Effects Of Exenatide Plus Rosiglitazone On Beta Cell Function And Insulin Sensitivity In Subjects With Type 2 Diabetes On Metformin

Running Title: Exenatide Plus Rosiglitazone, Metabolic Effects

Ralph A. DeFronzo, MD\textsuperscript{1}, Curtis Triplitt, PharmD\textsuperscript{1}, Yongming Qu, PhD\textsuperscript{2}, Michelle S. Lewis, PhD\textsuperscript{3}, David Maggs, MD\textsuperscript{4}, Leonard C. Glass, MD\textsuperscript{2}

A list of participating investigators is available online at http://care.diabetesjournals.org

\textsuperscript{1}Division of Diabetes, Department of Medicine, University of Texas Health Science Center, San Antonio, TX, USA; \textsuperscript{2}Eli Lilly and Company, Indianapolis, IN; \textsuperscript{3}US Medical Division, Lilly USA, LLC; \textsuperscript{4}Amylin Pharmaceuticals, San Diego, CA.

Address Correspondence to:
Ralph A. DeFronzo, MD
Email: albarado@uthscsa.edu

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

Clinical Trial Registration No.: NCT00135330; (www.clinicaltrials.gov)

Submitted 14 August 2009 and accepted 20 January 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.
Objective. Study the effects of exenatide (EXE) plus rosiglitazone (ROSI) on beta-cell function and insulin sensitivity using hyperglycemic and euglycemic insulin clamp techniques in participants with type 2 diabetes on metformin.

Research Design and Methods. In this 20-week, randomized, open-label, multicenter study, participants (mean age 56 ± 10 years, weight 93 ± 16 kg, A1C 7.8 ± 0.7%) continued their metformin regimen and received either EXE 10 µg twice daily (BID) (n = 45), ROSI 4 mg BID (n = 45), or EXE 10 µg BID + ROSI 4 mg BID (n = 47). 73 participants underwent clamp procedures to quantitate insulin secretion and insulin sensitivity.

Results. A1C declined in all groups (P < 0.05), but decreased most with EXE+ROSI (EXE+ROSI -1.3 ± 0.1%; ROSI -1.0 ± 0.1%, EXE -0.9 ± 0.1%; EXE+ROSI vs. EXE or ROSI, P < 0.05). ROSI resulted in weight gain, while EXE and EXE+ROSI resulted in weight loss (EXE -2.8 ± 0.5 kg; EXE+ROSI -1.2 ± 0.5 kg; ROSI +1.5 ± 0.5 kg; P < 0.05 between and within all groups). At week 20, first and second phase insulin secretion was significantly higher in EXE and EXE+ROSI versus ROSI (both P < 0.05). Insulin sensitivity (M value) was significantly higher in EXE+ROSI versus EXE (P = 0.014).

Conclusion. Therapy with EXE plus ROSI offset the weight gain observed with ROSI, and elicited an additive effect on glycemic control, with significant improvements in beta-cell function and insulin sensitivity.
Hyperglycemia in type 2 diabetes is caused by decreased insulin secretion due to progressive beta-cell dysfunction, insulin resistance in peripheral tissues, and increased hepatic glucose output(1,2). Clinical questions focus on treatment approaches that may address these multiple defects and delay the progression of the disease. Although thiazolidinediones (TZDs) have been shown to improve beta-cell function(1-5), their primary effect is to decrease peripheral insulin resistance(6-10), while biguanides decrease hepatic glucose output(11). Exenatide, a glucagon-like peptide-1 (GLP-1) receptor agonist, enhances glucose-dependent insulin secretion and suppresses elevated glucagon levels, resulting in a decline in hepatic glucose output(12-15). Since biguanides, TZDs, and GLP-1 agonists exert their effects on different pathophysiologic defects, it seems reasonable to combine these agents in the treatment strategy.

To improve our understanding of the metabolic effects of combination therapy targeted at pathophysiologic defects in type 2 diabetes, we designed the present study to quantitate insulin secretion and insulin sensitivity when combining exenatide and rosiglitazone versus each therapy alone in patients already on metformin.

**Research Design and Methods**

**Participants:** Seventeen sites in the United States recruited participants with type 2 diabetes from 2006 to 2008. Inclusion criteria included age = 18-75 years, BMI = 25-40 kg/m², stable body weight for at least 6 months prior to screening, glycosylated hemoglobin (A1C) = 6.8%-10.0%, stable dose of metformin for at least 6 weeks prior to screening and no treatment with any other antidiabetic medication, and absence of islet cell autoantibodies. The study was approved at each site by a local institutional review board in accordance with principles described in the Declaration of Helsinki. All participants gave informed written consent before participation.

