Diabetes Care Publish Ahead of Print, published online March 9, 2010

DURATION-1: Exenatide Once Weekly Produces Sustained Glycemic Control and Weight Loss Over 52 Weeks

Running Title: Exenatide once weekly, 52-wk safety & efficacy

John B Buse[1] MD PhD, Daniel J Drucker[2] MD, Kristin L Taylor[3] PhD, Terri Kim[3] MS, Brandon Walsh[3] PhD, Hao Hu[3] MS, Ken Wilhelm[3] MD, Michael Trautmann[4] MD, Larry Z Shen[3] PhD, Lisa E Porter[3] MD for the DURATION-1 Study Group

[1] Division of Endocrinology, Department of Medicine, University of North Carolina School of Medicine, Chapel Hill, North Carolina, USA
[2] Department of Medicine, Banting and Best Diabetes Centre, Samuel Lunenfeld Research Institute, Mount Sinai Hospital, University of Toronto, Ontario, Canada.
[3] Amylin Pharmaceuticals, Inc., San Diego, CA, USA
[4] Lilly Research, Eli Lilly and Company, Indianapolis, IN, USA

Corresponding Author
John B Buse, MD PhD
Email: jbuse@med.unc.edu

Clinical trial reg. no. NCT00308139; (www.clinicaltrials.gov

Additional information for this article can be found in an online appendix at http://care.diabetesjournals.org

Submitted 14 October 2009 and accepted 24 February 2010.

This is an uncopyedited electronic version of an article accepted for publication in *Diabetes Care*. The American Diabetes Association, publisher of *Diabetes Care*, is not responsible for any errors or omissions in this version of the manuscript or any version derived from it by third parties. The definitive publisher-authenticated version will be available in a future issue of *Diabetes Care* in print and online at http://care.diabetesjournals.org.

Copyright American Diabetes Association, Inc., 2010

Objective: In the DURATION-1 study, the safety and efficacy of 30 weeks of treatment with the GLP-1 receptor agonist exenatide once weekly (exenatide QW; 2mg) was compared to exenatide BID in 295 patients with type 2 diabetes. We now report the safety and efficacy of exenatide QW in a) patients who continued treatment for an additional 22 weeks (52 weeks total), and b) patients who switched from exenatide BID to exenatide QW after 30 weeks.

*Research Design and Methods***:** In this randomized, multicenter, comparator-controlled, open-label trial, 258 patients entered the 22-week open-ended assessment phase (n=128 QW-only; n=130 BID→QW). A1C, fasting plasma glucose (FPG), body weight, blood pressure, fasting lipids, safety, and tolerability were assessed.

*Results***:** Patients continuing exenatide QW maintained A1C improvements through 52 weeks (-2.0% [-2.1 to -1.8%]; LS mean [95% CI]). Patients switching from exenatide BID to exenatide QW achieved further A1C improvements; both groups exhibited the same A1C reduction and mean A1C (6.6%) at week 52. At week 52, 71% and 54% of all patients achieved an A1C <7.0% and ≤6.5%, respectively. In both treatment arms, FPG was reduced by >40 mg/dL and body weight was reduced by >4 kg after 52 weeks. Nausea occurred less frequently in this assessment period and was predominantly mild. No major hypoglycemia was observed.

Conclusion: Exenatide QW elicited sustained improvements in glycemic control and body weight through 52 weeks of treatment; patients switching to exenatide QW experienced further improvements in A1C and FPG, with sustained weight loss.

ClinicalTrials.gov identifier: NCT00308139

Type 2 diabetes is a complex and increasingly prevalent disease associated with interrelated comorbidities, including obesity, dyslipidemia, and hypertension. The importance of treating not only hyperglycemia, but also the associated comorbidities, is recognized as necessary to reduce the risk of complications, particularly cardiovascular disease (1). Lifestyle modification can improve glycemic control as well as body weight, blood pressure, and lipid profiles; however, behavioral modifications are inherently difficult and most patients eventually require multiple medications (2,3,4,5,6). Although several classes of antihyperglycemic medications are currently indicated for the treatment of type 2 diabetes, most of them do not improve the comorbidities and several are associated with weight gain.

Exenatide, a glucagon-like peptide-1 receptor (GLP-1R) agonist, improves glycemic control in patients with type 2 diabetes through multiple mechanisms of action: increased glucose-dependent insulin secretion, attenuated postprandial glucagon secretion, slowed gastric emptying, and increased satiety (7,8). The twice-daily formulation of exenatide (exenatide BID) improves both fasting and postprandial glucose control, resulting in A1C reductions of roughly 0.8%-1.0% in placebo controlled trials (9,10,11,12) and 1.0-1.4% in open-label trials (13,14,15). These improvements in glucose control were maintained in patients completing 3 years of treatment (-1.0%) (16). Exenatide therapy is also associated with weight loss and improvement in cardiovascular risk factors, including blood pressure and serum lipid profiles (16). Furthermore, the glucose-dependent mechanisms of action of exenatide minimize the risk of hypoglycemia. GLP-1R agonists have recently been added to the ADA and EASD consensus algorithm for the treatment of type 2 diabetes as an option after the addition of metformin in patients in which body weight and hypoglycemia risk are concerns (1).

Exenatide BID is administered within the 60-minute period before the morning and evening meals and primarily exerts its pharmacodynamic effects on glucose concentrations during the postprandial period. A long-acting once-weekly formulation of exenatide (exenatide QW) has been developed and is under review by regulatory authorities. Weekly administration of 2 mg exenatide QW results in therapeutic plasma exenatide concentrations within 2 weeks and steady-state plasma exenatide concentrations within the therapeutic target range 6 to 7 weeks after initiation of therapy (17,18).

