Comparison of safety and tolerability with continuous (exenatide once weekly) or intermittent (exenatide twice daily) GLP-1 receptor agonism in patients with type 2 diabetes

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Aims: Exenatide is a glucagon-like peptide-1 receptor agonist shown to improve glycaemic control in patients with type 2 diabetes (T2DM). Intermittent exenatide exposure is achieved with the twice-daily formulation (ExBID), while the once-weekly formulation (ExQW) provides continuous exenatide exposure. This integrated, retrospective analysis compared safety and tolerability of ExQW vs. ExBID in patients with T2DM.

Methods: Data were pooled from two open-label, randomized, comparator-controlled, trials directly comparing ExQW (N = 277) to ExBID (N = 268). Between-group differences in adverse event (AE) and hypoglycaemia incidences were calculated. Incidence over time and duration of selected AEs (nausea, vomiting, and injection-site-related AEs) were also summarized.

Results: The most common AEs were nausea, diarrhoea, injection-site pruritus, and vomiting. Nausea and vomiting occurred less frequently with ExQW vs. ExBID, peaking at initiation (ExQW) or at initiation and dose escalation (ExBID), and decreasing over time. Few patients discontinued because of gastrointestinal-related AEs. Injection-site AEs were more common with ExQW but decreased over time in both groups. No major hypoglycaemia occurred; minor hypoglycaemia occurred with low incidence in patients not using concomitant sulphonylurea, with no difference between ExQW and ExBID. Serious AEs and discontinuations because of AEs were reported with similar frequency in both groups.

Conclusions: Both exenatide formulations were generally safe and well-tolerated, with ExQW associated with less nausea and vomiting but more injection-site AEs. Continuous vs. intermittent exposure did not impact the overall tolerability profile of exenatide, with no evidence of prolonged duration or worsened intensities of AEs with continuous exposure.

Keywords: adverse event, exenatide once weekly, exenatide twice daily, safety, tolerability

Introduction

Type 2 diabetes mellitus (T2DM) is a chronic disorder characterized by a dysfunction in glucose regulation leading to hyperglycaemia. The glucagon-like peptide-1 (GLP-1) receptor agonist class of drugs has been showed to improve glycaemic control by coordinating multiple mechanisms of action including induction of glucose-dependent insulin secretion, inhibition of glucagon secretion, enhancement of satiety, and slowing of gastric emptying [1–7]. Thus, GLP-1 receptor agonists act on several systems to modulate plasma glucose concentrations.

Exenatide is a subcutaneously injected, peptide GLP-1 receptor agonist that has been shown to improve glycaemic control, promote weight loss, and improve some cardiovascular risk markers in patients with T2DM [8,9]. The two formulations of exenatide, exenatide once weekly (ExQW) and exenatide twice daily (ExBID), both approved for the treatment of T2DM in the US and Europe, provide continuous or intermittent GLP-1 receptor activation, respectively. ExQW encapsulates the exenatide molecule of ExBID into poly-(D,L-lactide-co-glycolide) microspheres, allowing a gradual rise in exenatide plasma concentration as it is released via diffusion from the biodegradable microspheres [10]. With weekly dosing, this formulation reaches minimally effective therapeutic concentrations of exenatide within 2 weeks and steady state concentrations providing continuous exposure to exenatide by about 6–7 weeks [9,11,12]. In contrast, the ExBID formulation is administered as a bolus injection prior to the two largest meals of the day and has a systemic half-life of 2.4 h [13].

Two open-label, randomized, controlled, clinical studies directly compared the efficacy, safety and tolerability of the two formulations of exenatide in patients with T2DM over 24 or 30 weeks of treatment. ExQW was showed to be superior to ExBID in reducing haemoglobin A1c (HbA1c) over 24 or 30 weeks of treatment. ExQW was showed to be superior to ExBID in reducing haemoglobin A1c (HbA1c) over 24 or 30 weeks [11,14]. In these studies, least squares (LS) mean changes from baseline in HbA1c were −1.9% (ExQW) and −1.5% (ExBID) [11] and −1.6% (ExQW) and −0.9% (ExBID) [14], with significant LS mean treatment differences of 0.33 and 0.67%.
Body mass index of 25–45 kg/m^2, and stable body weight for 18 years of age and had a baseline HbA1c of 7.1-11.0%, a for 3 days prior to randomization [11]. Patients were at least study (all patients in DURATION-1 received 5 \( \mu \)g ExQW). Patients had a glucose value of <54 mg/dl prior to treatment. As hypoglycaemia is more frequently observed when exenatide is used in combination with SU, a subgroup analysis by concomitant SU usage was performed [11,13]. Patients were considered to have concomitant SU use if the patient used SU at any point during the 24- or 30-week controlled study period.