**Experimental Design:** This was a 20-week, randomized, open-label, comparator-controlled, three-arm, multicenter study. Participants continued their metformin regimen and were randomized and stratified based on study site by computer-generated random sequence to one of 3 treatment groups: (1) exenatide injection (EXE) 5µg BID for the first month, and then 10µg BID thereafter; (2) rosiglitazone (ROSI) 2 mg BID for the first month and then 4 mg BID thereafter; (3) combination of exenatide plus rosiglitazone (EXE+ROSI), dosed as above. Efficacy measurements included A1C, glucose, insulin, C-peptide, lipids and body weight. Safety measurements included adverse events, vital signs, hematology, and chemistries. The study was powered to detect a significant difference in the primary and the secondary endpoints between the EXE+ROSI and ROSI groups. The primary endpoint of the study was the measurement of glucose-potentiated arginine-stimulated incremental insulin area under the curve (ASI-iAUC) during the hyperglycemic clamp test, for which a sample size of 39 would provide 80% power to detect a significant difference of 0.6 in the log-transformed ratio of ASI-iAUC at 20 weeks over baseline. The secondary endpoint was the glucose area under the curve (AUC) from 15 to 180 minutes during the meal challenge. An additional 51 participants (total = 90) who underwent only meal challenges would provide 80% power to detect a significant difference of 380 mmol/L•min between EXE+ROSI and ROSI. Eight of the 17 sites recruited subjects to undergo the hyperglycemic and hyperinsulinemic euglycemic clamp test, in addition to the meal tolerance test. Subjects recruited at these “clamp” sites could
participate only by consenting to all procedures.

**Standardized Meal Challenge:** Participants underwent a standardized meal challenge test after an overnight fast at baseline and endpoint, consisting of 8 ounces of a liquid meal supplement (Boost, Mead Johnson Nutritional: 240 kcal, 4 g fat, 40 g carbohydrate, 10 g protein). Plasma glucose, insulin, and C-peptide were measured at -15, 0, 15, 30, 60, 90, 120, 150, and 180 minutes. At study end, ROSI and/or EXE were administered 15 minutes prior to meal ingestion.

**Hyperglycemic Clamp:** The hyperglycemic clamp was performed at baseline and endpoint as described previously(16). Medications were withheld the morning of the procedure. At endpoint, participants administered study medication 15 minutes prior to the clamp. At time zero, body weight-adjusted IV bolus of 20% glucose was administered over 10 minutes to raise the plasma glucose concentration to approximately 8.3 mmol/L (150 mg/dL) above baseline. A variable glucose infusion was then adjusted to maintain the targeted glucose level. At 80 minutes, an IV bolus of 5 g arginine (dissolved in 50 mL) was given over 45 seconds, and the glucose level was maintained at 8.3 mmol/L (150 mg/dL) above baseline for 30 minutes.

**Hyperinsulinemic Euglycemic Clamp.** Participants returned within one week after the hyperglycemic clamp(16). Medications were withheld the morning of the procedure. Insulin was given as an intravenous (IV) bolus (0.1 units × kg body weight × desired plasma insulin concentration of 100 mU/L) over 10 minutes followed by a continuous infusion at 80 mU/min·m² for 120 minutes. Plasma glucose concentration was maintained at 5 mM, by a variable infusion of 20% glucose.

**Statistical Analyses:** The absolute and incremental AUCs for glucose, insulin, and C-peptide concentrations during the meal challenge and hyperglycemic clamp were calculated by the trapezoid method. For the meal test, the insulinogenic index (I/G) was calculated by the insulin AUC divided by the glucose AUC, the Matsuda whole-body insulin sensitivity index and the disposition index (I/G × Matsuda was calculated as described by Matsuda et al. (17). The M-value, measured by insulin-stimulated glucose disposal during the euglycemic clamp, was used to quantify whole body insulin sensitivity (16). The insulin secretion/insulin resistance (disposition) index from the clamp tests was calculated by the insulin iAUC multiplied by M/I, where M is the M-value, I is the steady-state plasma insulin concentration during the euglycemic clamp, and iAUC is the incremental area under the curve (17).

Statistical analyses were performed by SAS Drug Development (SAS Inc. Cary, NC). Tests were performed with alpha = 0.05 without adjustment for multiplicities. Unless specified otherwise, all analyses were performed based on the intent-to-treat (ITT) principle and included participants with a baseline and at least one post-baseline value. The least squares mean (LSmean) ± standard error (SE) is reported for all continuous variables except for baseline characteristics, where mean ± standard deviation (SD) is reported. Fisher’s exact test was used to compare categorical variables. An analysis of covariate (ANCOVA) model with treatment group as a factor and baseline value of the dependent variable as a covariate was used to compare continuous variables without repeated measurements after randomization. A mixed model repeated measures (MMRM) approach was used to analyze continuous variables with repeated measurements.

