

Bon Secours Richmond  
Pharmacy & Therapeutics Committees  
Exenatide (BYETTA®)  
5/2006

**Overview:**

Byetta is an injectable synthetic peptide (incretin mimetic), given twice daily within 60 minutes before meals, with actions including the following: increased glucose-dependent insulin secretion, improved first phase insulin release, inhibition of glucagon secretion during periods of hyperglycemia, delayed gastric emptying, decreased food intake, and dose dependent weight loss of 0.5-3 kg. It is supplied as a pen injector, 5 mcg and 10 mcg sizes, each containing one month's therapy. It must be refrigerated. It is indicated for type II diabetics receiving metformin, a sulfonylurea, or a combination of the two. Byetta has a high rate of nausea, 44%, and vomiting, 13%, which decreases slowly over the next 6 months, at which time the rates are still multiple times the placebo rate. Weight loss occurs independently of nausea and vomiting, but does not approach the 10% weight reduction required to improved cardiovascular risk factors. It has a high rate of hypoglycemia when combined with a sulfonylurea or the combination of sulfonylurea and metformin. A decrease in HAlc of approximately 0.5 –1% occurs with 5 mcg and 10 mcg bid respectively. Byetta is renally eliminated and is not recommended if the creatinine clearance is less than 30 ml/min. As with other agents used for type II diabetics there appears to be a waning of effectiveness and HAlc levels increase over time. It is the most expensive antidiabetic agent currently on the market.

**Recommendations:**

- At this time it is not recommended to add BYETTA to formulary.
- Initiation of therapy in Byetta naive patients in the hospital is not recommended due to the high initial rate of nausea and vomiting.
- Patients using Byetta at home may continue to use their medication from home while in the hospital.
  - Patients still experiencing nausea and/or vomiting secondary to Byetta should not continue Byetta in the hospital as it may complicate their clinical picture.

Cost Analysis for Approximately 30 Day Supply			
Description	Strength	Size	Acquisition Cost
NOVOLIN N	100 Units/ml	10 ml	\$10.98
NOVOLIN NPH PEN	150 Units/1.5ml	5 x 1.5ml	\$41.69
BYETTA 10 mcg PEN	250 mcg/ml	2.4 ml	\$177.66
BYETTA 5 mcg PEN	250 mcg/ml	1.2 ml	\$151.39

**Table 2: Incidence (%) of Hypoglycemia\* by Concomitant Antidiabetic Therapy**

	BYETTA			BYETTA			BYETTA		
	Placebo	5 mcg	10 mcg	Placebo	5 mcg	10 mcg	Placebo	5 mcg	10 mcg
	BID	BID	BID	BID	BID	BID	BID	BID	BID
	With Metformin			With a Sulfonylurea			With MET/SFU		
N	113	110	113	123	125	129	247	245	241
Hypoglycemia	5.3%	4.5%	5.3%	3.3%	14.4%	35.7%	12.6%	19.2%	27.8%

\* In three 30-week placebo-controlled clinical trials.

BYETTA and placebo were administered before the morning and evening meals.

Abbreviations: BID, twice daily; MET/SFU, metformin and a sulfonylurea.

**Table 3: Frequent Treatment-Emergent Adverse Events ( $\geq 5\%$  Incidence and Greater Incidence With BYETTA Treatment) Excluding Hypoglycemia\***

	Placebo BID N = 483	All BYETTA BID N = 963
	%	%
Nausea	18	44
Vomiting	4	13
Diarrhea	6	13
Feeling Jittery	4	9
Dizziness	6	9
Headache	6	9
Dyspepsia	3	6

\* In three 30-week placebo-controlled clinical trials.

GI side effects are dose dependent and severity decreases over time in most patients.



Byetta's molecular weight is 4186 daltons, amino acid sequence

H-His-Gly-Glu-Gly-Thr-Phe-Thr-Ser-Asp-Leu-Ser-Lys-Gln-Met-Glu-Glu-Glu-Ala-Val-Arg-Leu-Phe-Ile-Glu-Tyr-Leu-Lys-Asn-Gly-Gly-Pro-Ser-Ser-Gly-Ala-Pro-Pro-Pro-Ser-NH<sub>2</sub>

#### Findings:

- Progressive beta-cell dysfunction and insulin resistance are the core defects of type 2 diabetes, resulting in hyperglycemia and a host of devastating microvascular and cardiovascular complications.
- When diet and exercise modifications no longer maintain glycemic targets, oral blood glucose-lowering drugs are usually administered. However, the long-term effectiveness of these drugs can be unsatisfactory because of modest or short-lived efficacy, adverse effects and tolerability issues, and an inability to affect the progressive decline in beta-cell function.
- When 1 or more oral blood glucose-lowering drugs no longer adequately control escalating hyperglycemia, addition of basal insulin is common practice.
- Although basal insulin can improve glycemic control, its use can be complicated by inadequate control of postprandial hyperglycemia, an increased risk for hypoglycemia compared with that observed with oral blood glucose-lowering drugs alone, and the need for complicated dose-titration regimens.
- In addition, insulin therapy often causes weight gain, compounding any preexisting obesity – a common contributing factor to insulin resistance that is difficult to manage effectively.

