


BRIEF REPORT

Variability in and predictors of glycaemic responses after 24 weeks of treatment with exenatide twice daily and exenatide once weekly

Jonathan E. Shaw MD¹  | Baptist Gallwitz MD² | Jenny Han MS³ | Elise Hardy MD⁴ | Guntram Schernthaner MD⁵

¹Baker Heart and Diabetes Institute, Melbourne, Australia

²Eberhard Karls Universität Tübingen, Tübingen, Germany

³Pharmapace, Inc., San Diego, California

⁴AstraZeneca, Gaithersburg, Maryland

⁵Krankenanstalt Rudolfstiftung, Vienna, Austria

Correspondence

Professor Jonathan E. Shaw MD, Baker Heart and Diabetes Institute, 99 Commercial Road, Melbourne, Victoria 3004, Australia.
Email: jonathan.shaw@baker.edu.au

Funding information

This analysis was supported by AstraZeneca. Mollie Marko PhD, of inScience Communications, Springer Healthcare (New York, NY), provided medical writing support funded by AstraZeneca

The range of glycosylated haemoglobin (HbA1c) responses and characteristics associated with above-average response to exenatide twice daily and once weekly were examined. Data were pooled from 8 exenatide-twice-daily and 5 exenatide-once-weekly studies. A baseline HbA1c-corrected measure of change in HbA1c after 24 weeks identified high, average and low responses. Multiple linear regression and multivariate generalized estimating equation models identified factors associated with high response. Among 2355 participants (exenatide twice daily, n = 1414; exenatide once weekly, n = 941), baseline HbA1c correlated with change in HbA1c ($P < .0001$). Across baseline HbA1c levels, the 25th to 75th percentile of HbA1c change ranged from -0.3% to -3.2% with exenatide twice daily and from -0.5% to -3.6% with exenatide once weekly. Asian ethnicity and older age were significantly associated with high response to exenatide twice daily; no factors were significantly associated with response to exenatide once weekly. These data provide clinically useful information for estimating the likelihood that, depending on baseline HbA1c, an individual can achieve HbA1c goals. The association between Asian ethnicity, age and high response to exenatide twice daily may relate to the specific effects of exenatide twice daily on postprandial glucose.

KEYWORDS

exenatide once weekly, exenatide twice daily, glucagon-like peptide-1 receptor agonist, predictors

1 | INTRODUCTION

Personalization of treatment is a central tenet of care for type 2 diabetes (T2D),¹ yet little information is available about which patients are more likely to respond to a given drug. Furthermore, responses to drugs are typically described as mean changes in glycosylated haemoglobin (HbA1c) without details on the range of changes for individuals, which would assist clinicians in determining the likelihood a specific drug will lower HbA1c enough to achieve target.

Exenatide is a glucagon-like peptide-1 (GLP-1) receptor agonist, available in twice-daily and once-weekly formulations, that improves glycaemic control.^{2,3} Median peak plasma concentrations are

observed in 2.1 hours with exenatide twice daily, whereas exenatide once weekly peaks in the first few hours, at week 2 and weeks 6 to 7, as a result of gradual release of exenatide from poly (D,L-lactide-coglycolide) microspheres.⁴ In head-to-head studies, exenatide once weekly led to greater improvements in HbA1c and fasting plasma glucose levels, whereas exenatide twice daily led to greater improvement in 2-hour postprandial glucose (PPG).⁵⁻⁷

Most studies of T2D show significant between-participant variability in response to glucose-lowering drugs.^{5,6} Baseline HbA1c is an important contributor to observed variability; patients with higher baseline HbA1c exhibit greater overall change in HbA1c,⁸ however, significant variability exists beyond this relationship, suggesting that

other characteristics also contribute to response.^{9,10} Identifying such characteristics would be of great clinical utility.

The aim of the present analysis was to (1) describe the distribution of HbA1c responses to exenatide twice daily and exenatide once weekly after 24 weeks of therapy and (2) identify baseline characteristics associated with above-average glycaemic response to exenatide twice daily or once weekly after adjustment for baseline HbA1c.

2 | METHODS

Individual participant data were pooled from separate randomized controlled exenatide studies of 24 weeks to 48 months (Table S1 in File S1). The 24-week completer population of each study and glycaemic response at week 24 was used in the analyses. Included participants received exenatide twice daily or exenatide once weekly for at least 168 days and had baseline self-monitored blood glucose (SMBG) measurements.