**RESULTS**

**Participant Characteristics:** 137 participants were randomized and received
EXE (45 randomized, 33 completed), EXE+ROSI (47 randomized, 34 completed), ROSI (45 randomized, 34 completed). Seventy-three participants participated in the clamp studies (EXE: 23 with 7 withdrawals, EXE+ROSI: 24 with 6 withdrawals, ROSI: 23 with 7 withdrawals) (Supplemental Figure 1 which is available in the online appendix at http://care.diabetesjournals.org). Four participants withdrew before receiving study medication. For the entire population, baseline characteristics were similar between the three groups (mean ± SD): A1C = 7.8 ± 0.7% ; age = 56 ± 10 years; BMI = 32.5 ± 4.3 kg/m²; diabetes duration = 4.7 ± 3.7 years; number (percent) female = 67 (49%); Caucasian 84 (61%), Hispanic 32 (23%), African American 16 (12%), Others 5 (4%). Corresponding values in the clamp subset were: A1C = 8.0 ± 0.8%; age = 52 ± 9 years; BMI = 32.4 ± 4.2 kg/m²; diabetes duration = 4.7 ± 4.6 years; number (percent) female = 27 (54%); Caucasian 19 (38%), Hispanic 21 (42%), African American 8 (16%), Others 2 (4%).

Metabolic Parameters: A1C decreased in all groups, but the decrement in EXE+ROSI was significantly greater than with EXE or ROSI alone (Table 1). After 20 weeks, fasting plasma glucose (FPG) was significantly reduced to a similar extent in all groups; fasting insulin decreased significantly from baseline with ROSI and EXE+ROSI (P < 0.001), but did not change with EXE (Table 1).

Weight increased significantly in the ROSI group, and decreased significantly in EXE and EXE+ROSI groups (EXE and EXE+ROSI vs. ROSI, P < 0.001) (Table 1). Total cholesterol increased significantly in ROSI and EXE+ROSI, and did not change significantly in the EXE group (Table 1). Fasting HDL cholesterol did not change significantly from baseline in any group. Fasting LDL cholesterol increased significantly from baseline with ROSI (P = 0.001). At endpoint, ROSI had significantly greater fasting LDL than EXE (P = 0.008). Fasting triglycerides declined significantly from baseline with EXE, but the change was not significantly different from other groups (Table 1).

Standardized Meal Challenge: At 20 weeks, the AUC for glucose (AUCG), insulin (AUCI), and C-peptide (AUCCP) significantly decreased for all treatment groups during the meal challenge (Table 2, Figure 1). The AUCG was lower in EXE+ROSI (P = 0.004) and tended to be lower with EXE (P = 0.065) vs. ROSI. AUCI was reduced to a greater extent with ROSI versus EXE (P = 0.047) but this did not reach statistical significance for AUCCP. The insulinogenic index (I/G) increased from baseline by 0.82 µIU-min/mL/mmol-min/L in EXE (P = 0.003), by 0.03 µIU-min/mL/mmol-min/L in EXE+ROSI and decreased from baseline by 0.53 µIU-min/mL/mmol-min/L in ROSI, but these changes were not statistically significant (p = 0.926 and 0.061 for EXE+ROSI and ROSI, respectively) (Table 2). The Matsuda whole-body insulin sensitivity index (17) during the meal challenge was similar in all groups at baseline and increased significantly in all groups at endpoint (all P < 0.05) (Table 2). At endpoint the increase in the Matsuda index was greater in EXE+ROSI vs. EXE (P = 0.015) (Table 2). The disposition index (I/G × Matsuda) was significantly improved in all groups, but there were no significant differences between groups at endpoint (Table 2).

Insulin Secretion, Hyperglycemic Clamp: In the 50 participants who completed the baseline and endpoint hyperglycemic clamps (Figure 1), first phase (0-10 minutes) and second phase (10-70 minutes) insulin iAUC were increased from baseline with both EXE and EXE+ROSI (both P < 0.05) but not with ROSI (Table 2, Figure 1), and the increase in insulin iAUC tended to be greater
in EXE vs. EXE+ROSI (P = 0.09). ASI-iAUC, a measure of beta cell secretory capacity, was significantly increased with EXE (Table 2). At 20 weeks, ASI-iAUC was significantly higher with EXE versus EXE+ROSI and ROSI (both P < 0.05). C-peptide iAUC results paralleled the insulin iAUC results (data not shown).

Insulin Sensitivity, Euglycemic Insulin Clamp: Forty-seven participants completed both baseline and endpoint euglycemic insulin clamps. EXE+ROSI and ROSI significantly improved the M-value at 20 weeks (P < 0.05), while EXE had no significant effect on insulin-stimulated glucose disposal. When M was adjusted for the steady-state plasma insulin concentration during the clamp (M/I), similar results were observed (Figure 2).

Beta-Cell Function: The disposition index, derived from the hyperglycemic and euglycemic insulin clamps, provides the gold standard measure of beta cell function (17). The disposition index from 80-90 minutes of the hyperglycemic clamp increased significantly and similarly with EXE and EXE+ROSI (both P < 0.001) but not with ROSI (Figure 2). The disposition index from 0-70 minutes during the hyperglycemic clamp increased with EXE and EXE+ROSI (both P < 0.001) but not with ROSI.