- Glucagon-like peptide-1 (GLP-1), an incretin hormone, is an essential component of normal glucose homeostasis. The actions of GLP-1 include enhancement of glucose-dependent insulin secretion and regulation of glucagon release and the rate of gastric emptying, thereby reducing hyperglycemia. In addition, GLP-1 enhances beta-cell function and promotes satiety, resulting in reduced caloric intake and weight reduction.
- Incretin mimetics are an emerging class of compounds that elicit glucoregulatory actions similar to those of GLP-1. BYETTA® (exenatide) belongs to this class of agents and shares many of the same glucoregulatory actions. However, unlike GLP-1 which is rapidly inactivated by dipeptidyl peptidase-IV (the active form of GLP-1 has a half-life of 1-2 minutes), exenatide is resistant to degradation and has a pharmacokinetic profile that is more amenable to long-term administration.
- Studies have shown that a 10% weight loss lower glucose and improves cardiovascular risk factors

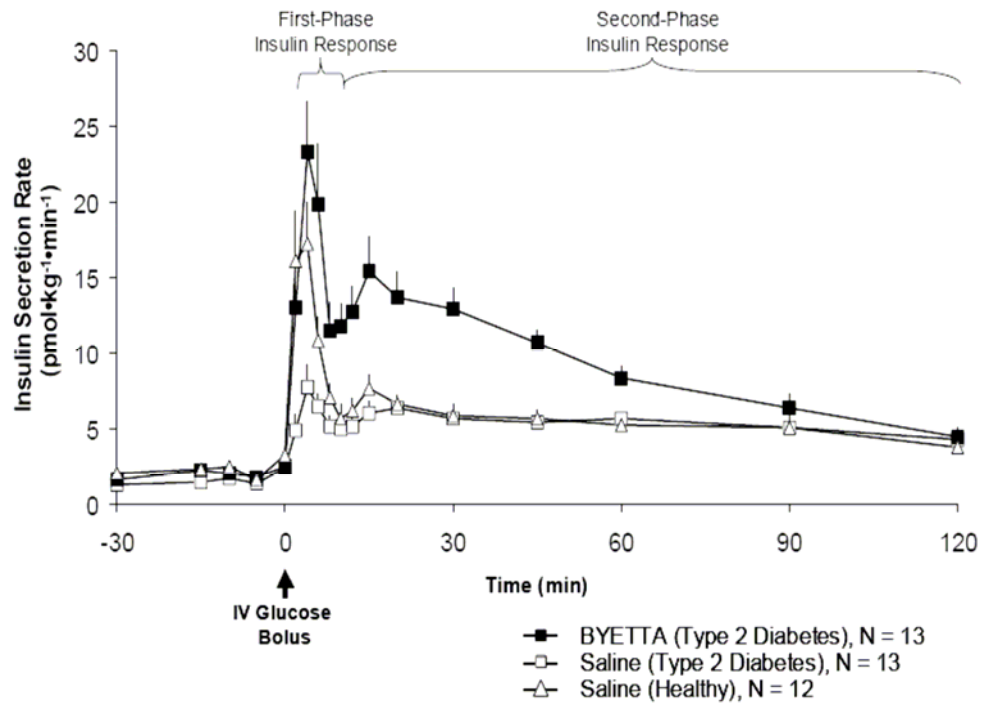
	<b>BYETTA® (exenatide)</b>
Indication	<ul style="list-style-type: none"> <li>Indicated as adjunctive therapy to improve glycemic control in patients with type 2 diabetes mellitus who are taking metformin, a sulfonylurea, or a combination of metformin and a sulfonylurea but have not achieved adequate glycemic control.</li> </ul>
How Supplied	<ul style="list-style-type: none"> <li>Supplied for subcutaneous (SC) injection as a sterile, preserved isotonic solution in a glass cartridge that has been assembled in a pen-injector (pen).</li> <li>Clear and colorless</li> <li>Two prefilled pens are available to deliver unit doses of 5 mcg or 10 mcg. Each prefilled pen will deliver 60 doses to provide 30 days of twice daily administration (BID).</li> </ul>
Ingredients	<ul style="list-style-type: none"> <li>Each milliliter (mL) contains 250 micrograms (mcg) synthetic exenatide, 2.2 mg metacresol as an antimicrobial preservative, mannitol as a tonicity-adjusting agent, and glacial acetic acid and sodium acetate trihydrate in water for injection as a buffering solution at pH 4.5.</li> </ul>
Mechanism of Action	<ul style="list-style-type: none"> <li>Incretins, such as glucagon-like peptide-1 (GLP-1), enhance glucose-dependent insulin secretion and exhibit other antihyperglycemic actions following their release into the circulation from the gut.</li> <li>Exenatide is an incretin mimetic agent that mimics the enhancement of glucose-dependent insulin secretion and several other antihyperglycemic actions of incretins. Actions include glucose-dependent insulin secretion, improved first phase insulin response in type II DM, inhibition of glucagons secretion during periods of elevated blood sugar, delayed gastric emptying, and decrease food intake.</li> </ul>
Absorption	<ul style="list-style-type: none"> <li>SQ administration of exenatide reaches median peak plasma concentrations in 2.1 h.</li> <li>(C<sub>max</sub>) was 211 pg/mL and (AUC<sub>0-inf</sub>) was 1036 pg•h/mL following SC administration of a 10 mcg dose</li> </ul>
Volume of Distribution	<ul style="list-style-type: none"> <li>The mean apparent volume of distribution following SC administration of a single dose is 28.3 L.</li> </ul>
Elimination	<ul style="list-style-type: none"> <li>Renal: predominantly eliminated by glomerular filtration with subsequent proteolytic degradation.</li> </ul>
Clearance	<ul style="list-style-type: none"> <li>The mean apparent clearance in humans is 9.1 L/h.</li> </ul>
Terminal Half-life Normal End stage renal disease	<ul style="list-style-type: none"> <li>2.4 hours</li> <li>21 hours</li> <li><math>K_{elimination} = 0.00289 * Clcr + 0.0318</math></li> </ul>
Dosage	<ul style="list-style-type: none"> <li>Initiate at 5 mcg per dose administered BID at any time within the 60-minute period before the morning and evening meals.</li> <li>Should not be administered after a meal.</li> <li>Based on clinical response, the dose can be increased to 10 mcg twice daily after 1 month of therapy.</li> <li>Each dose should be administered as a SC injection in the</li> </ul>