The DURATION-1 trial was designed as a two-stage protocol. We previously reported the first stage, a randomized open-label comparison of exenatide QW to exenatide BID in patients with type 2 diabetes over 30 weeks (17). Both therapies improved glycemic control, and the improvement in A1C observed with exenatide QW treatment was significantly greater than that observed with exenatide BID (-1.9% vs. -1.5%, respectively). Similar improvements in body weight, blood pressure, and fasting lipids were demonstrated with both forms of exenatide therapy. We now describe 52-week results from the second phase of the DURATION-1 trial which examined the safety and efficacy of a) switching from exenatide BID to exenatide QW after 30 weeks of treatment, and b) continuing exenatide QW treatment for an additional 22 weeks (52 weeks total).

RESEARCH DESIGN AND METHODS

Randomization and Interventions. Patients were randomized to one of two open-label treatment groups: weekly subcutaneous injections of 2 mg exenatide QW, or

exenatide 5 μg BID for the first 28 days followed by a required dose increase to 10 μg BID for the remainder of the 30-week assessment period. The inclusion and exclusion criteria, as well as results from the initial 30 weeks have previously been reported (17). At 30 weeks, participants entered a second, open-ended treatment period in which all patients received exenatide QW. Patients who switched from exenatide BID to exenatide QW treatment and were concomitantly using a sulfonylurea (SFU) were required to reduce their SFU dose to the minimum recommended dose until Week 40. Subsequently, SFU dose was up-titrated based on daily glucose measurements to reach a target FPG of ≤110 mg/dL. Patients originally randomized to exenatide QW maintained their treatment regimen.

A common clinical protocol was approved for each site by the appropriate Institutional Review Board. Patients provided written informed consent prior to participation. The study was conducted in accordance with the principles described in the Declaration of Helsinki, including all amendments through the South Africa revision (19).

Outcomes. For this second phase of the study, glucose control during the transition from exenatide BID to exenatide QW was examined, as well as the safety, tolerability, and efficacy of 52 weeks of exenatide QW treatment. Plasma analytes and A1C were quantitated by Quintiles Laboratories (Smyrna, GA) using standard methods. A1C was measured using high-performance liquid chromatography. Plasma antibodies to exenatide were measured by Millipore Corporation Drug Discovery (St. Charles, MO) using an enzyme-linked immunosorbant assay (20). Titers of antibodies to exenatide were determined by serial 1/5 dilutions after an initial dilution of 1/25 (also expressed as the reciprocal of the highest dilution of sample serum that tests positive in the assay). Blood pressure was measured after approximately 5 minutes of quiet rest in a sitting position, repeated after at least 30 seconds, and the two measurements were averaged.

Statistical Analysis. The intent-to-treat (ITT) population comprised all randomized patients who received at least one injection of exenatide in the previously reported phase of this study (17). The 52-week evaluable population consisted of ITT patients who completed the study visits to at least week 48 in compliance with the protocol. Descriptive statistics on demographics, analysis of primary glycemic endpoints, body weight, and fasting lipid concentrations are provided for the 52-week evaluable population. All safety analyses, including blood pressure measurements, are provided for the ITT population. The analyses of A1C were based on a general linear model (ANOVA) including original treatment assignment, baseline A1C stratum, and concomitant SFU use at screening. Baseline FPG, body weight, and blood pressure were added in the model (ANCOVA) for FPG, body weight, and blood pressure, respectively. Data for these efficacy endpoints are expressed as least square (LS) means. There were no substantial differences in A1C (Figure 2B) or other measures (data not shown) when examining the evaluable population, the 52-week ITT population, or those that participated after 30 weeks. Therefore, only data for the evaluable population were reported. Statistical analysis was performed using SAS (8.2; SAS Institute, Inc., North Carolina).

Treatment-emergent adverse events were defined as those occurring during or after the first injection of exenatide QW in the open-ended assessment period. Treatment-emergent adverse events during the initial 30 weeks of the trial were previously reported (17). Hypoglycemia was categorized as major if the event: 1) in the judgment of the investigator or physician, resulted in a loss of consciousness, seizure, or coma and resolved

after administration of glucagon or glucose; or 2) required third-party assistance to resolve and had a glucose value of <54 mg/dL. Minor hypoglycemia was defined as a report of symptoms consistent with hypoglycemia and a glucose value of <54 mg/dL prior to treatment of the episode.

RESULTS

Patient disposition and baseline characteristics. Of the 295 ITT patients, 258 patients (87%) continued into the second phase of the trial (Figure 1). Demographics and background therapy were similar between the two 52-week evaluable cohorts. Overall, 243 patients completed 52 weeks of treatment, representing 82% of the original ITT population and 94% of the population entering the second predefined treatment period.

Efficacy of exenatide QW. During this 22-week assessment period, patients who continued exenatide QW treatment maintained improvements in A1C (Figure 2A), with an LS mean (95% CI) change from baseline A1C of -2.1% (-2.2 to -1.9%) at week 30 and -2.0% (-2.1 to -1.8%) at week 52. The time course and durability of A1C improvements were similar for the ITT population and 52-week evaluable population (Figure 2B). Patients who switched from exenatide BID to exenatide QW (week 30 A1C reduction: -1.8% [-1.9 to -1.6%]) exhibited further improvements in glycemic control such that they achieved the same A1C reduction (-2.0%) and mean A1C (6.6%) at week 52 as patients receiving only exenatide QW. After 52 weeks of treatment, 71% of all patients achieved A1C <7.0% and 54% achieved A1C ≤6.5% (similar between cohorts; Figure 2D). In patients with a baseline A1C <9.0% (baseline A1C: 7.8%), A1C reduction at week 52 was -1.2% (-1.4 to -1.1%) and -1.3% (-1.5 to -1.2%) in the exenatide QW-only and exenatide BID→exenatide QW groups, respectively (Online Appendix Figure 1which is available at http://care.diabetesjournals.org). Larger reductions in A1C at week 52 were achieved in patients with a baseline A1C ≥9.0%: -2.8% (-3.1 to -2.5%) for exenatide QW-only group (baseline A1C: 9.7%) and -2.6% (-3.0 to -2.3%) in the exenatide BID→exenatide QW group (baseline A1C: 9.6%).