Safety: The most common adverse events were nausea (EXE 47%; EXE+ROSI 47%; ROSI 4%), vomiting (EXE 22%; EXE + ROSI 19%; ROSI 0%), and diarrhea (EXE 7%; EXE+ROSI 21%; ROSI 4%). Two participants in EXE discontinued due to nausea; two in EXE+ROSI discontinued due to nausea, one due to vomiting, and one due to breast cancer); one participant in ROSI discontinued due to peripheral edema. Pedal edema occurred in 21 (47%) of ROSI participants vs. 8 (18%) treated with EXE (P = 0.007). Fourteen participants (30%) in ROSI+EXE developed pedal edema (P = NS vs. EXE and vs. ROSI). The occurrence of hypoglycemia (defined as signs or symptoms associated with hypoglycemia and with a glucose meter reading of < 3.0 mmol/L) was not significantly different among EXE (n = 2), EXE + ROSI (n = 2), and ROSI (n = 0). One participant treated with EXE+ROSI reported severe hypoglycemia, defined as requiring the assistance of another person and associated with a glucose meter reading of < 2.84 mmol/L.

Discussion

Abnormalities in both insulin action and insulin secretion occur early in the pathogenesis of diabetes(1;2;18-24). Therefore, treatment of type 2 diabetes should be initiated early and target these pathogenic mechanisms in order to improve beta-cell function and ameliorate the underlying insulin resistance.

This is the first study to examine the metabolic effects of combined TZD (rosiglitazone) and GLP-1 (exenatide) therapy in inadequately controlled (mean A1C=7.8 ± 0.7%) metformin-treated patients. Limitations include the open label design and, despite randomization, a slightly lower baseline M value in the EXE+ROSI group. As per study design, study medications were given prior to the procedures, and, although this prevented discrimination between the acute and chronic effects of these therapies, the primary aim was to study the effects of these therapies as used in general practice.

The incidence of gastrointestinal side effects was higher in subjects treated with exenatide and pedal edema was more common in those on rosiglitazone. While the overall percentage of subjects withdrawing from the study due to adverse events was higher in the EXE+ROSI group there were no statistically significant differences between treatments in withdrawal rates due to adverse events (EXE 2 [4%]; EXE+ROSI 5 [11%]; ROSI 1 [2%], P > 0.05 between all groups).

The study employs the 'gold' standard measurements of insulin resistance.
Exenatide Plus Rosiglitazone, Metabolic Effects

... (euglycemic insulin clamp) and beta-cell function (disposition index) and demonstrates that exenatide has a major effect to improve beta-cell function, but does not exert any significant insulin sensitizing action as determined by the M value during the insulin clamp. Consistent with recently published results (25), exenatide treatment markedly improved both first and second phase insulin secretion (Table 2, Figure 1); glucose-potentiated, arginine-stimulated insulin secretion increased more than 2-fold following exenatide therapy. The disposition index during the hyperglycemic clamp (0-10, 10-70, and response to arginine stimulation) also increased dramatically. These favorable effects of exenatide on beta-cell function also were observed during the meal tolerance test (I/G × Matsuda index), demonstrating the physiologic relevance of the observations. Further, exenatide significantly reduced weight, A1C (-0.9%) and plasma triglyceride concentrations (-0.34 mmol/L).

Rosiglitazone treatment for 20 weeks reduced A1C (-1.0%) similarly to exenatide, but did so by different mechanisms. The TZD caused a two-fold increase in insulin sensitivity, measured as M/I during the euglycemic insulin clamp or the Matsuda index during the meal tolerance test. The improvement in insulin sensitivity was associated with significant reduction in the insulin response during the meal tolerance test. Despite the reductions in insulin response, the disposition index during the meal tolerance test increased significantly (Table 2). Thus, in addition to its insulin sensitizing effect, rosiglitazone also improved beta-cell function despite modest weight gain, consistent with previously published results (9).

In metformin-treated patients, combination exenatide-rosiglitazone therapy reduced A1C (Δ=-1.3%) to a greater extent than either exenatide alone (Δ=-0.9%) or rosiglitazone alone (Δ=-1.0%). This greater reduction in A1C primarily was accounted for by a greater reduction in postprandial plasma glucose excursion after the meal (Table 2) with a similar decrement in FPG (Table 1). The beneficial effect of EXE+ROSI on A1C was due to two factors: (i) a significantly greater improvement in insulin sensitivity (M/I during the insulin clamp) (Figure 2) and (ii) a significant improvement in beta-cell function as measured by the disposition index. Although the amount of insulin secreted in response to glucose alone or with arginine during the hyperglycemic clamp was markedly reduced in the group receiving combination therapy compared to exenatide alone, the disposition index of beta-cell function was similar in the exenatide and EXE+ROSI groups. This indicates that combination therapy improves insulin secretion as a function of insulin sensitivity. These improvements in glucose metabolism were accompanied by a decrease in weight, in contrast to the weight gain observed with rosiglitazone alone.

Although studies of longer duration and with a larger number of subjects will be necessary to examine the long-term effects of combination therapy with exenatide plus a TZD in type 2 diabetic patients inadequately controlled on metformin, the present results indicate that this combination improves both insulin resistance and the defect in insulin secretion.

