glucose-dependent manner, slowing gastric emptying, reducing food intake, and promoting satiety [4]. Dispersing exenatide in poly-(D,L-lactide-co-glycolide [PLG]) polymer microspheres—a biodegradable polymer—allows for the continuous release of exenatide with regular QW therapy [6]. Exenatide is primarily released through diffusion and erosion of the microspheres. With regular dosing, plasma concentrations of exenatide QW increase gradually to steady state in

approximately 6–8 weeks [7–10]; however, treatment response may begin earlier, when concentrations surpass the therapeutic threshold [9].

The clinical development program for exenatide QW consisted of six pivotal phase 3 studies: the Diabetes Therapy Utilization: Researching Changes in A1C, Weight and Other Factors through Intervention with Exenatide Once Weekly (DURATION) trials. Data from DURATION-5 were used in this post hoc analysis [11], in which exenatide concentrations and clinical responses were measured for up to 24 weeks.

This analysis examined the relationships between exenatide concentrations and clinical responses to inform physician and patient expectations of exenatide QW therapy for treatment of T2D.

METHODS

Details of the DURATION-5 (ClinicalTrials.gov identifier: NCT00877890) study design were previously published [11]. Briefly, patients with T2D aged ≥ 18 years who were treated for ≥ 2 months with diet and exercise alone or with a stable, maximally effective regimen of metformin, sulfonylurea, thiazolidinedione, or a combination of these medications and had a glycated hemoglobin (HbA1c) of 7.1–11.0%, fasting plasma glucose (FPG) < 280 mg/dL, and a body mass index of 25–45 kg/m² were included in the trial. Patients were randomized to receive exenatide QW 2.0 mg subcutaneously (SC) for 24 weeks ($n = 129$) or exenatide twice daily (BID) 5 μ g SC for 4 weeks followed by exenatide BID 10 μ g SC for 20 weeks ($n = 123$). Only patients treated with exenatide QW were included in this post hoc analysis. This article is based on a previously conducted study and does

not involve any new studies of human or animal subjects performed by any of the authors.

FPG, HbA1c, and body weight were measured at weeks 1 (body weight only), 4, 8, 14, 20, and 24 in the intent-to-treat (ITT) population consisting of all randomized patients who received ≥ 1 dose of study medication.

Exenatide concentration was determined by a validated immunoenzymetric assay [9] in a subset of patients in the ITT population, which was designated the pharmacokinetic (PK)-evaluable population, at baseline, at weeks 4, 8, 14, and 20 (prior to administration of the next dose of study medication), and at study termination (week 24).

Nausea and vomiting adverse events (AEs) were self-reported at all office visits and categorized according to the *Medical Dictionary for Regulatory Activities* (MedDRA) version 12.0 in the ITT population.

Statistical Analyses

Demographics and baseline characteristics were reported descriptively. Because exenatide concentrations were not normally distributed, exenatide concentration was calculated as the geometric mean \pm standard error (SE). FPG was reported in mg/dL [conversion factor to SI units (mmol/L) = 0.0555]. The least-squares (LS) mean \pm SE changes from baseline for FPG and HbA1c were calculated using an analysis of variance model based on a general linear model including factors for treatment group, HbA1c stratum ($< 9.0\%$ or $\geq 9.0\%$), and concomitant sulfonylurea use at screening. The LS mean \pm SE change from baseline in body weight was analyzed using a general linear model including factors for treatment group, baseline HbA1c stratum, concomitant sulfonylurea use

at screening, and baseline body weight. Missing post-baseline values up to week 24 were imputed using the last observation carried forward approach. The statistical analyses were performed using SAS version 9.2 (SAS Institute, Cary, NC, USA).

A subanalysis examined mean (\pm standard deviation) changes from baseline in FPG, HbA1c, and body weight among patients who had nausea AEs versus those without nausea (ITT population).

RESULTS

Baseline demographics and characteristics were generally well-matched between patients in the ITT ($n = 129$) and PK-evaluable ($n = 72$) populations, with small differences in age and race (Table 1). In the ITT population, 20 patients (15.5%) treated with exenatide QW withdrew during the study (withdrawal of consent, $n = 6$; AE, $n = 6$; lost to follow-up, $n = 5$; loss of glucose control, $n = 3$) [11].