A patient was defined as having treatment-emergent antibodies to exenatide if antibodies were present after the first injection of randomized study medication following absence of antibodies or a missing antibody measurement at baseline, or if the titre increased by at least three dilutions from a detectable measurement at baseline. The incidence of AEs by antibody status was compared in each treatment group.

**Results**

**Patient Demographics and Disposition**

The ITT population included 545 patients (ExQW N = 277, ExBID N = 268; figure 1). At baseline, patients were either drug-naïve (17%), or treated with one (45%) or a combination (38%) of oral antidiabetes medications (metformin, SU and TZD). Patient demographics were balanced between groups (figure 1), including similar HbA1c (8.3%), fasting plasma glucose (163–168 mg/dl), body mass index (34 kg/m^2), body weight (98–99 kg), background antidiabetes medications, and duration of diabetes (7 years). Similar numbers of patients withdrew from both groups (14 and 16% with ExQW and ExBID respectively; figure 1). Withdrawals due to AEs occurred in 5% of patients in each group, with <1% of patients withdrawing because of nausea or vomiting (Table 1).
Intent-to-Treat Population N = 545

**Figure 1.** Patient disposition and demographics. Patients were pooled from two open-label, randomized, controlled studies. Patient demographic data are mean ± SD. *Subjects receiving a combination of 2 or more oral antidiabetes medications were included in more than one category. BMI, body mass index; FPG, fasting plasma glucose; MET, metformin; OAD, oral antidiabetes drug; SU, sulphonylurea; TZD, thiazolidinedione.

**Treatment-emergent and SAEs**

Overall incidence of all TEAEs was similar in patients treated with ExQW (79.4%) and ExBID (76.1%). The majority of AEs were mild or moderate in intensity in both groups.

There was no identifiable pattern of SAEs in either population, with no significant differences observed across System Organ Class AE designations, including cardiac, gastrointestinal (GI), and renal disorders. SAEs occurred with similar incidence with ExQW [4.0% (n = 11)] and ExBID [3.7% (n = 10)], with a non-significant between-group difference of 0.2 (−3.0, 3.5). Two ExQW-treated patients (pancreatitis with no acute inflammatory abnormality which resolved in 3 days while still receiving study medication [14] and fatal myocardial infarction) and one ExBID-treated patient (fatal myocardial infarction) discontinued because of SAEs.

**Adverse Events of Interest**

**GI Adverse Events.** The majority of patients in both treatment groups did not experience nausea (79.1% ExQW and 65.3% ExBID) or vomiting (92.1% ExQW and 85.8% ExBID) during the 24- or 30-week study duration. While the overall frequency of GI disorders was not significantly different between ExQW and ExBID groups (−7% (−15, 1.4)), significantly fewer ExQW-treated patients experienced nausea or vomiting compared to ExBID (Table 2). The incidence of nausea and vomiting, as assessed over 2-week intervals, declined over time with continued ExQW or ExBID therapy (figure 2A). The highest incidence of nausea with ExQW (7.6%) occurred at initiation of therapy (within the first 2 weeks). With ExBID, most nausea events occurred during the first 6 weeks of treatment, peaking at initiation of therapy (12.7%) and again between 4 and 6 weeks (12.5%), consistent with the increased ExBID dose at week 4. With continued treatment beyond week 10, nausea occurred in <1% of patients after week 10 for both groups (figure 2A).