	<p>thigh, abdomen, or upper arm.</p> <ul style="list-style-type: none"> <li>If added to sulfonylurea therapy, a dosage reduction of the sulfonylurea medication may be considered to reduce the risk of hypoglycemia</li> </ul>
Drug Interactions	<ul style="list-style-type: none"> <li>The effect of exenatide to slow gastric emptying may reduce the extent and rate of absorption of oral drugs.</li> <li>Use caution in patients receiving oral medications that require rapid GI absorption. Take these drugs 1 hour before Byetta</li> </ul>
Adverse Reactions (Common)	<ul style="list-style-type: none"> <li>Endocrine metabolic: Hypoglycemia (5% to 36%)</li> <li>Gastrointestinal: Diarrhea (13%), Dyspepsia (6%), Nausea (44%), Vomiting (13%)</li> <li>Neurologic: Dizziness (9%), Headache (9%), Nervousness (9%)</li> </ul>
Contraindications	<ul style="list-style-type: none"> <li>Should not be used in patients with type 1 diabetes or for treatment of diabetic ketoacidosis</li> <li>Known hypersensitivity to exenatide or any of its components</li> </ul>
Precautions	<ul style="list-style-type: none"> <li>Concurrent use with insulin, thiazolidinediones, D-phenylalanine derivatives, meglitinides, or alpha-glucosidase inhibitors (lack of data)</li> <li>ESRD or severe renal impairment (<math>Cl_{cr} &lt; 30</math> ml/min); not recommended. Gastrointestinal side effects are increased.</li> <li>Severe gastrointestinal disease, including gastroparesis (exenatide is commonly associated with gastrointestinal adverse effects); not recommended</li> <li>Hypoglycemia (increased risk when used with a sulfonylurea)</li> <li>Not a substitute for insulin in insulin-requiring patients</li> </ul>
Pregnancy Category	<ul style="list-style-type: none"> <li>Category C</li> </ul>
Breast Feeding	<ul style="list-style-type: none"> <li>Infant risk cannot be ruled out</li> </ul>