ACKNOWLEDGMENTS

We thank Dr. Mark Hartman and Dr. John Holcombe for their careful scientific review of the manuscript, Rebeca Wolfe and Eric Meskimen for coordination of the study, Ying Guo for statistical analysis support, and Lorrie Albarado for administrative support. Disclosure. Dr. DeFronzo receives grants from Bristol Myers Squibb, Amylin, Eli Lilly, Novartis, Pfizer, Takeda, Roche, and Merck, participates in Speakers Bureau for Amylin, Eli Lilly, and Takeda, and is on the Advisory
Boards for Bristol Myers Squibb, Amylin, Eli Lilly, Novartis, Pfizer, Takeda, Roche, Merck, and Johnson & Johnson. Dr. Triplitt participates in Speaker’s Bureau for Amylin and Eli Lilly, and is on the Advisory Board for Amylin. Drs Glass, Qu, and Lewis are employed by Lilly and Dr. Maggs is employed by Amylin. Previous presentation: DeFronzo RA, Triplitt C, Qu Y, Lewis MS, Gray A, Maggs D, Glass LC. Effects of Exenatide plus Rosiglitazone on Beta Cell Function and Insulin Sensitivity in Subjects with Type 2 Diabetes on Metformin. Presented at: American Diabetes Association; 2009; New Orleans, LA. Poster presentation.

**Figure Legend**

**Figure 1.** Glucose and insulin concentrations during the meal challenge test and insulin concentrations during the hyperglycemic clamp before (closed squares, broken line) and after (open circles, solid line) treatment with EXE, EXE + ROSI, or ROSI. Arrows indicate time of arginine stimulation (ARG) during the hyperglycemic clamp. Data are presented as LSmean ± SE for the meal challenge test and LSmean for the hyperglycemic clamp.