As with nausea, the highest incidence of vomiting in patients treated with ExBID occurred during treatment initiation and dosage increase and declined over time with continued therapy.
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Table 1. TEAEs leading to withdrawal.

| Preferred term                     | Treatment       | Incidence (ExQW) | Incidence (ExBID) | Difference in incidence (ExQW – ExBID) (95% CI) |
|-----------------------------------|-----------------|------------------|-------------------|-----------------------------------------------|
| All AELW                          | ExQW (N = 277)  | 15 (5.4)         | 13 (4.9)          | 0.6 (−3.1, 4.3)                               |
|                                   | ExBID (N = 268) |                  |                   |                                               |
| Myocardial infarction             |                 | 1 (0.4)          | 1 (0.4)           | −0.0 (−1.0, 1.0)                              |
| Abdominal pain                    |                 | 0                | 1 (0.4)           | −0.4 (−1.1, 0.4)                              |
| Diarrhoea                         |                 | 0                | 1 (0.4)           | −0.4 (−1.1, 0.4)                              |
| Impaired gastric emptying         |                 | 1 (0.4)          | 0                 | 0.4 (−0.3, 1.1)                               |
| Nausea                            |                 | 1 (0.4)          | 4 (1.5)           | −1.1 (−2.7, 0.5)                              |
| Pancreatitis                      |                 | 1 (0.4)          | 0                 | 0.4 (−0.3, 1.1)                               |
| Regurgitation                     |                 | 0                | 1 (0.4)           | −0.4 (−1.1, 0.4)                              |
| Vomiting                          |                 | 1 (0.4)          | 4 (1.5)           | −1.1 (−2.7, 0.5)                              |
| Injection-site nodule             |                 | 1 (0.4)          | 0                 | 0.4 (−0.3, 1.1)                               |
| Injection-site pruritus           |                 | 1 (0.4)          | 0                 | 0.4 (−0.3, 1.1)                               |
| Malaise                           |                 | 1 (0.4)          | 0                 | 0.4 (−0.3, 1.1)                               |
| Posttraumatic pain                |                 | 1 (0.4)          | 0                 | 0.4 (−0.3, 1.1)                               |
| Alanine aminotransferase increased|                 | 1 (0.4)          | 0                 | 0.4 (−0.3, 1.1)                               |
| Blood creatinine increased        |                 | 1 (0.4)          | 0                 | 0.4 (−0.3, 1.1)                               |
| Blood potassium increased         |                 | 1 (0.4)          | 0                 | 0.4 (−0.3, 1.1)                               |
| Lipase increased                  |                 | 1 (0.4)          | 0                 | 0.4 (−0.3, 1.1)                               |
| Weight decreased                  |                 | 1 (0.4)          | 0                 | 0.4 (−0.3, 1.1)                               |
| Anorexia                          |                 | 0                | 1 (0.4)           | −0.4 (−1.1, 0.4)                              |
| Parasthesia                       |                 | 1 (0.4)          | 0                 | 0.4 (−0.3, 1.1)                               |

AELW, treatment-emergent adverse event leading to withdrawal; CI, confidence interval; ExQW, exenatide once-weekly; ExBID, exenatide twice-daily; TEAEs, treatment-emergent adverse events.