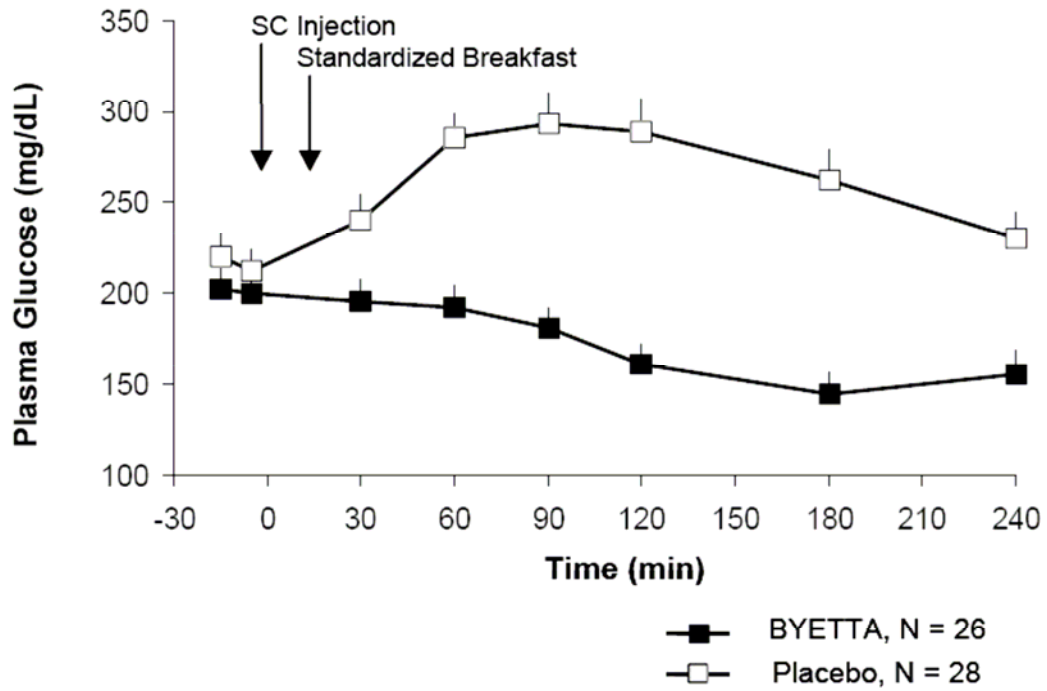
Exenatide Drug Interactions <sup>1</sup>			
Precipitant drug	Object drug <sup>a</sup>		Description
Exenatide	Acetaminophen	↓	When given concomitantly, acetaminophen AUC and $C_{max}$ decreased and $T_{max}$ increased. Give acetaminophen 1 hour before exenatide injection.
Exenatide	Digoxin	↓	Coadministration of repeated doses of exenatide decreased $C_{max}$ 17% and delayed $T_{max}$ approximately 2.5 hours. AUC was not changed.
Exenatide	Lisinopril	↓	Lisinopril steady-state $T_{max}$ was delayed 2 hours.
Exenatide	Lovastatin	↓	Lovastatin AUC and $C_{max}$ were decreased $\approx 40\%$ and $28\%$ , respectively, and $T_{max}$ was delayed approximately 4 hours when administered concomitantly with exenatide.
Exenatide	Oral antibiotics	↓	Advise patients to take oral antibiotics at least 1 hour before exenatide injection.
Exenatide	Oral contraceptives	↓	Advise patients to take oral contraceptives at least 1 hour before exenatide injection.

<sup>a</sup>↓ = drug decrease.

**Figure 1: Mean (+SEM) Insulin Secretion Rate During Infusion of BYETTA or Saline in Patients With Type 2 Diabetes and During Infusion of Saline in Healthy Subjects**