Mean exenatide concentrations with exenatide QW treatment gradually increased until reaching steady state at approximately 8 weeks (PK-evaluable population; Fig. 1). In the ITT population, reductions in FPG were observed at 4 weeks, with further reductions at 8 weeks that plateaued thereafter. By week 4, when exenatide concentrations were 31% of the peak concentration, the FPG reduction (-32.4 ± 4.3 mg/dL) was equivalent to 94% of the week 24 reduction at steady state (-34.6 ± 4.9 mg/dL). A reduction in HbA1c of $-0.6\% \pm 0.1\%$ occurred at week 4, and change in HbA1c plateaued by week 14. At week 24, the reduction in HbA1c was $-1.6\% \pm 0.1\%$. Weight loss occurred at week 4 (-0.7 ± 0.2 kg), and weight continued to decrease with treatment (week 24: -2.3 ± 0.4 kg).

Table 1 Baseline demographics and characteristics

Characteristics	Exenatide QW	
	ITT population (<i>n</i> = 129)	PK-evaluable population (<i>n</i> = 72)
Male, <i>n</i> (%)	77 (59.7)	45 (62.5)
Age at consent, years	56 ± 11	59 ± 10
Race/ethnicity, <i>n</i> (%)		
White	81 (62.8)	50 (69.4)
Hispanic	37 (28.7)	14 (19.4)
Black	6 (4.7)	4 (5.6)
Asian	5 (3.9)	4 (5.6)
Weight, kg	97.0 ± 20.7	98.3 ± 22.1
BMI, kg/m ²	33.6 ± 5.5	33.7 ± 5.7
HbA1c, % ^a	8.5 ± 1.1	8.4 ± 1.1
FPG, mg/dL	173 ± 47	173 ± 50
Duration of diabetes, years	7 ± 5	8 ± 6

Data are mean ± standard deviation unless otherwise noted

BMI body mass index, *FPG* fasting plasma glucose, *HbA1c* glycated hemoglobin, *ITT* intent-to-treat, *PK* pharmacokinetic, *QW* once weekly

^a One patient had missing baseline HbA1c; ITT population, *n* = 128; PK-evaluable population, *n* = 71

Exenatide QW was generally well tolerated, with no discontinuations due to nausea or vomiting [11]. Reductions in FPG and HbA1c were similar among patients with and without nausea although weight loss was numerically greater in patients with nausea (difference of 0.7 kg; ITT population; Table 2). Nausea and vomiting decreased over the 24-week treatment period (Fig. 2). The incidence of nausea peaked at week 6 (7.2%) and that of vomiting at week 8 (2.4%), declining thereafter.

DISCUSSION

Physicians and patients may be interested to know when novel long-acting therapies, such as the GLP-1RA exenatide QW, become effective and when maximum efficacy is achieved. This

post hoc analysis demonstrated that glycemic control from exenatide QW begins before steady state concentrations are achieved, with near-maximal FPG reductions and clinically relevant HbA1c reductions within 4 weeks and near-maximal HbA1c reductions by 14 weeks.

In this study, measured plasma exenatide concentrations progressively increased to steady state at week 8. Similarly, reports on the PK and pharmacodynamics of exenatide QW among patients with T2D in the United States, China, and Japan showed exenatide concentrations reaching steady state after 6–8 weeks of weekly dosing [7–10].

Consistent with multiple mechanisms of action for exenatide, multiple relationships of exenatide exposure with clinical responses were demonstrated. FPG reduction was observed