Table 2. Frequent (≥5%) TEAEs.*

| Preferred term                     | Treatment       | Incidence (ExQW) | Incidence (ExBID) | Difference in incidence (ExQW – ExBID) (95% CI) |
|-----------------------------------|-----------------|------------------|-------------------|-----------------------------------------------|
|                                   | ExQW (N = 277)  |                  |                   |                                               |
|                                   | ExBID (N = 268) |                  |                   |                                               |
| Nausea                            |                 | 58 (20.9)        | 93 (34.7)         | −13.8 (−21.2, −6.3)                           |
| Diarrhoea                         |                 | 34 (12.3)        | 24 (9.0)          | 3.3 (−1.8, 8.5)                               |
| Injection-site pruritus           |                 | 33 (11.9)        | 3 (1.1)           | 10.8 (6.8, 14.8)                              |
| Vomiting                          |                 | 22 (7.9)         | 38 (14.2)         | −6.2 (−11, −1.0)                              |
| Upper respiratory tract infection |                 | 21 (7.6)         | 30 (11.2)         | −3.6 (−8.5, 1.3)                              |
| Urinary tract infection           |                 | 19 (6.9)         | 16 (6.0)          | 0.9 (−3.2, 5.0)                               |
| Injection-site erythema           |                 | 18 (6.5)         | 3 (1.1)           | 5.4 (2.2, 8.5)                                |
| Constipation                      |                 | 17 (6.1)         | 14 (5.2)          | 0.9 (−3.0, 4.8)                               |
| Headache                          |                 | 15 (5.4)         | 17 (6.3)          | −0.9 (−4.9, 3.0)                              |
| Gastroenteritis viral             |                 | 15 (5.4)         | 8 (3.0)           | 1.1 (−0.5, 2.7)                               |
| Dyspepsia                         |                 | 15 (5.4)         | 6 (2.2)           | 3.2 (−0.6, 6.4)                               |
| Nasopharyngitis                   |                 | 15 (5.4)         | 9 (3.4)           | 2.1 (−1.4, 5.5)                               |
| Injection-site hematoma           |                 | 13 (4.7)         | 22 (8.2)          | −3.5 (−7.6, 0.6)                              |
| Dizziness                         |                 | 8 (2.9)          | 17 (6.3)          | −3.5 (−7.0, 0.1)                              |

ExQW, exenatide once-weekly; ExBID, exenatide twice-daily; TEAEs, treatment-emergent adverse events.

*All TEAEs with a frequency of ≥5% in either group are listed. (Table includes events assessed as related and unrelated to study drug.)

(figure 2B). Beyond 14 weeks, the occurrence of vomiting in patients treated with ExBID decreased to <1%. ExQW-treated patients exhibited an incidence of vomiting between 1.8 and 2.7% starting at initiation and continuing through week 8 which decreased to 0–1.6% of patients beyond week 8.

Most instances of nausea and vomiting in both groups were mild in intensity and no patients treated with ExQW experienced severe nausea or vomiting. With ExBID, four patients experienced severe nausea and two patients experienced severe vomiting. The duration of nausea was shorter on average with ExQW vs. ExBID. The majority of nausea events, including events of intermittent nausea, were ≤2 days in duration with ExQW and 33% of events resolved in ≤2 days with ExBID. The majority of vomiting events resolved within one day in both ExQW- and ExBID-treated patients.

Injection-site-related Adverse Events. The incidence of all injection-site-related adverse events was 22.0% in patients treated with ExQW and 12.7% in patients treated with ExBID with a between-group difference of 9.3% (95% CI: 3.0, 15.6). Two patients discontinued ExQW due to injection-site-related AEs (both mild and resolved) while no injection-site-related withdrawals occurred with ExBID.

The majority of ExQW (84.5%) and ExBID (97.8%) patients did not experience any of the four common injection-site-related adverse events (injection-site erythema, pruritus, urticaria, or rash) over the course of the studies. The most commonly reported injection-site-related adverse events were injection-site erythema [6.5% ExQW vs. 1.1% ExBID; between-group difference of 5.4% (2.2, 8.5)] and injection-site pruritus [11.9% vs. 1.1%; between-group difference of 10.8% (6.8, 14.8)]. Other injection-site-related adverse events included injection-site urticaria (0.7% vs. 0.4%) and injection-site rash (1.4% vs. 0.4%), both having no significant between-group differences in incidence rate. The incidence of these injection-site-related events decreased over time in both groups with no events reported beyond 14 weeks in either group (figure 2C). With ExQW, the majority of injection-site-related events resolved within 14 days. With ExBID, the majority (6 of 8) of injection-site-related events required greater than 14 days to resolve. Most events in either group were mild in intensity, with only a single patient treated with ExQW experiencing a severe injection-site adverse event. This patient had an AE of indurated macular rash with severe itching that was deemed non-serious and resolved without patient withdrawal from the study. No patients treated with ExBID reported severe injection-site AEs. Injection-site nodules, primarily transient and mild, were the only other AE reported significantly more frequently with ExQW than ExBID (2.2% vs. 0.0% for a between-group difference of 2.2% (0.5, 3.9)).