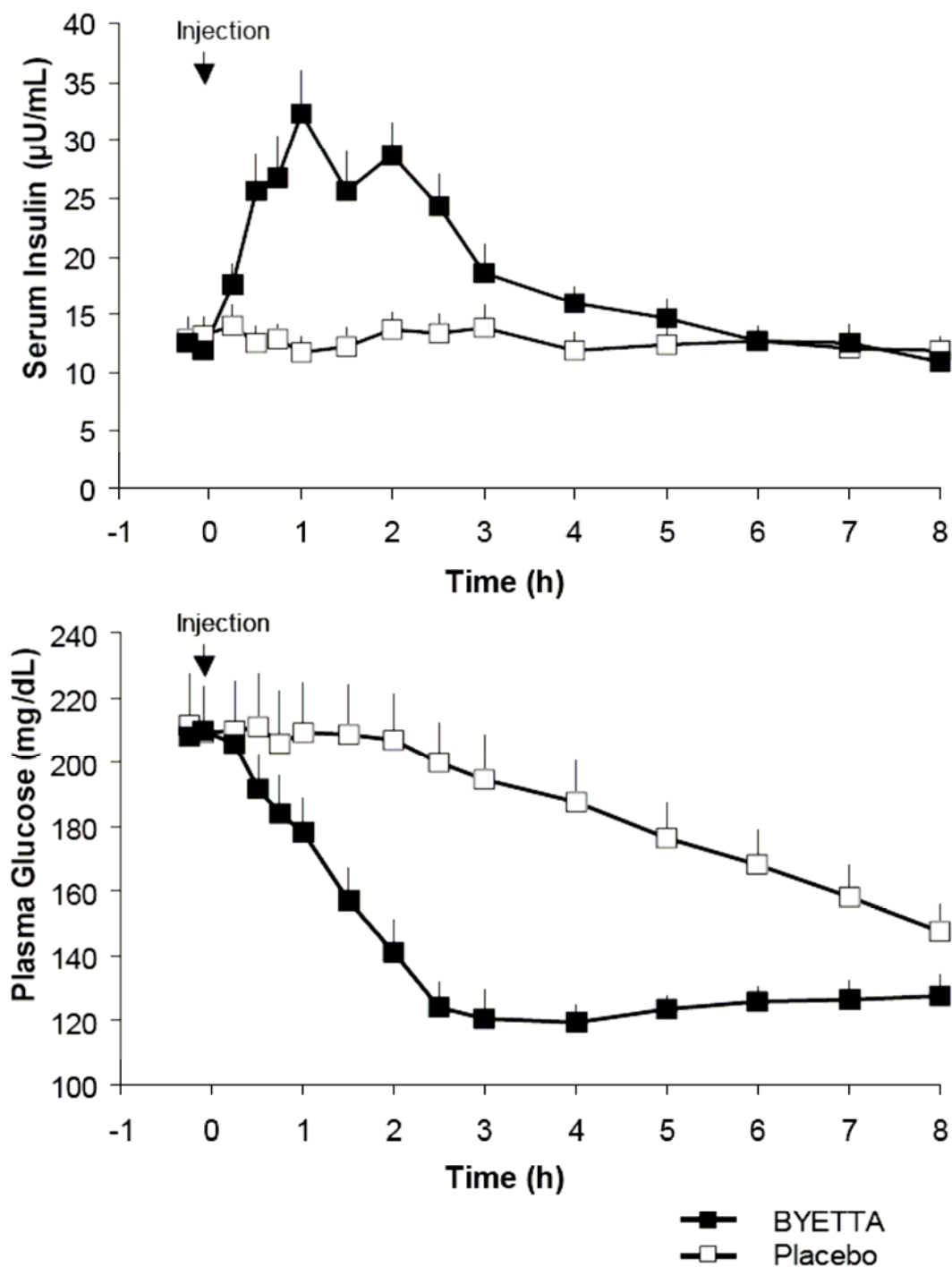


**Figure 2: Mean (+SEM) Postprandial Plasma Glucose Concentrations on Day 1 of BYETTA<sup>a</sup> Treatment in Patients With Type 2 Diabetes Treated With Metformin, a Sulfonylurea, or Both (N = 54)**



<sup>a</sup> Mean dose (7.8 mcg based on body weight) was administered by subcutaneous (SC) injection.

Figure 3: Mean (+SEM) Serum Insulin and Plasma Glucose Concentrations Following a One-Time Injection of BYETTA<sup>a</sup> or Placebo in Fasting Patients With Type 2 Diabetes (N = 12)



<sup>a</sup> BYETTA administration was based on body weight at baseline; mean dose was 9.1 mcg.

**Table 1: Results of Thirty-Week Placebo-Controlled Trials of BYETTA in Patients With Inadequate Glucose Control Despite the Use of Metformin, a Sulfonylurea, or Both**

	Placebo BID	BYETTA 5 mcg BID	BYETTA 10 mcg* BID
	<b>In Combination With Metformin</b>		
<b>Intent-to-Treat Population (N)</b>	113	110	113
<b>HbA<sub>1c</sub> (%), Mean</b>			
Baseline	8.2	8.3	8.2
Change at Week 30	+0.1	-0.4 <sup>†</sup>	-0.8 <sup>‡</sup>
<b>Proportion Achieving HbA<sub>1c</sub> ≤7%<sup>§</sup></b>	13.0%	31.6% <sup>†</sup>	46.4% <sup>†</sup>
<b>Body Weight (kg), Mean</b>			
Baseline	99.9	100.0	100.9
Change at Week 30	-0.3	-1.6 <sup>†</sup>	-2.8 <sup>‡</sup>
	<b>In Combination With a Sulfonylurea</b>		
<b>Intent-to-Treat Population (N)</b>	123	125	129
<b>HbA<sub>1c</sub> (%), Mean</b>			
Baseline	8.7	8.5	8.6
Change at Week 30	+0.1	-0.5 <sup>†</sup>	-0.9 <sup>‡</sup>
<b>Proportion Achieving HbA<sub>1c</sub> ≤7%<sup>§</sup></b>	8.8%	32.6% <sup>†</sup>	41.3% <sup>‡</sup>
<b>Body Weight (kg), Mean</b>			
Baseline	99.1	94.9	95.2
Change at Week 30	-0.6	-0.9	-1.6 <sup>†</sup>
	<b>In Combination With Metformin and a Sulfonylurea</b>		
<b>Intent-to-Treat Population (N)</b>	247	245	241
<b>HbA<sub>1c</sub> (%), Mean</b>			
Baseline	8.5	8.5	8.5
Change at Week 30	+0.2	-0.6 <sup>‡</sup>	-0.8 <sup>‡</sup>
<b>Proportion Achieving HbA<sub>1c</sub> ≤7%<sup>§</sup></b>	9.2%	27.4% <sup>‡</sup>	33.5% <sup>‡</sup>
<b>Body Weight (kg), Mean</b>			
Baseline	99.1	96.9	98.4
Change at Week 30	-0.9	-1.6 <sup>†</sup>	-1.6 <sup>†</sup>

\* BYETTA 5 mcg twice daily (BID) for 1 month followed by 10 mcg BID for 6 months before the morning and evening meals.

† p ≤0.05, treatment vs. placebo

‡ p ≤0.0001, treatment vs. placebo

§ Patients eligible for the analysis with baseline HbA<sub>1c</sub> >7%.

[Horm Metab Res](#). 2005 Oct;37(10):627-32.

**Day-long subcutaneous infusion of exenatide lowers glycemia in patients with type 2 diabetes.**

[Taylor K](#), [Kim D](#), [Nielsen LL](#), [Aisporna M](#), [Baron AD](#), [Fineman MS](#).