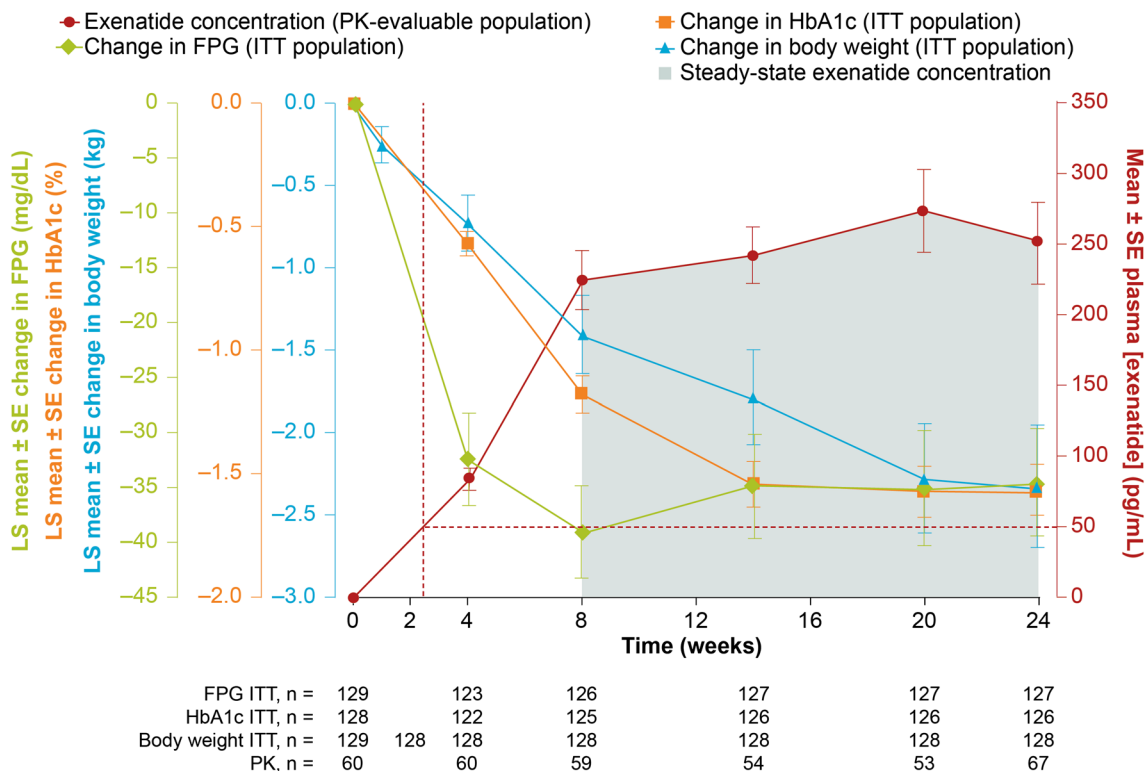


Fig. 1 Initial reductions in FPG, HbA1c, and body weight occurred before steady state exenatide concentrations were reached. Geometric mean ± SE exenatide concentrations (PK-evaluable population) and LS mean ± SE changes from baseline (ITT population) in FPG, HbA1c, and body

weight. The PK threshold for FPG lowering with exenatide QW (~50 pg/mL) is typically reached at ~2 weeks [9]. *FPG* fasting plasma glucose, *HbA1c* glycated hemoglobin, *ITT* intent-to-treat, *LS* least-squares, *PK* pharmacokinetic, *SE* standard error

Table 2 Changes from baseline in FPG, HbA1c, and body weight in patients treated with exenatide QW with or without nausea (intent-to-treat population)

Change in end point	Patients with nausea (n = 18) ^a	Patients without nausea (n = 111) ^b
FPG, mg/dL	-32.5 ± 44.2	-31.5 ± 50.6
HbA1c, % ^c	-1.3 ± 1.2	-1.4 ± 1.2
Body weight, kg	-3.2 ± 3.5	-2.5 ± 3.5

Data are mean ± standard deviation

FPG fasting plasma glucose, *HbA1c* glycated hemoglobin, *QW* once weekly

^a One patient had missing end point measures

^b Four patients had missing end point measures

^c Patients without nausea, baseline n = 110

most rapidly (at week 4—the earliest time point measured), as the PK threshold for FPG lowering (~50 pg/mL) [12] is typically reached at 2 weeks

[9]. A recent post hoc analysis of pooled data from 12 clinical trials reported significant reductions in FPG, HbA1c, body weight, and