Body weight decreased similarly in both treatment groups. At week 52, the LS mean (95% CI) changes in body weight were -4.1 kg (-5.3 to -2.9 kg) and -4.5 kg (-5.7 to -3.3 kg) in the exenatide QW-only and exenatide BID→exenatide QW groups, respectively (Figure 2E). The distribution of the change in A1C with respect to changes in body weight is shown in Figure 2F. Ninety-seven percent of all patients achieved reductions in A1C over 52 weeks (similar between cohorts) and most patients (77% and 79% of exenatide QW-only and exenatide BID→exenatide QW, respectively) achieved reductions in both A1C and body weight. Significant A1C reductions were observed in both treatment groups regardless of weight loss (Appendix Figure 2).

Glucose control during transition from exenatide BID to exenatide QW. In patients who received exenatide QW for 52 weeks, LS mean (95%CI) reductions in FPG at Week 30 (-46 mg/dL [-52 to -40 mg/dL]) were maintained through week 52 (-47 mg/dL [-53 to -41 mg/dL]; Figure 2C). Patients who switched from exenatide BID to exenatide QW achieved similar reductions in FPG at week 52 (-43 mg/dL [-49 to-37 mg/dL]; Figure 2C) relative to patients who received exenatide QW for 52 weeks. Subsequent to week 30, BID-treated patients who switched to exenatide QW experienced a transient rise in mean FPG concentration followed by a rapid decrease within 2 weeks of the switch (Figure 2C). By 3 to 4 weeks following initiation of QW treatment, the mean FPG in this group of subjects had returned to levels observed prior to switching to exenatide QW,

which was followed by further improvements such that ultimately the two groups exhibited similar reductions in FPG. Patients concomitantly taking an SFU (n=44) reduced their SFU dose to the minimum recommended dose at week 30 according to protocol and experienced a greater rise in FPG during the transition than patients not taking an SFU (data not shown). At week 52, 45% (n=20) of these patients received a lower SFU dose compared to their SFU dose immediately prior to switching to exenatide QW, while 43% (n=19) received the same SFU dose and 9% (n=4) increased SFU dose at week 52 compared to week 30. One patient discontinued SFU after switching to exenatide QW.

Effects on blood pressure and fasting lipids. Clinically significant blood pressure improvements were observed in patients treated with exenatide QW for 52 weeks (SBP: -6.2 mmHg [-8.5 to -3.9 mmHg], DBP: -2.8 mmHg [-4.3 to -1.3 mmHg]; LS mean change from baseline [95% CI]) and in patients switching from exenatide BID to exenatide QW (SBP: -3.8 mmHg [-6.1 to -1.5 mmHg], DBP -1.8 mmHg [-3.2 to -0.3 mmHg]; Figure 3A). Fifty and 46% of patients (exenatide QW and exenatide BID→exenatide QW, respectively) with elevated SBP (≥130 mmHg) at baseline achieved normal SBP at week 52. Changes in concomitant antihypertensive medications were only allowed if deemed necessary by the investigator. The majority (84%) of the 154 subjects who had been using an antihypertensive medication at screening and completed 52 weeks of treatment did not change their dose. Of patients who did change their dose, 9 patients increased their dose, 13 patients decreased their dose, and 1 patient stopped their medication. In addition, 14 patients initiated antihypertensive medication after screening. Improvements in serum lipid profiles were demonstrated in both treatment groups, with clinically significant reductions in total cholesterol (-9.6 mg/dL [-14.8 to -4.3 mg/dL] and -9.0 mg/dL [-14.5 to -3.6 mg/dL] ; Figure 3B) and triglycerides (-15% [-21 to -9%] and -13% [-20 to -7%]) for exenatide QW-only and exenatide BID→exenatide QW, respectively.

Safety and tolerability. Treatment-emergent adverse events that occurred for the first time or worsened during this second phase of DURATION-1 were similar to those observed during the 30-week assessment period (Table 1). Nausea reported was predominantly mild in intensity. No severe nausea was reported. Twenty-one patients (8%; n=4 for exenatide QW-only and n=17 exenatide BID→exenatide QW) reported injection-site related adverse events including bruising, erythema, hemorrhage, induration, pain, and pruritus. Mild to moderate injection-site pruritus was observed after switching from exenatide BID to exenatide QW in 6 patients (5 of these patients did not experience pruritus during the initial 30-week assessment). No injection-site related adverse events led to withdrawal. There were no episodes of major hypoglycemia; the incidence of minor hypoglycemia was low and was limited to patients using a concomitant SFU during Weeks 30 – 52 (9% of patients receiving an SFU; Appendix Table 1). Antibodies to exenatide titer peaked at week 6 for both treatment groups (geometric mean ±SE: 33.2±8.2 and 12.6±3.4 for exenatide QW-only and exenatide BID →exenatide QW groups, respectively). At week 52, geometric mean ±SE antibody titers to exenatide were 12.8±3.4 and 8.9±2.1 for exenatide QW-only and exenatide BID→exenatide QW groups, respectively (Appendix Table 2). Antibodies to exenatide were not predictive of individual A1C change or incidence of treatment-emergent adverse events. One patient withdrew due to an adverse event (worsening of type 2 diabetes) during the 22-week assessment period (exenatide QW-only

group). No cases of pancreatitis were reported.