Amylin Pharmaceuticals, Inc., San Diego, CA 92121, USA.

Exenatide (exendin-4) is an incretin mimetic with potential antidiabetic activity. This study examined the effects of a continuous subcutaneous (SC) infusion of exenatide (0.2, 0.4, 0.6, or 0.8 microg/kg/day) or placebo (PBO) on glycemic control over 23 h intervals. Twelve subjects with type 2 diabetes treated with metformin and/or diet received 10 infusions (4 exenatide, 6 PBO) on consecutive days. Exenatide was given in a dose-increasing design with at least one placebo infusion between each exenatide infusion, and with meals and a snack provided during the first 14 h of infusion. Plasma exenatide concentrations were dose-proportional. Plasma glucose (4-23 h) was lower in all exenatide arms compared to placebo ( $p < 0.0001$ ). The change in insulin/glucagon ratio and amylin concentrations from pre-infusion to post-infusion was increased ( $p < 0.005$ ,  $p < 0.05$ , respectively) in the combined exenatide arms, but remained unchanged in the placebo groups. Nausea and vomiting were the most common treatment emergent adverse events. Exenatide infusion also appeared to have positive effects on beta-cell and alpha-cell function as measured by proinsulin/insulin ratios and mean glucagon concentrations. In summary, exenatide lowered plasma glucose during both prandial and fasting states when delivered as a continuous SC infusion over twenty-three hours, suggesting that exenatide can provide day-long glycemic control in patients with type 2 diabetes.

[Ann Intern Med](#). 2005 Oct 18;143(8):559-69.

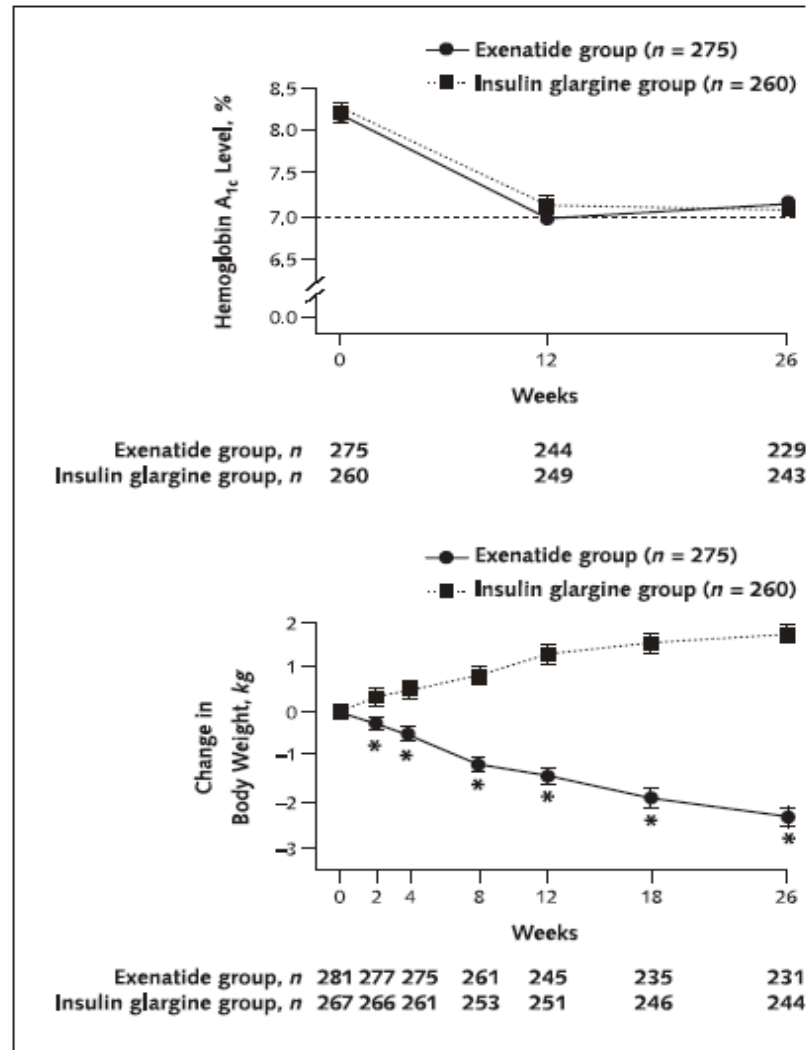
**Exenatide versus insulin glargine in patients with suboptimally controlled type 2 diabetes: a open label randomized trial.**

[Heine RJ](#), [Van Gaal LF](#), [Johns D](#), [Mihm MJ](#), [Widel MH](#), [Brodows RG](#); [GWAA Study Group](#).

VU University Medical Center, Amsterdam, The Netherlands.