It was noted that although there was no relationship between antibody status and overall incidence of AEs within a treatment group, antibody-positive ExQW-treated patients had a higher incidence of injection-site-related adverse events including injection-site erythema (8.5% vs. 1.4%) and injection-site pruritus (15% vs. 4.2%) compared to antibody-negative patients.
ExQW-treated patients. ExBID-treated patients showed no difference in incidence of adverse events by antibody status. Anaphylactic or other systemic immune-related reactions were not observed with either treatment.

**Hypoglycaemia.** No major hypoglycaemia events were reported with either ExBID or ExQW treatments. Patients in either group using concomitant SU had a higher incidence of minor hypoglycaemia events than patients not using a concomitant SU. The incidence of minor hypoglycaemia was similarly low in patients not using concomitant SU in ExQW and ExBID groups (Table 3). There was no apparent pattern in the incidence of hypoglycaemia events over time in either group. There was, however, a trend for less new hypoglycaemia events over time, particularly in patients using concomitant SU.

**Discussion**

Efficacy and safety/tolerability profiles for T2DM treatment options are considered in selecting the therapy best-suited to a patient and their particular comorbidities and tolerances [16]. Thus, understanding differences in the safety and tolerability profiles of different agents is a key aspect of making therapeutic decisions.

While ExQW and ExBID contain the same active therapeutic compound, they have different pharmacokinetic profiles, allowing one to remain in the systemic circulation in a continuous manner (ExQW) and the other to provide intermittent exposure over a 24-h period (ExBID). Integrated analyses of the safety and tolerability of intermittent exenatide exposure with ExBID have been previously described [17–19].
ExQW, exenatide once-weekly; ExBID, exenatide twice-daily; SU, sulphonylurea.
*Difference calculated for minor hypoglycaemia only.

In this pooled analysis of two randomized, head-to-head, controlled clinical trials over 24 or 30 weeks of treatment, the safety and tolerability profiles of ExQW and ExBID were directly compared. Both ExQW and ExBID had an equally low incidence of SAEs (4%) and AEs that led to withdrawal (5%). The safety and tolerability profile of ExQW was largely consistent with that of the immediate-release ExBID formulation; there were no indications that continuous exposure to exenatide resulted in an increase in the types, intensity, and duration of AEs observed in the patient [9].

The results of this analysis showed that the primary differences in tolerability between the two therapies were in GI-related and injection-site related AEs. Mild-to-moderate GI-related AEs were the most common AE, with nausea reported most frequently in both groups [11,14]. However, GI tolerability was improved with ExQW vs. ExBID; the incidence of nausea and vomiting was lower with ExQW than ExBID and study withdrawal because nausea occurred less frequently with ExQW than ExBID. Similar to findings in other studies of exenatide or other GLP-1 receptor agonists, the incidence of nausea and vomiting declined over time in both groups, with few reports of GI-related events with longer-term treatment [8,14,20–22]. There was no prolongation in the duration of nausea or vomiting events with ExQW, nor worsened intensity despite the continuous presence of exenatide.

Exenatide-associated nausea and vomiting is thought to be GLP-1-dependent, resulting from slowed gastric emptying, appetite suppression and/or stimulation of neural GLP-1 receptors [23]. While most cases of exenatide-related nausea and vomiting have been reported as mild/moderate in intensity, further mitigation by use of anti-emetics, increased fluid intake, slower eating or smaller meal size has been suggested [23,24]; however, robust data supporting these options is not available. Gradual dose escalation of ExBID has been shown to reduce the proportion of patients experiencing exenatide-related nausea and vomiting [25]. The gradual escalation of exenatide concentrations imposed by the release properties of ExQW may underlie the improved GI tolerability with ExQW compared to ExBID. It is of note that nausea and vomiting are generally not associated with higher concentrations of exenatide. Higher circulating exenatide concentrations, as measured in some individuals administered 2 mg ExQW, did not appear to affect tolerability (Amylin Pharmaceuticals, Inc., data on file). This observation was further supported in the current analysis by the evaluation of GI events over time, in which the highest incidence of nausea and vomiting occurred at initiation, when ExQW levels were at their lowest. A plateau in the incidence of nausea and vomiting was observed as exenatide concentrations continued to increase during the approach to steady state. Thus the decrease in GI events over time, despite the presence of high concentrations of exenatide at steady state, suggests an acclimation to the GI effects of exenatide over time.