**Figure 2.** Disposition index, M value, and M/I index before (white bar) and after (black bar) treatment with EXE, EXE + ROSI, and ROSI. *P < 0.05 when compared to baseline, †P < 0.05 between EXE + ROSI and ROSI at baseline. Data are LSmean ± SE. Abbreviations: BL = baseline; E = exenatide; E+R = exenatide plus rosiglitazone; EP = endpoint; I= steady-state plasma insulin concentration during the euglycemic clamp; M= insulin-stimulated glucose disposal during the euglycemic clamp; R = rosiglitazone
REFERENCES
1. Reaven, GM: Banting lecture 1988. Role of insulin resistance in human disease. *Diabetes* 37:1595-1607, 1988
2. Wajchenberg, BL: beta-cell failure in diabetes and preservation by clinical treatment. *Endocr Rev* 28:187-218, 2007
3. Buchanan, TA, Xiang, AH, Peters, RK, Kjos, SL, Marroquin, A, Goico, J, Ochoa, C, Tan, S, Berkowitz, K, Hodis, HN, Azen, SP: Preservation of pancreatic beta-cell function and prevention of type 2 diabetes by pharmacological treatment of insulin resistance in high-risk Hispanic women. *Diabetes* 51:2796-2803, 2002
4. Gastaldelli, A, Ferrannini, E, Miyazaki, Y, Matsuda, M, Mari, A, DeFronzo, RA: Thiazolidinediones improve beta-cell function in type 2 diabetic patients. *Am J Physiol Endocrinol Metab* 292:E871-E883, 2007
5. Kahn, SE, Haffner, SM, Heise, MA, Herman, WH, Holman, RR, Jones, NP, Kravitz, BG, Lachin, JM, O'Neill, MC, Zinman, B, Viberti, G: Glycemic durability of rosiglitazone, metformin, or glyburide monotherapy. *N Engl J Med* 355:2427-2443, 2006
6. Bajaj, M, Suraamornkul, S, Piper, P, Hardies, LJ, Glass, L, Cersosimo, E, Pratipanawatr, T, Miyazaki, Y, DeFronzo, RA: Decreased plasma adiponectin concentrations are closely related to hepatic fat content and hepatic insulin resistance in pioglitazone-treated type 2 diabetic patients. *J Clin Endocrinol Metab* 89:200-206, 2004
7. Bajaj, M, Suraamornkul, S, Romanelli, A, Cline, GW, Mandarino, LJ, Shulman, GI, DeFronzo, RA: Effect of a sustained reduction in plasma free fatty acid concentration on intramuscular long-chain fatty Acyl-CoAs and insulin action in type 2 diabetic patients. *Diabetes* 54:3148-3153, 2005
8. DeFronzo, RA: Pharmacologic therapy for type 2 diabetes mellitus. *Ann Intern Med* 131:281-303, 1999
9. Miyazaki, Y, Glass, L, Triplitt, C, Matsuda, M, Cusi, K, Mahankali, A, Mahankali, S, Mandarino, LJ, DeFronzo, RA: Effect of rosiglitazone on glucose and non-esterified fatty acid metabolism in Type II diabetic patients. *Diabetologia* 44:2210-2219, 2001
10. Miyazaki, Y, He, H, Mandarino, LJ, DeFronzo, RA: Rosiglitazone improves downstream insulin receptor signaling in type 2 diabetic patients. *Diabetes* 52:1943-1950, 2003
11. DeFronzo, RA, Barzilai, N, Simonson, DC: Mechanism of metformin action in obese and lean noninsulin-dependent diabetic subjects. *J Clin Endocrinol Metab* 73:1294-1301, 1991
12. Vilsboll, T: On the role of the incretin hormones GIP and GLP-1 in the pathogenesis of Type 2 diabetes mellitus. *Dan Med Bull* 51:364-370, 2004
13. San Diego, CA. Amylin Pharmaceuticals Inc. Byetta® (exenatide) injection [package insert]. 2008. Ref Type: Generic
14. Egan, JM, Clocquet, 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* 87:1282-1290, 2002
15. Vilsboll, T, Toft-Nielsen, MB, Krarup, T, Madsbad, S, Dinesen, B, Holst, JJ: Evaluation of beta-cell secretory capacity using glucagon-like peptide 1. *Diabetes Care* 23:807-812, 2000
16. DeFronzo, RA, Tobin, JD, Andres, R: Glucose clamp technique: a method for quantifying insulin secretion and resistance. *Am J Physiol* 237:E214-E223, 1979
17. Matsuda,M, DeFronzo,RA: Insulin sensitivity indices obtained from oral glucose tolerance testing: comparison with the euglycemic insulin clamp. *Diabetes Care* 22:1462-1470, 1999
18. DeFronzo,RA: From the Triumvirate to the Ominous Octet: A New Paradigm for the Treatment of Type 2 Diabetes Mellitus. *Diabetes* 58:773-795, 2009
19. DeFronzo,RA: Lilly lecture 1987. The triumvirate: beta-cell, muscle, liver. A collusion responsible for NIDDM. *Diabetes* 37:667-687, 1988
20. Gastaldelli,A, Ferrannini,E, Miyazaki,Y, Matsuda,M, DeFronzo,RA: Beta-cell dysfunction and glucose intolerance: results from the San Antonio metabolism (SAM) study. *Diabetologia* 47:31-39, 2004
21. Abdul-Ghani,MA, Jenkinson,CP, Richardson,DK, Tripathy,D, DeFronzo,RA: Insulin secretion and action in subjects with impaired fasting glucose and impaired glucose tolerance: results from the Veterans Administration Genetic Epidemiology Study. *Diabetes* 55:1430-1435, 2006
22. Weyer,C, Bogardus,C, Mott,DM, Pratley,RE: The natural history of insulin secretory dysfunction and insulin resistance in the pathogenesis of type 2 diabetes mellitus. *J Clin Invest* 104:787-794, 1999
23. Ferrannini,E, Gastaldelli,A, Miyazaki,Y, Matsuda,M, Mari,A, DeFronzo,RA: Beta-Cell function in subjects spanning the range from normal glucose tolerance to overt diabetes: a new analysis. *J Clin Endocrinol Metab* 90:493-500, 2005
24. Jallut,D, Golay,A, Munger,R, Frascarolo,P, Schutz,Y, Jequier,E, Felber,JP: Impaired glucose tolerance and diabetes in obesity: a 6-year follow-up study of glucose metabolism. *Metabolism* 39:1068-1075, 1990
25. Bunck,MC, Diamant,M, Corner,A, Eliasson,B, Malloy,IL, Shaginian,RM, Deng,W, Kendall,DM, Taskinen,MR, Smith,U, Yki-Jarvinen,H, Heine,RJ: One-Year Treatment With Exenatide Improves Beta-Cell Function, Compared To Insulin Glargine, In Metformin Treated Type 2 Diabetes Patients: A Randomized, Controlled Trial. *Diabetes Care* 32:762-768, 2009
### Table 1. Metabolic Parameters