DISCUSSION

The improvements in glycemic control and body weight observed following 30 weeks of exenatide QW treatment (17) were sustained in patients continuing exenatide QW treatment for 52 weeks. Patients switching from exenatide BID to exenatide QW exhibited further improvements in glycemic control. Similar improvements in glycemic control, body weight, and cardiovascular risk factors were observed at week 52 regardless of initial randomized treatment. While the absence of a comparator arm is a limitation of this study, and the open-label trial design inherently offers the potential for bias and can affect patient expectations, the results of the present study demonstrated comparable reductions in A1C and body weight to a previously reported double-blind, placebo-controlled study of exenatide QW at the same dose (18) and were consistent with continuous exenatide exposure. These improvements were greater than those previously observed with exenatide BID in both placebo-controlled (9,10,11,12) and open-label comparator trials (13,14,15). It is important to note that improvements in A1C were observed across the spectrum of baseline A1C values and weight loss categories. Treatment with exenatide QW was generally well tolerated and treatment-emergent adverse events were generally mild to moderate. As in the initial 30-week phase, the only incidences of mild-moderate hypoglycemia occurred in patients concomitantly receiving an SFU.

It is noteworthy that patients switching from exenatide BID to exenatide QW experienced a transient elevation in FPG, which generally improved within 2 weeks after initiation of QW therapy. This transient rise in FPG can be largely attributed to the time required for plasma exenatide levels to reach the therapeutic range after initiation of exenatide QW, and was of a magnitude (~15 mg/dL) that is unlikely to be associated with symptoms or harm over a short period of time. In addition, subjects who switched treatment and were using a concomitant SFU were required to reduce their SFU dose to the minimum recommended dose for initiation of exenatide QW treatment. Therefore, the transient rise in FPG concentration may also reflect SFU dose adjustments. It is important to note that the highest point in the transient FPG rise represented a mean decrease of -16 mg/dL from baseline. There was no clinically significant effect on overall glycemic control following the switch to exenatide QW (mean rise in mean A1C was approximately +0.1%). A1C values subsequently declined below those observed with 30 weeks of exenatide BID treatment and by Week 44 matched those observed with continuous exenatide QW treatment. Overall, these findings suggest that switching from exenatide BID to QW, while associated with a transient increase in glycemia, ultimately leads to significantly improved glycemic control.

Achieving glycemic targets remains an elusive goal for many patients with type 2 diabetes. Furthermore, improving weight and cardiovascular risk markers and avoiding hypoglycemia are desired components of a diabetes treatment program. GLP-1R agonists were recently recommended as second-step treatment option in patients in whom avoidance of hypoglycemia, or promotion of weight loss, are major concerns (1). In the present study, the transition from exenatide BID to exenatide QW was made without additional safety and tolerability concerns. Furthermore, clinical benefits of exenatide QW were maintained and resulted in a mean A1C of 6.6% after 52 weeks of treatment.

ACKNOWLEDGEMENTS

The authors thank the exenatide DURATION-1 (**D**iabetes Therapy **U**tilization : **R**esearching

Changes in **A**1c, Weight and Other Factors **T**hrough **I**ntervention with Exenatide **ON**ce Weekly) clinical team for their assistance in the conduct, reporting, and quality control of the studies; the DURATION-1 study site investigators (Sherwyn Schwartz, Sam Miller, Richard Weinstein, Bethany Klopfenstein, Andrew Ahmann, Julio Rosenstock, John Pullman, Fred Whitehouse, G.M. Gollapudi, Douglas Schumacher, Mervyn Weerasinghe, Peter Weissman, Lyle Myers, Eric Klein, Thomas Littejohn, Thomas Moretto, Jon Shapiro, Daniel Lorber, Athena Philis-Tsimikas, David Kayne, Richard Bergenstal, Elizabeth Stevens, Danny Sugimoto, Bruce Berwald, Diane Krieger, Dean Kereiakes, Gary Lewis, Robert Henry, Mark Comianos, Munni Selagamsetty, Ronald Mayfield, John Buse and Daniel Drucker) and their staffs for conducting the study; the study patients for their participation; and Alkermes, Inc. for the development of and for manufacturing the long-acting release formulation of exenatide.

The University of North Carolina has contracts with a variety of companies for Dr. Buse' services as an investigator and/or consultant including: Amylin, Bristol-Myers Squibb, Eli Lilly, GlaxoSmithKline, Hoffman-La Roche, Merck, Novo Nordisk, Pfizer, sanofi-aventis, and Wyeth. Dr. Drucker has served as an advisor or consultant within the past 12 months to Amylin Pharmaceuticals, Arena Pharmaceuticals Inc., Arisaph Pharmaceuticals Inc., Eli Lilly Inc, Glaxo Smith Kline, Hoffman LaRoche Inc, Isis Pharmaceuticals Inc., Merck Research Laboratories, Metabolex Inc., Novartis Pharmaceuticals, Novo Nordisk Inc., and Transition Pharmaceuticals Inc. Neither Dr. Drucker or his family members hold stock directly or indirectly in any of these companies. Drs Drucker and Buse had full access to the primary data and led decisions on content. Kristin Taylor, Brandon Walsh, Hao Hu, Terri Kim, Larry Shen, Ken Wilhelm, and Lisa Porter are employees and stockholders of Amylin Pharmaceuticals, Inc. Michael Trautmann is an employee and stockholder of Eli Lilly & Co. Amylin Pharmaceuticals Inc. and Eli Lilly & Company were study sponsors and thus were involved in the study design, protocol development, and the collection, review and analysis of the data. Portions of these data were previously presented at the ADA 69th Scientific Sessions, New Orleans, LA 2009 and the 45th EASD Annual meeting, Vienna, Austria, 2009.