Injection-site related AEs occurred more frequently with ExQW compared to ExBID. However, these events were rarely treatment-limiting and few patients (<1%) discontinued as a result of injection-site events. In general, injection-site events were mild and transient, and their frequency diminished over time.

Injection-site nodules were also observed as low-grade foreign body-type reactions occurring in response to the poly-(d,1-lactide-co-glycolide) microspheres that encapsulate exenatide in the ExQW formulation [10,26]. As with other injection-site events, nodules rarely lead to withdrawal and were typically mild and transient in nature.

Consistent with the glucose-dependent mechanism of action of exenatide [27], the overall incidence of hypoglycaemia was low with both ExQW and ExBID treatment and no major hypoglycaemia events occurred. The incidence of minor hypoglycaemia was similar for both groups; however, incidence of minor hypoglycaemia was increased in patients using concomitant SU therapy compared to patients not using SU.

A limitation of this analysis is that it did not include sufficient patient numbers to detect extremely rare AEs and the duration of the trials may not have been long enough to observe AEs that may occur only with extended use of the study drug. Other limitations of this analysis include the open-label nature of the studies and the retrospective analysis of the data.

Overall, continuous (ExQW) vs. intermittent (ExBID) exenatide exposure did not impact the general safety profile of exenatide. This pooled analysis has showed that both exenatide therapies were well-tolerated and resulted in few withdrawals because of AEs. Notably, sustained exenatide concentrations achieved with ExQW resulted in improved GI tolerability and were not associated with a general prolongation or worsened intensity of common AEs.

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Conflict of Interest

T. R., T. M., L. M., R. P., J. H., C. S., and L. P. participated in the design of the analysis. J. H. performed the statistical analysis. All authors were involved in the interpretation of the analysis. All authors were involved in drafting the manuscript or revising it critically for important intellectual content. All authors approved the final manuscript.

References

1. Egan JM, Cloquet AR, Elahi D. The insulinotropic effect of acute exendin-4 administered to humans: comparison of nondiabetic state to type 2 diabetes. J Clin Endocrinol Metab 2002; 87: 1282–1290.

2. Kolterman OG, Buse JB, Fineman MS et al. Synthetic exendin-4 (exenatide) significantly reduces postprandial and fasting plasma glucose in subjects with type 2 diabetes. J Clin Endocrinol Metab 2003; 88: 3082–3089.

3. Kolterman OG, Kim DD, Shen L et al. Pharmacokinetics, pharmacodynamics, and safety of exenatide in patients with type 2 diabetes mellitus. Am J Health Syst Pharm 2005; 62: 173–181.

4. Cevera A, Wajcberg E, Sriwijitkamol A et al. Mechanism of action of exenatide to reduce postprandial hyperglycemia in type 2 diabetes. Am J Physiol Endocrinol Metab 2001; 281: E155–E161.

5. DeFronzo RA, Okerson T, Viswanathan P, Guan X, Holcombe JH, MacConell L. Effects of exenatide versus sitagliptin on postprandial glucose, insulin and glucagon secretion, gastric emptying, and caloric intake: a randomized, cross-over study. Curr Med Res Opin 2008; 24: 2943–2952.

6. Edwards CM, Stanley SA, Davis R et al. Exendin-4 reduces fasting and postprandial glucose and decreases energy intake in healthy volunteers. Am J Physiol Endocrinol Metab 2001; 281: E155–E161.

7. Drucker DJ, Nauck MA. The incretin system: glucagon-like peptide-1 insulin secretagogue action in pancreatic β-cells. Prog Biophys Mol Biol 2011; 107: 236–247.

8. Klonoff DC, Buse JB, Nielsen LL et al. Exenatide effects on diabetes, obesity, cardiovascular risk factors and hepatic biomarkers in patients with type 2 diabetes treated for at least 3 years. Curr Med Res Opin 2008; 24: 275–286.