**BACKGROUND:** Physicians may use either insulin or exenatide injections for patients with type 2 diabetes mellitus who have poor glycemic control despite taking oral blood glucose-lowering drugs. **OBJECTIVE:** To compare effects of exenatide and insulin glargine on glycemic control in patients with type 2 diabetes mellitus that is suboptimally controlled with metformin and a sulfonylurea. **DESIGN:** 26-week multicenter, open-label, randomized, controlled trial. **SETTING:** 82 outpatient study centers in 13 countries. **PATIENTS:** 551 patients with type 2 diabetes and inadequate glycemic control (defined as hemoglobin A1c level ranging from 7.0% to 10.0%) despite combination metformin and sulfonylurea therapy. **INTERVENTION:** Exenatide, 10 microg twice daily, or insulin glargine, 1 daily dose titrated to maintain fasting blood glucose levels of less than 5.6 mmol/L (<100 mg/dL). **MEASUREMENTS:** Hemoglobin A1c level, fasting plasma glucose level, body weight, 7-point self-monitored blood glucose, standardized test-meal challenge, safety, and tolerability. **RESULTS:** Baseline mean hemoglobin A1c level was 8.2% for patients receiving exenatide and 8.3% for those receiving insulin glargine. At week 26, both exenatide and insulin glargine reduced hemoglobin A1c levels by 1.11% (difference, 0.017 percentage point [95% CI, -0.123 to 0.157 percentage point]). Exenatide reduced postprandial glucose excursions more than insulin glargine, while insulin glargine reduced fasting glucose concentrations more than exenatide. Body weight decreased 2.3 kg with exenatide and increased 1.8 kg with insulin glargine (difference, -4.1 kg [CI, -4.6 to -3.5 kg]). Rates of symptomatic hypoglycemia were similar, but nocturnal hypoglycemia occurred less frequently with exenatide (0.9 event/patient-year versus 2.4 events/patient-year; difference, -1.6 events/patient-year [CI, -2.3 to -0.9 event/patient year]). Gastrointestinal symptoms were more common in the exenatide group than in the insulin glargine group, *including nausea (57.1% vs. 8.6%), vomiting (17.4% vs. 3.7%) and diarrhea (8.5% vs. 3.0%), 18 exenatide patients withdrew from the study because of nausea or other IG symptoms*. **LIMITATIONS:** The trial was open-label and did not assess clinical complications related to diabetes. Of the 551 participants, 19.4% of those receiving exenatide and 9.7% of those receiving insulin glargine withdrew from the study. Only 21.6% of the insulin glargine group and 8.6% of the exenatide group achieved the target level for fasting plasma glucose of less than 5.6 mmol/L (<100 mg/dL). **CONCLUSIONS:** Exenatide and insulin glargine achieved similar improvements in overall glycemic control in patients with type 2 diabetes that was suboptimally controlled with oral combination therapy. Exenatide was associated with weight reduction and had a higher incidence of gastrointestinal adverse effects than insulin glargine.

Figure 2. Changes in hemoglobin A<sub>1c</sub> level (top) and body weight (bottom).



Time course for hemoglobin A<sub>1c</sub> level and body weight from week 0 to week 26 is shown for the exenatide group compared with the insulin glargine group; mean ( $\pm$  SE) is shown. Week 0 indicates baseline. Data are shown for intention-to-treat population. \* $P < 0.0001$  compared with insulin glargine measure at the same time point.

Table 2. Estimates of Mean Changes In Hemoglobin A<sub>1c</sub> Level from Baseline with Exenatide and Insulin Glargine

Variable	Exenatide Group (n = 275)	Insulin Glargine Group (n = 260)	Difference (95% CI)*
<b>Intention-to-treat</b>			
Baseline, %†	8.18	8.23	
Change from baseline to week 12, percentage points‡	-1.24	-1.08	-0.162 (-0.301 to -0.024)
Change from baseline to week 26, percentage points‡	-1.11	-1.11	0.017 (-0.123 to 0.157)
<b>Per protocol</b>			
Baseline, %†	8.25	8.29	
Change from baseline to week 12, percentage points‡	-1.31	-1.10	-0.209 (-0.352 to -0.066)
Change from baseline to week 26, percentage points‡	-1.16	-1.14	-0.016 (-0.161 to 0.129)

\* Exenatide minus insulin glargine.

† Baseline means are presented for descriptive purposes.

‡ Least-squares means are obtained from a statistical model that includes baseline as a covariate.

[J Clin Endocrinol Metab.](#) 2005 Nov;90(11):5991-7. Epub 2005 Sep 6.

**Exenatide augments first- and second-phase insulin secretion in response to intravenous glucose in subjects with type 2 diabetes.**

[Fehse F](#), [Trautmann M](#), [Holst JJ](#), [Halseth AE](#), [Nanayakkara N](#), [Nielsen LL](#), [Fineman MS](#), [Kim DD](#), [Nauck MA](#).

Diabeteszentrum Bad Lauterberg, Kirchberg 21, D-37431 Bad Lauterberg im Harz, Germany.