REFERENCES

1. Nathan DM, Buse JB, Davidson MB, Ferrannini E, Holman RR, Sherwin R and Zinman B: Medical Management of Hyperglycemia in Type 2 Diabetes: A Consensus Algorithm for the Initiation and Adjustment of Therapy: A consensus statement of the American Diabetes Association and the European Association for the Study of Diabetes. *Diabetes Care* 32:193-203, 2009

2. (UKPDS) UPDSG: Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). UK Prospective Diabetes Study (UKPDS) Group. *Lancet* 352:837-53, 1998

3. Brown JB, Nichols GA and Perry A: The burden of treatment failure in type 2 diabetes. *Diabetes Care* 27:1535-40, 2004

4. Matthews DR, Cull CA, Stratton IM, Holman RR and Turner RC: UKPDS 26: Sulphonylurea failure in non-insulin-dependent diabetic patients over six years. UK Prospective Diabetes Study (UKPDS) Group. *Diabet Med* 15:297-303, 1998

5. Pontiroli AE, Calderara A and Pozza G: Secondary failure of oral hypoglycaemic agents: frequency, possible causes, and management. *Diabetes Metab Rev* 10:31-43, 1994

6. Turner RC, Cull CA, Frighi V and Holman RR: Glycemic control with diet, sulfonylurea, metformin, or insulin in patients with type 2 diabetes mellitus: progressive requirement for multiple therapies (UKPDS 49). UK Prospective Diabetes Study (UKPDS) Group. *JAMA* 281:2005-12, 1999

7. Edwards CM, Stanley SA, Davis R, Brynes AE, Frost GS, Seal LJ, Ghatei MA and Bloom SR: Exendin-4 reduces fasting and postprandial glucose and decreases energy intake in healthy volunteers. *Am J Physiol Endocrinol Metab* 281:E155-61, 2001

8. Nielsen LL, Young AA and Parkes DG: Pharmacology of exenatide (synthetic exendin-4): a potential therapeutic for improved glycemic control of type 2 diabetes. *Regul Pept* 117:77-88, 2004

9. Buse JB, Henry RR, Han J, Kim DD, Fineman MS and Baron AD: Effects of exenatide (exendin-4) on glycemic control over 30 weeks in sulfonylurea-treated patients with type 2 diabetes. *Diabetes Care* 27:2628-35, 2004

10. DeFronzo RA, Ratner RE, Han J, Kim DD, Fineman MS and Baron AD: Effects of exenatide (exendin-4) on glycemic control and weight over 30 weeks in metformin-treated patients with type 2 diabetes. *Diabetes Care* 28:1092-100, 2005

11. Kendall DM, Riddle MC, Rosenstock J, Zhuang D, Kim DD, Fineman MS and Baron AD: Effects of exenatide (exendin-4) on glycemic control over 30 weeks in patients with type 2 diabetes treated with metformin and a sulfonylurea. *Diabetes Care* 28:1083-91, 2005

12. Zinman B, Hoogwerf BJ, Duran Garcia S, Milton DR, Giaconia JM, Kim DD, Trautmann ME and Brodows RG: The effect of adding exenatide to a thiazolidinedione in suboptimally controlled type 2 diabetes: a randomized trial. *Ann Intern Med* 146:477-85, 2007

13. Barnett AH, Burger J, Johns D, Brodows R, Kendall DM, Roberts A and Trautmann ME: Tolerability and efficacy of exenatide and titrated insulin glargine in adult patients with type 2 diabetes previously uncontrolled with metformin or a sulfonylurea: a multinational, randomized, open-label, two-period, crossover noninferiority trial. *Clin Ther* 29:2333-48, 2007

14. Heine RJ, Van Gaal LF, Johns D, Mihm MJ, Widel MH and Brodows RG: Exenatide versus insulin glargine in patients with suboptimally controlled type 2 diabetes: a randomized trial. *Ann Intern Med* 143:559-69, 2005

15. Nauck MA, Duran S, Kim D, Johns D, Northrup J, Festa A, Brodows R and Trautmann M: A comparison of twice-daily exenatide and biphasic insulin aspart in patients with type 2 diabetes who were suboptimally controlled with sulfonylurea and metformin: a non-inferiority study. *Diabetologia* 50:259-67, 2007
16. Klonoff DC, Buse JB, Nielsen LL, Guan X, Bowlus CL, Holcombe JH, Wintle ME and Maggs DG: 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* 24:275-86, 2008
17. Drucker DJ, Buse JB, Taylor K, Kendall DM, Trautmann M, Zhuang D and Porter L: Exenatide once weekly versus twice daily for the treatment of type 2 diabetes: a randomised, open-label, non-inferiority study. *Lancet* 372:1240-50, 2008
18. Kim D, MacConell L, Zhuang D, Kothare PA, Trautmann M, Fineman M and Taylor K: Effects of once-weekly dosing of a long-acting release formulation of exenatide on glucose control and body weight in subjects with type 2 diabetes. *Diabetes Care* 30:1487-93, 2007
19. World Medical Association declaration of Helsinki. Recommendations guiding physicians in biomedical research involving human subjects. *JAMA* 277:925-6, 1997
20. Fineman MS, Bicsak TA, Shen LZ, Taylor K, Gaines E, Varns A, Kim D and Baron AD: Effect on glycemic control of exenatide (synthetic exendin-4) additive to existing metformin and/or sulfonylurea treatment in patients with type 2 diabetes. *Diabetes Care* 26:2370-7, 2003

Table 1: Treatment-emergent adverse events ≥5% incidence during open-ended assessment period (week 30 through week 52)

Preferred Term	Exenatide QW ITT, N=128 %	Exenatide BID → Exenatide QW ITT, N=130 %
Upper respiratory tract infection	12.5	12.3
Diarrhea	8.6	6.9
Nausea	7.0	7.7
Nasopharyngitis	7.8	4.6
Sinusitis	4.7	6.9
Vomiting	6.3	4.6
Urinary tract infection	2.3	5.4
Injection site bruising	0	5.4

Adverse events are reported that that occur for the first time, or existed prior to Week 30 and worsened, after the first injection at Week 30 through study termination.

FIGURE LEGENDS

Figure 1. Enrollment, patient disposition, and baseline characteristics. Of the 303 patients originally randomized to the study, 258 entered the subsequent 22-week assessment period (Evaluable Population). Fifteen patients withdrew during the 22-week assessment period, resulting in an Evaluable Population of N=241 (n=120 QW only; n=121 BID → QW). Demographics of ITT population available in reference 17 and represent the information at the original baseline.