| Parameter                          | LS Mean ± SE       | P-Value       |
|------------------------------------|--------------------|---------------|
|                                   | EXE (n = 45)       | EXE+ROSI (n = 47) | EXE (n = 45) | EXE vs. EXE+ROSI | EXE vs. ROSI | EXE+ROSI vs. ROSI |
| **HbA1c (%)**                      |                    |               |              |                 |             |                |
| Baseline                           | 7.8 ± 0.1          | 7.8 ± 0.1     | 7.9 ± 0.1    | 0.016           | 0.720       | 0.039           |
| 20 weeks                           | 7.0 ± 0.1*         | 6.6 ± 0.1*    | 6.9 ± 0.1*   | < 0.001         | < 0.001     | < 0.001         |
| Change                             | -0.9 ± 0.1         | -1.3 ± 0.1    | -1.0 ± 0.1   |                |             |                |
| **Weight (kg)**                    |                    |               |              |                 |             |                |
| Baseline                           | 93.0 ± 2.4         | 93.8 ± 2.4    | 91.8 ± 2.4   | 0.038           | < 0.001     | < 0.001         |
| 20 weeks                           | 89.7 ± 0.5*        | 91.3 ± 0.5*   | 94.0 ± 0.5*  | < 0.001         | 0.01        | 0.316           |
| Change                             | -2.8 ± 0.5         | -1.2 ± 0.5    | 1.5 ± 0.5    | 0.693           | 0.331       | 0.555           |
| **Fasting glucose (mmol/L)**       |                    |               |              |                 |             |                |
| Baseline                           | 8.42 ± 0.28        | 8.43 ± 0.27   | 8.48 ± 0.27  | < 0.001         | 0.01        | 0.316           |
| 20 weeks                           | 6.98 ± 0.25*       | 6.84 ± 0.24*  | 6.63 ± 0.25* | < 0.001         | 0.01        | 0.316           |
| Change                             | -1.46 ± 0.25       | -1.60 ± 0.24  | -1.80 ± 0.25 | 0.693           | 0.331       | 0.555           |
| **Fasting insulin (µIU/ml)**       |                    |               |              |                 |             |                |
| Baseline                           | 17.9 ± 2.0         | 13.8 ± 2.0    | 16.2 ± 2.0   | < 0.001         | 0.01        | 0.316           |
| 20 weeks                           | 16.3 ± 1.2         | 10.2 ± 1.2*   | 11.9 ± 1.2*  | < 0.001         | 0.01        | 0.316           |
| Change                             | 0.2 ± 1.2          | -5.9 ± 1.2    | -4.2 ± 1.2   |                |             |                |
| **Total fasting cholesterol (mmol/L)** |                |              |              |                 |             |                |
| Baseline                           | 4.42 ± 0.15        | 4.41 ± 0.14   | 4.62 ± 0.15  |                |             |                |
| 20 weeks                           | 4.33 ± 0.12        | 4.71 ± 0.11*  | 4.89 ± 0.12* | < 0.001         | < 0.001     | 0.276           |
| Change                             | -0.13 ± 0.12       | 0.26 ± 0.11   | 0.44 ± 0.12  | 0.020           | < 0.001     | 0.276           |
| **Fasting HDL (mmol/L)**           |                    |               |              |                 |             |                |
| Baseline                           | 1.13 ± 0.05        | 1.17 ± 0.05   | 1.17 ± 0.05  | < 0.001         | 0.01        | 0.316           |
| 20 weeks                           | 1.16 ± 0.03        | 1.19 ± 0.03   | 1.20 ± 0.03  | < 0.001         | 0.01        | 0.316           |
| Change                             | 0.02 ± 0.03        | 0.05 ± 0.03   | 0.06 ± 0.03  | 0.566           | 0.445       | 0.840           |
| **Fasting LDL (mmol/L)**           |                    |               |              |                 |             |                |
| Baseline                           | 2.59 ± 0.13        | 2.57 ± 0.13   | 2.71 ± 0.13  |                |             |                |
| 20 weeks                           | 2.55 ± 0.10        | 2.69 ± 0.10   | 2.93 ± 0.10* | < 0.001         | < 0.001     | 0.096           |
| Change                             | -0.05 ± 0.10       | 0.10 ± 0.10   | 0.33 ± 0.10  | 0.308           | 0.008       | 0.096           |
| **Fasting Triglycerides (mmol/L)** |                    |               |              |                 |             |                |
| Baseline                           | 1.77 ± 0.19        | 1.82 ± 0.18   | 2.14 ± 0.18  |                |             |                |
| 20 weeks                           | 1.59 ± 0.17*       | 1.94 ± 0.16   | 2.01 ± 0.17  | < 0.001         | 0.01        | 0.316           |
| Change                             | -0.34 ± 0.17       | 0.00 ± 0.16   | 0.07 ± 0.17  | 0.140           | 0.079       | 0.752           |
### Table 2. Meal Challenge and Hyperglycemic Clamp Results