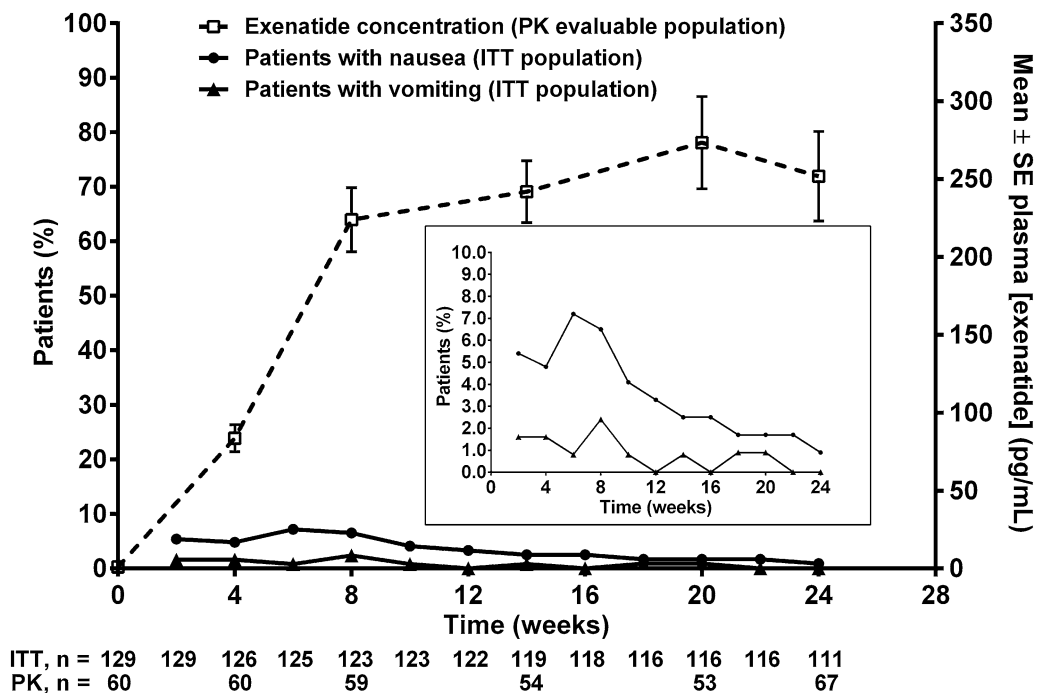


Fig. 2 Relationship of the incidences of nausea and vomiting (ITT population) with exenatide concentration (geometric mean \pm SE; PK-evaluable population). The

inset shows the incidences of nausea and vomiting on a scale from 0% to 10%. *ITT* intent-to-treat, *PK* pharmacokinetic, *SE* standard error

blood pressure as early as 2 weeks after initiating treatment with exenatide QW, further supporting an early onset of action [13]. In this study, the time course of HbA1c change, which is more gradual than FPG because it depends on red blood cell turnover, was near maximal 14 weeks after initiation of exenatide QW. Changes in weight also occurred more slowly than effects on FPG, as the physiology of weight loss is more gradual than that of FPG reductions.

It is important for physicians and patients to understand the time course of AEs associated with a long-acting medication. As shown in this study, the majority of gastrointestinal AEs with exenatide QW occurred early in therapy, after the efficacy threshold but before steady state was reached, and declined over time as tolerance developed. A gradual increase in

exenatide concentrations, as occurs with exenatide QW during microsphere dissolution, has been associated with improved gastrointestinal tolerability compared with rapid dose escalation [14]. Similarly, pooled analyses of randomized controlled trials found that gastrointestinal AEs occurred less frequently with exenatide QW (providing continuous exenatide exposure) compared with exenatide BID (providing intermittent exenatide exposure), and decreased over time [15, 16]. These analyses further support the notion that the gradual increase in exenatide concentration through the microspheres enhances gastrointestinal tolerability.

While some physicians and patients seek to avoid gastrointestinal AEs, others may believe that nausea indicates response to therapy. Our subanalysis results counter this belief, showing

that improvements in glyceemic control were similar in patients with or without nausea although weight loss may be slightly greater in patients with nausea.

Limitations of this study include the small number of patients and the post hoc nature of the analysis; in particular, there were a small number of patients with nausea in the subanalysis and it was not powered to analyze differences between patients with and without nausea. In addition, the time course of clinical responses and PK of exenatide QW were evaluated in different although well-matched, patient populations. This study also lacked glyceemic efficacy measures at earlier (1 or 2 week) time points because they were not indicated in the protocol.

CONCLUSIONS

Although exenatide-containing microspheres deliver exenatide via a gradual release mechanism, exenatide QW resulted in prompt treatment responses once the activity threshold was reached, which occurred weeks before steady state exenatide concentrations were attained. Near-maximal improvements in FPG and clinically relevant reductions in HbA1c (−0.6%) occurred by week 4, followed by weight loss. The occurrence of nausea and vomiting declined over time, with tolerance developing as exenatide reached steady state concentrations.

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Compliance with Ethics Guidelines. This article is based on a previously conducted study and does not involve any new studies of human or animal subjects performed by any of the authors.

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