Figure 2. Glycemic control and body weight over 52 weeks. A) LS mean ± SE changes in A1C over 52 weeks for the Evaluable Population (exenatide QW-only N=120; exenatide BID→exenatide QW N=121). **B)** LS mean ± SE change in A1C for ITT (N = 148) and Evaluable Population patients receiving only exenatide QW for 52 weeks. **C)** Change in fasting plasma glucose over 52 weeks for the Evaluable Population. **D)** Proportion of patients achieving A1C targets of <7.0%, ≤6.5%, ≤6.0% (D). * = P<0.05 vs. exenatide BID → exenatide QW. BL = Baseline. **E)** LS mean ± SE changes in body weight over 52 weeks for the Evaluable Population. **F)** The majority of patients in either treatment group lost body weight.

Figure 3. Change from baseline in blood pressure and serum lipids. A) Patients (ITT Population) in both treatment groups exhibited favorable changes (LS mean change from baseline ±SE) in blood pressure after 52 weeks of treatment. **B)** Treatment with exenatide QW was associated with favorable changes in serum lipids (Evaluable Population). Data are presented as LSmean ± SE for all lipids except for triglycerides (geometric LS mean mg/dL baseline; geometric LS mean percent change ± SE from baseline). ITT Population: exenatide QW-only N=148, exenatide BID → exenatide QW N= 147. Evaluable Population: exenatide QW-only N=120, exenatide BID → exenatide QW N= 121. BL = Baseline.