9. Aroda VR, DeYoung MB. Clinical implications of exenatide as a twice-daily or once-weekly therapy for type 2 diabetes. Postgrad Med 2011; 123: 228–238.

10. DeYoung MB, MacConell L, Sarin V, Troutmann M, Herbert P. Encapsulation of exenatide in poly-(ε-caprolactone) microspheres produced an investigational long-acting once-weekly formulation for type 2 diabetes. Diabetes Technol Ther 2011; 13: 1145–1154.

11. Drucker DJ, Buse JB, Taylor K et al. Exenatide once weekly versus twice daily for the treatment of type 2 diabetes: a randomised, open-label, non-inferiority study. Lancet 2008; 372: 1240–1250.

12. Fineman M, Flanagan S, Taylor K et al. Pharmacokinetics and pharmacodynamics of exenatide extended-release after single and multiple dosing. Clin Pharmacokinet 2010: 1–10.

13. Amylin Pharmaceuticals Inc. BYETTA® Exenatide Injection [prescribing information]. San Diego, CA: Amylin Pharmaceuticals, Inc., 2011.

14. Blevins TJ, Pullman J, Malloy J et al. DURATION-5: exenatide once weekly resulted in greater improvements in glycemic control compared with exenatide twice daily in patients with type 2 diabetes. J Clin Endocrinol Metab 2011; 96: 1301–1310.

15. World Medical Association. Declaration of Helsinki – ethical principles for medical research involving human subjects. Seoul, South Korea, 2008. Available from URL: http://www.wma.net/en/30publications/10policies/b3/index.html.

16. Bergenstal RM, Bailey CJ, Kendall DM. Type 2 diabetes: assessing the relative risks and benefits of glucose-lowering medications. Am J Med. 2010; 123: 374.e9–374.e18.

17. Ratner R, Han J, Nicewarner D, Yushmanova I, Hoogwerf BJ, Shen L. Cardiovascular safety of exenatide BID: an integrated analysis from controlled clinical trials in participants with type 2 diabetes. Cardiovasc Diabetol 2011; 10: 22.

18. Soll-Jones D. The safety and tolerability of GLP-1 receptor agonists in the treatment of type-2 diabetes. Int J Clin Pract 2010; 64: 1402–1414.

19. Stephens JW, Bain SC. Safety and adverse effects associated with GLP-1 analogues. Expert Opin Drug Saf 2007; 6: 417–422.

20. Bunck MC, Diamant M, Cornér A et al. One-year treatment with exenatide improves β-cell function, compared to insulin glargine, in metformin treated type 2 diabetes patients: a randomized, controlled trial. Diabetes Care 2009; 32: 762–768.

21. Buse JB, Drucker DJ, Taylor KL et al. DURATION-1: exenatide once weekly produces sustained glycemic control and weight loss over 52 weeks. Diabetes Care 2010; 33: 1255–1261.

22. Raskin P, Mora PF. Glycaemic control with liraglutide: the phase 3 trial programme. Int J Clin Pract Suppl 2010; 64: 21–27.

23. Ellero C, Han J, Bhavsar S et al. Prophylactic use of anti-emetic medications reduced nausea and vomiting associated with exenatide treatment: a retrospective analysis of an open-label, parallel-group, single-dose study in healthy subjects. Diabet Med 2010; 27: 1168–1173.

24. Freeman JS. Optimizing outcomes for GLP-1 agonists. J Am Osteopath Assoc 2011; 111: e515–e520.

25. Fineman MS, Shen LZ, Taylor K, Kim DD, Baron AD. Effectiveness of progressive dose-escalation of exenatide (exendin-4) in reducing dose-limiting side effects in subjects with type 2 diabetes. Diabetes Metab Res Rev 2004; 20: 411–417.

26. Anderson JM, Shive MS. Biodegradation and biocompatibility of PLA and PLGA microspheres. Adv Drug Deliv Rev 1997; 28: 5–24.

27. Leech CA, Dzhura I, Chepurny OG et al. Molecular physiology of glucagon-like peptide-1 insulin secretagogue action in pancreatic β cells. Prog Biophys Mol Biol 2011; 107: 236–247.