The spread of HbA1c reductions was assessed via plots of distribution of HbA1c change. To identify factors other than baseline HbA1c that were related to change in HbA1c, the analysis was corrected for baseline HbA1c. The linear relationship between baseline HbA1c and change in HbA1c was determined from all participant data for each therapy. Participants were then divided into tertiles based on residuals to the regression line: for a given baseline HbA1c, tertile 1 included participants with the greatest HbA1c reductions ('high responders'); tertile 2 included average reductions ('average responders'); and tertile 3 included the smallest reductions ('low responders').

Variables assessed were based on availability of the information in routine practice and potential relevance (Table S2 in File S1). Correlations between each variable and change in HbA1c after 24 weeks of treatment were examined using univariate regression. Variables with $r \sim 0.1$ and $P < .05$ were considered to be potentially associated with treatment. Because of collinearity, mean daily blood glucose was excluded from exenatide twice daily assessments in favour of pre- and postmeal blood glucose (believed to be more relevant to exenatide twice daily's time course of action). For longer-acting exenatide once weekly, mealtime glucose was excluded and mean daily blood glucose included.

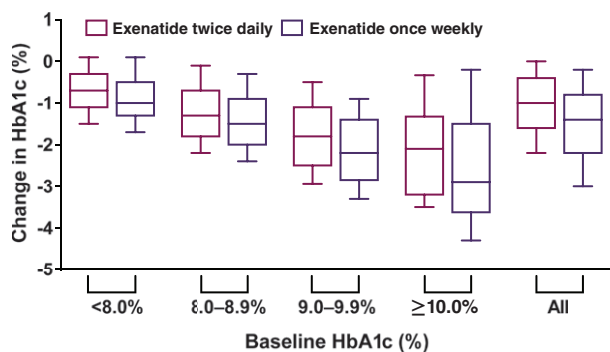


FIGURE 1 Box and whiskers plot of the change in HbA1c for a given baseline HbA1c. Midline represents the 50th percentile, the box represents the 25th and 75th percentiles, and whiskers represent the 10th and 90th percentiles

Baseline characteristics identified from univariate regression analyses were then included in stepwise multivariate linear regression models. Variables with a significance level $P < .15$ were subsequently modelled via multivariate generalized estimating equation (GEE) models to estimate the odds of being in tertile 1. Significantly increased odds were defined as $P < .05$.

3 | RESULTS

Data were pooled from 8 studies of exenatide twice daily and from 5 studies of exenatide once weekly (Table S1 in File S1) with 1640 and 1092 participants in the exenatide arms, respectively. Of those, 1414 and 941 participants, respectively, with all baseline data were included in the analysis.

There was a larger mean HbA1c reduction for exenatide once weekly than exenatide twice daily (Figure S1A in File S1), potentially attributable in part to higher mean baseline HbA1c in the exenatide-once-weekly vs exenatide-twice-daily groups (8.50% vs 7.98%). For both formulations, baseline HbA1c was significantly correlated with change in HbA1c ($P < .0001$), with extensive variability around the mean response (Figure S1B and S1C in File S1). With increasing baseline HbA1c, the 25th percentile of HbA1c change ranged from -0.3% to -1.4% with exenatide twice daily and -0.5% to -1.5% with exenatide once weekly (Figure 1). The 75th percentile of HbA1c reduction ranged from -1.1% to -3.2% with exenatide twice daily and -1.3% to -3.6% with exenatide once weekly.

Baseline characteristics (Tables S3 and S4 in File S1) were generally similar across responder tertiles. For exenatide twice daily, participants in tertile 1 were older and more often Asian than participants in tertile 3 ($P < .05$ for both). For exenatide once weekly, there were more Asian participants in tertile 3 than in tertile 1 ($P < .05$). For both formulations, baseline HbA1c was lowest in tertile 2 ($P < .05$). There were small differences among SMBG measurements.

3.1 | Stepwise multivariate linear regression analysis and GEE analysis

For exenatide twice daily, greater baseline pre-breakfast blood glucose, baseline PPG excursion for breakfast, age and Asian ethnicity were all ($P \leq .0001$) associated with greater HbA1c reduction after 24 weeks. For exenatide once weekly, greater baseline mean daily blood glucose and baseline fasting blood glucose were both ($P < .05$) associated with a greater HbA1c reduction. Using factors identified by multivariate linear regression models, GEE models were run to determine the odds of being in tertile 1 (Table 1). For exenatide twice daily, the odds of being in tertile 1 were 2.1 times greater for Asian than non-Asian participants ($P < .0001$), and increased by 12.4% for every 5-year increase in age ($P < .0001$). The odds of being in tertile 1 increased slightly ($+2.2\%$; $P = .06$) for every 0.56-mmol/L increase in baseline PPG excursion for breakfast and decreased slightly (-2.4% ; $P = .07$) for every 0.56-mmol/L increase in baseline fasting blood glucose.