|                          | LS Mean ± SE | P-Value          |
|--------------------------|--------------|------------------|
|                          | EXE          | EXE+ROSI        | ROSI           |
|                          |              | p-value          |                |
|                          |              | EXE vs. EXE+ROSI| EXE+ROSI vs. ROSI| EXE vs. ROSI|
| **Meal Challenge**       |              |                  |                |
|                          | (n = 33)     | (n = 34)        | (n = 34)       |
| **Glucose AUC (mmol-min/L)** |            |                  |                |
| Baseline                 | 1783 ± 60    | 1800 ± 60       | 1742 ± 60     |
| Endpoint                 | 1215 ± 51*   | 1140 ± 50*      | 1349 ± 51*    |
| Change                   | -560 ± 51    | -635 ± 50       | -426 ± 51     | 0.296 0.065 0.004 |
| **Insulin AUC (µIU-min/mL)** |            |                  |                |
| Baseline                 | 6116 ± 723   | 5203 ± 712      | 6797 ± 734    |
| Endpoint                 | 5024 ± 339*  | 4152 ± 336*     | 4050 ± 346*   |
| Change                   | -999 ± 339   | -1871 ± 336     | -1973 ± 346   | 0.071 0.047 0.833 |
| **C-peptide AUC (nmol-min/L)** |            |                  |                |
| Baseline                 | 333 ± 18     | 330 ± 18        | 342 ± 18      |
| Endpoint                 | 310 ± 13     | 277 ± 13*       | 282 ± 13*     |
| Change                   | -24 ± 13     | -58 ± 13        | -53 ± 13      | 0.067 0.118 0.805 |
| **I/G Index (AUC) (µIU-min/mL)/(mmol-min/L)** |            |                  |                |
| Baseline                 | 3.64 ± 0.48  | 3.05 ± 0.47     | 4.10 ± 0.48   |
| 20 weeks                 | 4.41 ± 0.27* | 3.61 ± 0.27     | 3.06 ± 0.28   |
| Change                   | 0.82 ± 0.27  | 0.03 ± 0.27     | -0.53 ± 0.28  | 0.041 0.001 0.160 |
| **Matsuda Index**        |              |                  |                |
| Baseline                 | 4.0 ± 0.6    | 4.4 ± 0.6       | 3.4 ± 0.6     |
| 20 weeks                 | 5.6 ± 0.8*   | 8.4 ± 0.8*      | 7.1 ± 0.8*    |
| Change                   | 1.6 ± 0.8    | 4.4 ± 0.8       | 3.1 ± 0.8     | 0.015 0.205 0.258 |
| **I/G (AUC) × Matsuda**  |              |                  |                |
| Baseline                 | 10.8 ± 1.0   | 8.8 ± 1.0       | 10.9 ± 1.0    |
| 20 weeks                 | 17.1 ± 1.4*  | 20.4 ± 1.4*     | 18.4 ± 1.5*   |
| Change                   | 7.0 ± 1.4    | 10.3 ± 1.4      | 8.2 ± 1.5     | 0.111 0.550 0.325 |
| **Hyperglycemic Clamp (µIU-min/ml)** | (n = 16)     | (n = 18)       | (n = 16)      |
| **ASI-iAUC**             |              |                  |                |
| Baseline                 | 643 ± 107    | 686 ± 104       | 786 ± 114     |
| 20 weeks                 | 1449 ± 187*  | 896 ± 182       | 602 ± 200     |
| Change                   | 747 ± 187    | 195 ± 182       | -100 ± 200    | 0.039 0.004 0.282 |
| **First Phase iAUC (0-10 minutes)** |            |                  |                |
| Baseline                 | 6 ± 14       | -10 ± 14        | 23 ± 15       |
| 20 weeks                 | 105 ± 24*    | 59 ± 24*        | 17 ± 26       |
Exenatide Plus Rosiglitazone, Metabolic Effects

| Change                     | 99 ± 24 | 54 ± 25 | 12 ± 26 | 0.195  | 0.018  | 0.252  |
|----------------------------|---------|---------|---------|---------|---------|---------|
| **Second Phase iAUC (10-70 minutes)** |         |         |         |         |         |         |
| Baseline                   | 937 ± 291 | 740 ± 282 | 1125 ± 309 |       |         |         |
| 20 weeks                   | 5436 ± 833* | 3422 ± 813* | 487 ± 891 |       |         |         |
| Change                     | 4513 ± 833 | 2500 ± 813 | -435 ± 891 | 0.09  | < 0.001 | 0.019  |
| **First and Second Phase iAUC (0-70 minutes)** |         |         |         |         |         |         |
| Baseline                   | 955 ± 306 | 742 ± 297 | 1162 ± 326 |       |         |         |
| 20 weeks                   | 5611 ± 862* | 3527 ± 842* | 503 ± 922 |       |         |         |
| Change                     | 4671 ± 862 | 2587 ± 842 | -437 ± 922 | 0.09  | < 0.001 | 0.02   |

Abbreviations: ASI-iAUC = arginine-stimulated incremental area under the curve; AUC = area under the curve; EXE = exenatide; iAUC = insulin area under the curve; LSmean = least squares mean; ROSI = rosiglitazone; SE = standard error.

*P < 0.05 from baseline. Data are LSmeans ± SE.

Matsuda Index = \(\frac{10,000 \times FPG \times FPI}{G2}\), where FPG and FPI = fasting plasma glucose and insulin and G2 = average glucose during the meal challenge.

**Figure 1**

### MEAL CHALLENGE

- **EXE**
- **EXE+ROSI**
- **ROSI**

### HYPERGLYCEMIC CLAMP

- **ARG**
Exenatide Plus Rosiglitazone, Metabolic Effects

Figure 2

HYPERGLYCEMIC CLAMP

Disposition Index: Arginine stimulation

Disposition Index: 1st and 2nd phase

INSULIN CLAMP

M Value

M/I Index × 100

E (n=15)  E+R (n=16)  R (n=14)

E (n=16)  E+R (n=16)  R (n=15)

E (n=15)  E+R (n=16)  R (n=14)