Figure 1

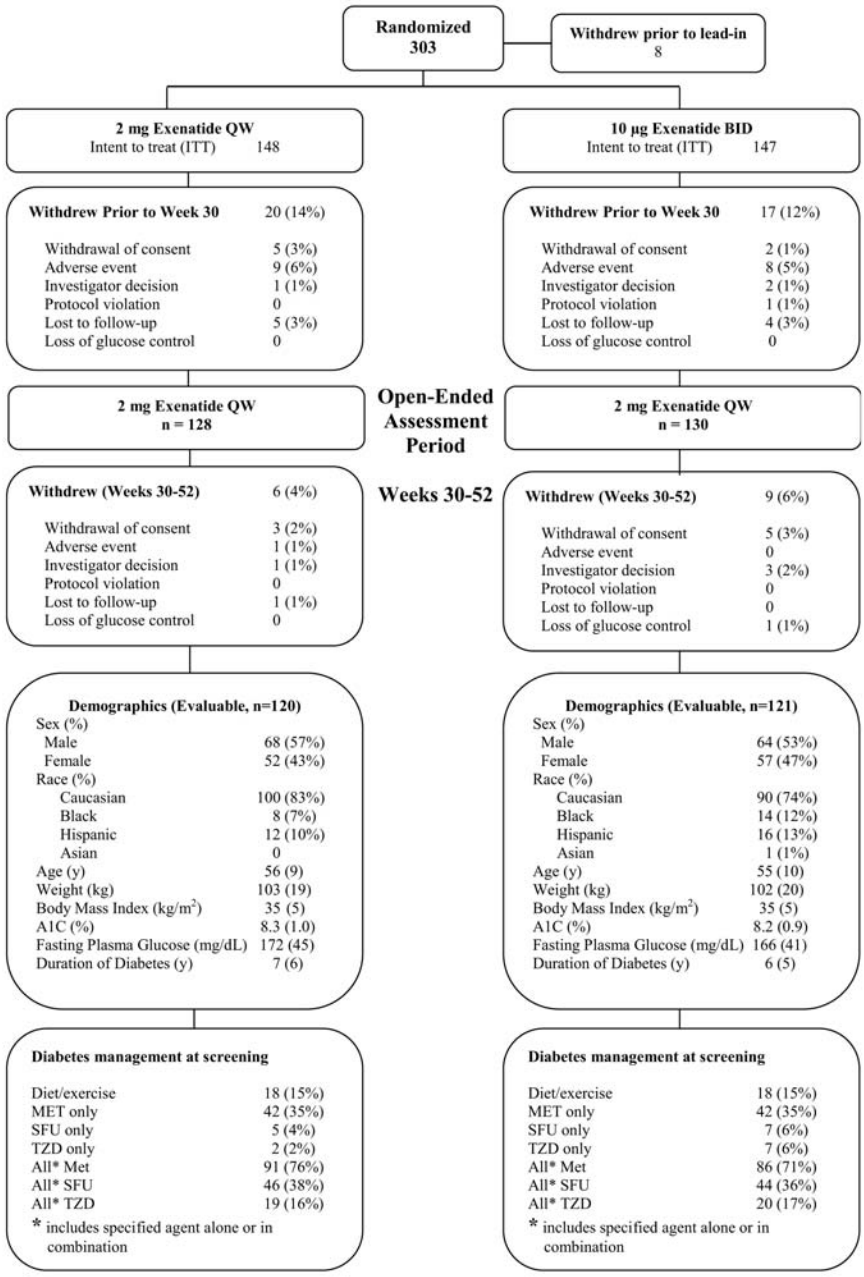

Randomized 303
Withdrew prior to lead-in 8
2 mg Exenatide QW
Intent to treat (ITT) 148
10 µg Exenatide BID
Intent to treat (ITT) 147
Withdrew Prior to Week 30 20 (14%)
Withdrawal of consent 5 (3%)
Adverse event 9 (6%)
Investigator decision 1 (1%)
Protocol violation 0
Lost to follow-up 5 (3%)
Loss of glucose control 0
Withdrew Prior to Week 30 17 (12%)
Withdrawal of consent 2 (1%)
Adverse event 8 (5%)
Investigator decision 2 (1%)
Protocol violation 1 (1%)
Lost to follow-up 4 (3%)
Loss of glucose control 0
2 mg Exenatide QW n = 128
Open-Ended Assessment Period
Weeks 30-52
2 mg Exenatide QW n = 130
Withdrew (Weeks 30-52) 6 (4%)
Withdrawal of consent 3 (2%)
Adverse event 1 (1%)
Investigator decision 1 (1%)
Protocol violation 0
Lost to follow-up 1 (1%)
Loss of glucose control 0
Withdrew (Weeks 30-52) 9 (6%)
Withdrawal of consent 5 (3%)
Adverse event 0
Investigator decision 3 (2%)
Protocol violation 0
Lost to follow-up 0
Loss of glucose control 1 (1%)
Demographics (Evaluable, n=120)
Sex (%)
Male 68 (57%)
Female 52 (43%)
Race (%)
Caucasian 100 (83%)
Black 8 (7%)
Hispanic 12 (10%)
Asian 0
Age (y) 56 (9)
Weight (kg) 103 (19)
Body Mass Index (kg/m2) 35 (5)
A1C (%) 8.3 (1.0)
Fasting Plasma Glucose (mg/dL) 172 (45)
Duration of Diabetes (y) 7 (6)
Demographics (Evaluable, n=121)
Sex (%)
Male 64 (53%)
Female 57 (47%)
Race (%)
Caucasian 90 (74%)
Black 14 (12%)
Hispanic 16 (13%)
Asian 1 (1%)
Age (y) 55 (10)
Weight (kg) 102 (20)
Body Mass Index (kg/m2) 35 (5)
A1C (%) 8.2 (0.9)
Fasting Plasma Glucose (mg/dL) 166 (41)
Duration of Diabetes (y) 6 (5)
Diabetes management at screening
Diet/exercise 18 (15%)
MET only 42 (35%)
SFU only 5 (4%)
TZD only 2 (2%)
All* Met 91 (76%)
All* SFU 46 (38%)
All* TZD 19 (16%)
* includes specified agent alone or in combination
Diabetes management at screening
Diet/exercise 18 (15%)
MET only 42 (35%)
SFU only 7 (6%)
TZD only 7 (6%)
All* Met 86 (71%)
All* SFU 44 (36%)
All* TZD 20 (17%)
* includes specified agent alone or in combination

Figure 2

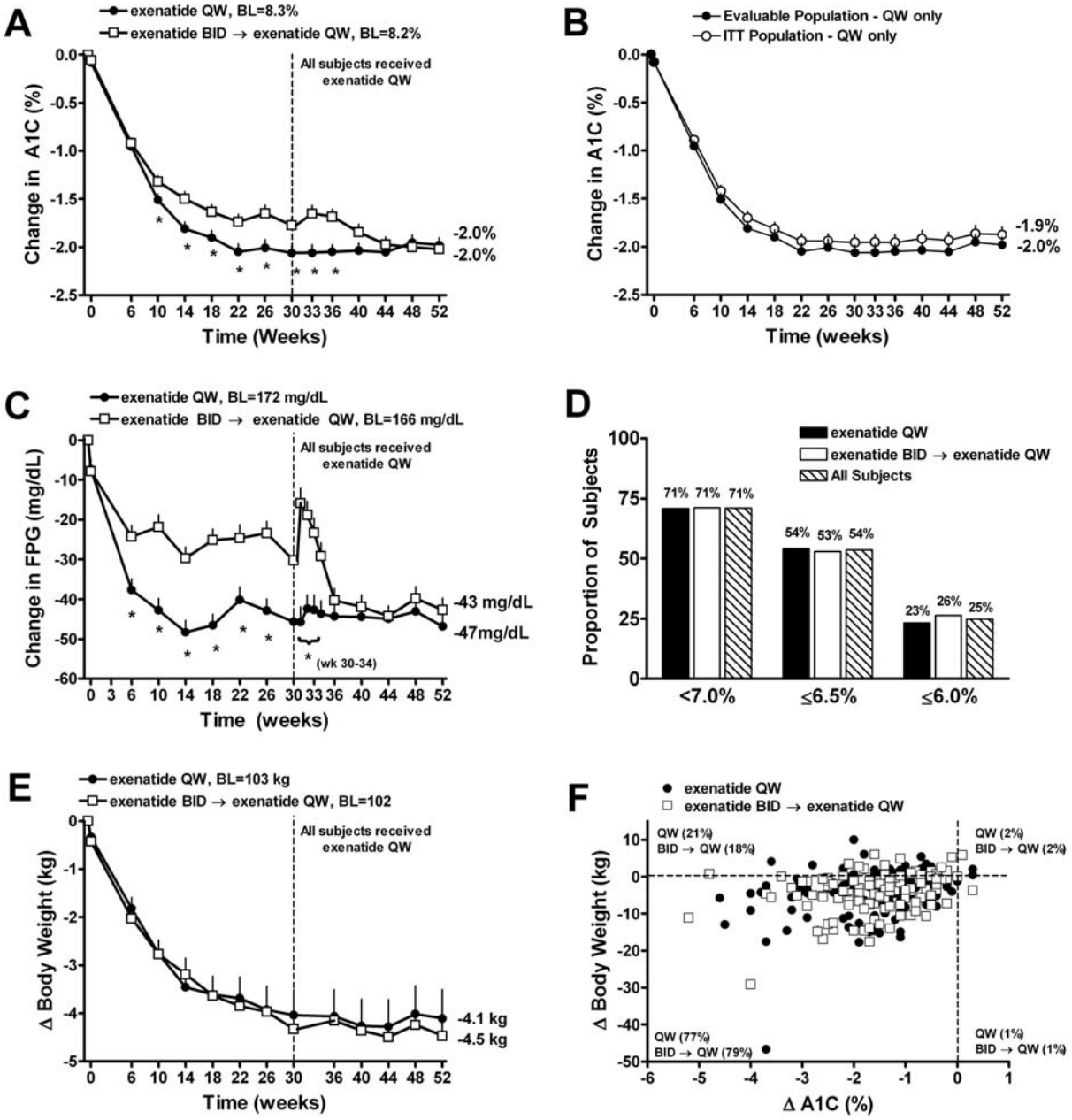
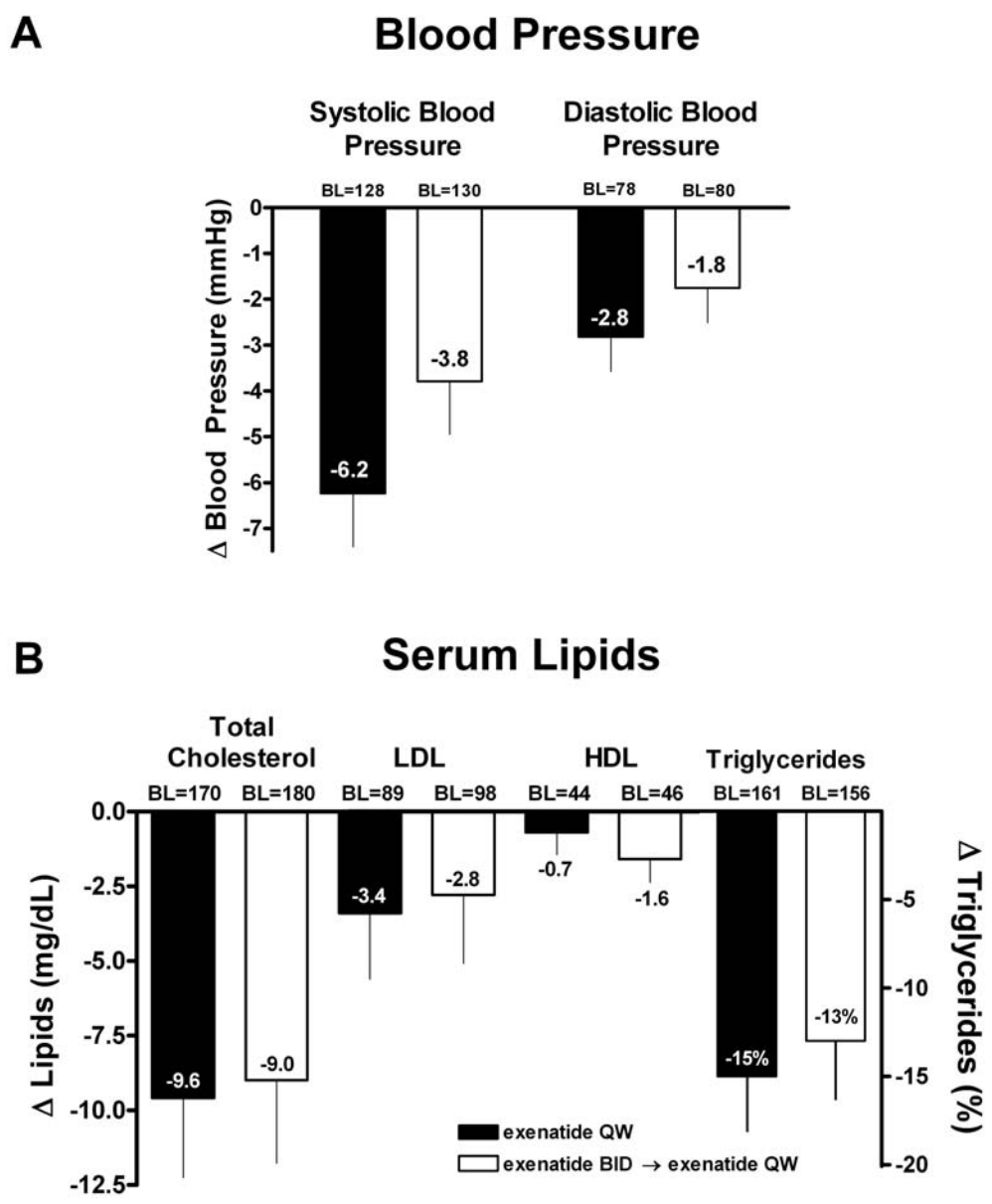