TABLE 1 Baseline characteristics associated with being in the high-responder tertile (tertile 1) to exenatide twice daily and exenatide once weekly

Baseline characteristic	Estimated odds ratio	95% confidence intervals for estimated odds ratio		P
Exenatide twice daily				
Fasting blood glucose (per 0.56-mmol/L increase)	0.98	0.95	1.00	.07
PPG excursion for breakfast (per 0.56-mmol/L increase)	1.02	1.00	1.05	.06
Ethnicity (Asian vs non-Asian)	2.11	1.51	2.95	<.0001
Age (per 5-years older)	1.12	1.07	1.18	<.0001
Exenatide once weekly				
Fasting blood glucose (per 0.56-mmol/L increase)	1.00	0.96	1.04	.96
Mean daily blood glucose (per 0.56-mmol/L increase)	0.98	0.95	1.02	.37

For glucose measurements, to convert mmol/L to mg/dL multiply by 18.

For exenatide once weekly, the GEE analysis found no baseline measures that were significantly associated with being in tertile 1 (Table 1).

4 | DISCUSSION

The aim of the present retrospective analysis was to demonstrate the range and distribution of HbA1c responses to exenatide and identify characteristics associated with optimum glycaemic response. First, this analysis demonstrated the wide range of HbA1c-lowering responses with both exenatide formulations, indicating that the mean reduction is of only modest value in assessing likely responses. Second, GEE analysis found that Asian ethnicity (predominantly Japanese in these studies) and increasing age were the only predictors of HbA1c reduction for exenatide twice daily. No independent predictors of response to exenatide once weekly were identified.

There are numerous reports of mean HbA1c reductions associated with glucose-lowering drugs; however, without an appreciation of the spread of reductions, and how that distribution relates to baseline HbA1c, it is difficult to provide individualized advice to patients about likely treatment outcomes. To the best of our knowledge, this is the first study to report such data, and the information in Figure 1 can be applied directly to patient-care decisions about the likelihood that an individual patient will reach goal when one of these drugs is commenced.

Previous studies in the same database suggested Asian participants with T2D respond to exenatide twice daily better than white participants.¹¹ This analysis extends these findings by showing this effect is independent of baseline HbA1c. It has been proposed that loss of PPG control, either through physiological or dietary means, is the primary glucose defect experienced by Asians with T2D.¹² Exenatide twice daily, which has a stronger effect on PPG relative to longer-acting treatments,⁵ may therefore be more efficacious for Asian patients; however, our finding that PPG is, at best, a weak predictor of response needs to be considered. The glycaemic profile of a single day may be too limited to describe longer-term glycaemic patterns. It should also be noted that the lack of relationship of baseline fasting blood glucose and PPG with HbA1c reduction does not imply that exenatide does not improve these variables but rather that, once

baseline HbA1c is known, information about fasting blood glucose and PPG is not useful in predicting HbA1c reduction.

This study also showed that age had an effect on participant responsiveness to exenatide twice daily but not exenatide once weekly. The trend of increased effectiveness in older participants has also been observed with dipeptidyl peptidase-4 inhibitors.¹³ Interestingly, the present analysis did not find that longer duration of diabetes, concomitant medication use, body weight, or body mass index were important predictors of treatment response; thus, although both exenatide formulations are generally effective treatments, our findings suggest that exenatide twice daily may be especially effective for Asian and older patients.

Other multivariate analyses have examined participant characteristics associated with treatment success (as opposed to above-average responsiveness) for exenatide twice daily. These analyses have found that greater weight loss and higher baseline estimated β -cell function or C-peptide levels are associated with treatment success,¹⁴⁻¹⁶ greater disease duration reduces likelihood of treatment success, and sex, race and ethnicity affect treatment response as well.^{14,17} However, these analyses failed to account for the substantial impact of baseline HbA1c.

The present analysis has a number of limitations. It was a retrospective pooled analysis that assumed all participants were compliant with therapeutic recommendations during the studies. Potential study heterogeneity was not formally assessed nor controlled for in the statistical model because of potential confounding with other baseline variables. Regarding the significant findings relating to Asian ethnicity, most Asian participants in the analysis of exenatide twice daily were in a single study,¹⁸ but the mean HbA1c reduction in the placebo arm of this study was intermediate between the HbA1c reductions in the other 2 placebo arms of studies on exenatide twice daily.^{19,20} Regarding the finding in relation to age, within-study age variation was much greater than between-study age variation; thus, from both an analytical and a study design perspective, we believe that it is unlikely that study heterogeneity explains our findings. The analysis population was limited by characteristics of the trial populations; results may differ in broader patient populations. SMBG measurements included in the present analysis relied on participant-reported measurements without standardized meals and were performed on a single day, so may have limited capacity to reflect daily glucose profiles. In addition, we selected participants who completed therapy; our results may not

apply to participants with less exposure to exenatide or to those excluded from clinical trials. Factors not considered as part of the analysis, such as β -cell function and insulin sensitivity, or factors not measured, such as plasma drug concentration, diet composition and GLP-1 receptor characteristics, may influence response to exenatide treatment. Multiplicity was not controlled for, which may increase the risk of false-positive results. Cross-validation from an independent data set and a controlled study would be needed to confirm the findings.

In conclusion, the present study quantified the wide range of HbA1c responses to treatment with exenatide twice daily and exenatide once weekly, to inform treatment choices in clinical practice. While baseline HbA1c affects response to exenatide, Asian ethnicity and higher participant age were also associated with larger HbA1c reductions for exenatide twice daily. No predictors were associated with an improved response to exenatide once weekly. This analysis may assist clinicians to individualize treatment by identifying patients with characteristics that may result in improved response to exenatide twice daily.

ACKNOWLEDGEMENTS

Mollie Marko PhD, of inScience Communications, Springer Healthcare (New York, NY), provided medical writing support funded by AstraZeneca. Mary Beth DeYoung PhD, of AstraZeneca, critically reviewed the manuscript.

Conflict of interest

J. E. S. has received honoraria for advisory boards and lectures from AstraZeneca, BGP Products, Boehringer Ingelheim, Eli Lilly, Janssen, Merck Sharp & Dohme, Novartis, Novo Nordisk, and Sanofi. B. G. has received honoraria for advisory boards and lectures from Amgen, AstraZeneca, Boehringer Ingelheim, Bristol-Myers Squibb, Eli Lilly, Janssen, Merck Sharp & Dohme, Novartis, Novo Nordisk, and Sanofi. J. H. is a consultant for AstraZeneca. E. H. is an employee of AstraZeneca. G. S. has received honoraria for advisory boards and lectures from AstraZeneca, Boehringer Ingelheim, Eli Lilly, Janssen, Novo Nordisk, Sanofi, and Takeda.

Author contributions

J. E. S. contributed to the design and conception of the analysis. E. H. contributed to the acquisition, analysis, and interpretation of data and the outline and revision of the manuscript. J. E. S., B. G., J. H., E. H., and G. S. contributed to the outline of the manuscript and were involved in the writing and discussion of the manuscript, analyses and interpretation of the data, and in all critical revisions of the manuscript. J. H. is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the work as a whole, including the study design and the decision to submit and publish the manuscript.

Prior presentation

Parts of this study were presented at the Australian Diabetes Society and the Australian Diabetes Educators Association Annual Scientific

Meeting 2016, Queensland, Australia, August 24–26, 2016, and at the American Diabetes Association 76th Scientific Sessions, New Orleans, LA, June 10–14, 2016.