A
exenatide QW, BL=8.3%
exenatide BID → exenatide QW, BL=8.2%
All subjects received exenatide QW
Change in A1C (%)
Time (Weeks)
-2.0%
-2.0%
B
Evaluable Population - QW only
ITT Population - QW only
Change in A1C (%)
Time (weeks)
-1.9%
-2.0%
C
exenatide QW, BL=172 mg/dL
exenatide BID → exenatide QW, BL=166 mg/dL
All subjects received exenatide QW
Change in FPG (mg/dL)
Time (weeks)
-43 mg/dL
-47mg/dL
(wk 30-34)
D
exenatide QW
exenatide BID → exenatide QW
All Subjects
Proportion of Subjects
71% 71% 71%
54% 53% 54%
23% 26% 25%
<7.0%
≤6.5%
≤6.0%
E
exenatide QW, BL=103 kg
exenatide BID → exenatide QW, BL=102
All subjects received exenatide QW
Δ Body Weight (kg)
Time (weeks)
-4.1 kg
-4.5 kg
F
exenatide QW
exenatide BID → exenatide QW
QW (21%)
BID → QW (18%)
QW (2%)
BID → QW (2%)
QW (77%)
BID → QW (79%)
QW (1%)
BID → QW (1%)
Δ Body Weight (kg)
Δ A1C (%)

Figure 3


A
Blood Pressure
Systolic Blood Pressure
Diastolic Blood Pressure
BL=128
BL=130
BL=78
BL=80
Δ Blood Pressure (mmHg)
0
-1
-2
-3
-4
-5
-6
-7
-6.2
-3.8
-2.8
-1.8
B
Serum Lipids
Total Cholesterol
LDL
HDL
Triglycerides
BL=170
BL=180
BL=89
BL=98
BL=44
BL=46
BL=161
BL=156
Δ Lipids (mg/dL)
0.0
-2.5
-5.0
-7.5
-10.0
-12.5
-9.6
-9.0
-3.4
-2.8
-0.7
-1.6
-15%
-13%
Δ Triglycerides (%)
-5
-10
-15
-20
exenatide QW
exenatide BID → exenatide QW