ORCID

Jonathan E. Shaw  <http://orcid.org/0000-0002-6187-2203>

REFERENCES

- Inzucchi SE, Bergenstal RM, Buse JB, et al. Management of hyperglycemia in type 2 diabetes, 2015: a patient-centered approach: update to a position statement of the American Diabetes Association and the European Association for the Study of Diabetes. *Diabetes Care*. 2015;38:140–149.
- McCormack PL. Exenatide twice daily: a review of its use in the management of patients with type 2 diabetes mellitus. *Drugs*. 2014;74:325–351.
- Kayaniyil S, Lozano-Ortega G, Bennett HA, et al. A network meta-analysis comparing exenatide once weekly with other GLP-1 receptor agonists for the treatment of type 2 diabetes mellitus. *Diabetes Ther*. 2016;7:27–43.
- DeYoung MB, MacConell L, Sarin V, Trautmann M, Herbert P. Encapsulation of exenatide in poly-(D,L-lactide-co-glycolide) microspheres produced an investigational long-acting once-weekly formulation for type 2 diabetes. *Diabetes Technol Ther*. 2011;13:1145–1154.
- 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.
- Blevins T, 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.
- Ji L, Onishi Y, Ahn CW, et al. Efficacy and safety of exenatide once-weekly vs exenatide twice-daily in Asian patients with type 2 diabetes mellitus. *J Diabetes Investig*. 2013;4:53–61.
- DeFronzo RA, Stonehouse AH, Han J, Wintle ME. Relationship of baseline HbA1c and efficacy of current glucose-lowering therapies: a meta-analysis of randomized clinical trials. *Diabet Med*. 2010;27:309–317.
- Esposito K, Chiodini P, Maiorino MI, et al. A nomogram to estimate the HbA1c response to different DPP-4 inhibitors in type 2 diabetes: a systematic review and meta-analysis of 98 trials with 24 163 patients. *BMJ Open*. 2015;5:e005892.
- Khan M, Ouyang J, Perkins K, Nair S, Joseph F. Determining predictors of early response to exenatide in patients with type 2 diabetes mellitus. *J Diabetes Res*. 2015;2015:162718.
- Sheu WH, Brunell SC, Blase E. Efficacy and tolerability of exenatide twice daily and exenatide once weekly in Asian versus white patients with type 2 diabetes mellitus: a pooled analysis. *Diabetes Res Clin Pract*. 2016;114:160–172.
- Shimizu H, Uehara Y, Okada S, Mori M. Contribution of fasting and postprandial hyperglycemia to hemoglobin A1c in insulin-treated Japanese diabetic patients. *Endocr J*. 2008;55:753–756.
- Mathews DR, Dejager S, Ahren B, et al. Vildagliptin add-on to metformin produces similar efficacy and reduced hypoglycaemic risk compared with glimepiride, with no weight gain: results from a 2-year study. *Diabetes Obes Metab*. 2010;12:780–789.
- Anichini R, Cosimi S, Di Carlo A, et al. Gender difference in response predictors after 1-year exenatide therapy twice daily in type 2 diabetic patients: a real world experience. *Diabetes Metab Syndr Obes*. 2013;6:123–129.
- Horton ES, Silberman C, Davis KL, Berria R. Weight loss, glycemic control, and changes in cardiovascular biomarkers in patients with type 2 diabetes receiving incretin therapies or insulin in a large cohort database. *Diabetes Care*. 2010;33:1759–1765.
- Song SO, Kim KJ, Lee BW, Kang ES, Cha BS, Lee HC. Tolerability, effectiveness and predictive parameters for the therapeutic

usefulness of exenatide in obese, Korean patients with type 2 diabetes. *J Diabetes Investig.* 2014;5:554–562.

17. Bihan H, Ng WL, Magliano DJ, Shaw JE. Predictors of efficacy of GLP-1 agonists and DPP-4 inhibitors: a systematic review. *Diabetes Res Clin Pract.* 2016;121:27–34.
18. Kadowaki T, Namba M, Imaoka T, et al. Improved glycemic control and reduced bodyweight with exenatide: a double-blind, randomized, phase 3 study in Japanese patients with suboptimally controlled type 2 diabetes over 24 weeks. *J Diabetes Investig.* 2011;2:210–217.
19. Apovian CM, Bergenstal RM, Cuddihy RM, et al. Effects of exenatide combined with lifestyle modification in patients with type 2 diabetes. *Am J Med.* 2010;123:468.e9–468.e17.
20. Moretto TJ, Milton DR, Ridge TD, et al. Efficacy and tolerability of exenatide monotherapy over 24 weeks in antidiabetic drug-naïve patients with type 2 diabetes: a randomized, double-blind, placebo-controlled, parallel-group study. *Clin Ther.* 2008;30:1448–1460.

SUPPORTING INFORMATION

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

How to cite this article: Shaw JE, Gallwitz B, Han J, Hardy E, Schernthaner G. Variability in and predictors of glycaemic responses after 24 weeks of treatment with exenatide twice daily and exenatide once weekly. *Diabetes Obes Metab.* 2017;19:1793–1797. <https://doi.org/10.1111/dom.13022>