CONTEXT: First-phase insulin secretion (within 10 min after a sudden rise in plasma glucose) is reduced in type 2 diabetes mellitus (DM2). The incretin mimetic exenatide has gluco-regulatory activities in DM2, including glucose-dependent enhancement of insulin secretion. OBJECTIVE: The objective of the study was to determine whether exenatide can restore a more normal pattern of insulin secretion in subjects with DM2. DESIGN: Fasted subjects received iv insulin infusion to reach plasma glucose 4.4-5.6 mmol/liter. Subjects received iv exenatide (DM2) or saline (DM2 and healthy volunteers), followed by iv glucose challenge. PATIENTS: Thirteen evaluable DM2 subjects were included in the study: 11 males, two females; age, 56 +/- 7 yr; body mass index, 31.7 +/- 2.4 kg/m<sup>2</sup>; hemoglobin A1c, 6.6 +/- 0.7% (mean +/- sd) treated with diet/exercise (n = 1), metformin (n = 10), or acarbose (n = 2). Controls included 12 healthy, weight-matched subjects with normal glucose tolerance: nine males, three females; age, 57 +/- 9 yr; and body mass index, 32.0 +/- 3.0 kg/m<sup>2</sup>. SETTING: The study was conducted at an academic hospital. MAIN OUTCOME MEASURES: Plasma insulin, plasma C-peptide, insulin secretion rate (derived by deconvolution), and plasma glucagon were the main outcome measures. RESULTS: DM2 subjects administered saline had diminished first-phase insulin secretion, compared with healthy control subjects. Exenatide-treated DM2 subjects had an insulin secretory pattern similar to healthy subjects in both first (0-10 min) and second (10-180 min) phases after glucose challenge, in contrast to saline-treated DM2 subjects. In exenatide-treated DM2 subjects, the most common adverse event was moderate nausea (two of 13 subjects). CONCLUSIONS: Short-term exposure to exenatide can restore the insulin secretory pattern in response to acute rises in glucose concentrations in DM2 patients who, in the absence of exenatide, do not display a first phase of insulin secretion. Loss of first-phase insulin secretion in DM2 patients may be restored by treatment with exenatide.

[J Clin Pharmacol.](#) 2005 Sep;45(9):1032-7.

**Effect of exenatide on the steady-state pharmacokinetics of digoxin.**

[Kothare PA](#), [Soon DK](#), [Linnebjerg H](#), [Park S](#), [Chan C](#), [Yeo A](#), [Lim M](#), [Mace KF](#), [Wise SD](#).

Global PK/PD and Trial Simulations, Eli Lilly and Company, Indianapolis, IN 46285, USA.

This open-label study investigated the effect of exenatide coadministration on the steady-state plasma pharmacokinetics of digoxin. A total of 21 healthy male subjects received digoxin (day 1, 0.5 mg twice daily; days 2-12, 0.25 mg once daily) and exenatide (days 8-12, 10 microg twice daily). Digoxin plasma and urine concentrations were measured on days 7 and 12. Exenatide coadministration did not change the overall 24-hour steady-state digoxin exposure (AUC<sub>tau,ss</sub>) and C<sub>min,ss</sub> but caused a 17% decrease in mean plasma digoxin C<sub>max,ss</sub> (1.40 to 1.16 ng/mL) and an increase in digoxin t<sub>max,ss</sub> (median increase, 2.5 hours). Although the decrease in digoxin C<sub>max,ss</sub> was statistically significant, peak concentrations were within the therapeutic concentration range in all subjects. Digoxin urinary pharmacokinetic parameters were not altered. Gastrointestinal symptoms, the most common adverse effects of exenatide, decreased over time. Exenatide administration does not cause any changes in digoxin steady-state pharmacokinetics that would be expected to have clinical sequelae; thus, dosage adjustment does not appear warranted, based on pharmacokinetic considerations.

[Diabetes Technol Ther.](#) 2005 Jun;7(3):467-77.

**Exenatide improves glycemic control and reduces body weight in subjects with type 2 diabetes: a dose-ranging study.**

[Poon T](#), [Nelson P](#), [Shen L](#), [Mihm M](#), [Taylor K](#), [Fineman M](#), [Kim D](#).

Amylin Pharmaceuticals, Inc., San Diego, California 92121, USA.

BACKGROUND: Exenatide is the first of a new class of agents known as incretin mimetics that are in development for the treatment of type 2 diabetes. Exenatide has been shown to reduce fasting and postprandial glucose in patients with type 2

diabetes, as well as provide sustained reductions in hemoglobin A 1c (HbA 1c). This study was designed to assess the dose dependencies of the glucoregulatory effects and tolerability of exenatide when added to diet and exercise or metformin monotherapy in patients with type 2 diabetes. **METHODS:** In this randomized, triple-blinded, placebo-controlled Phase 2 clinical trial, 156 patients were randomized to placebo or exenatide at 2.5, 5.0, 7.5, or 10.0 microg administered b.i.d. for 28 days. **RESULTS:** After 28 days of therapy, exenatide was associated with significant ( $P < 0.0001$ , linear contrast testing), dose-dependent reductions in HbA 1c (0.1 +/- 0.1%, -0.3 +/- 0.1%, -0.4 +/- 0.1%, +/-0.5 +/- 0.0%, and -0.5 +/- 0.1% for placebo and 2.5, 5.0, 7.5, and 10.0 microg b.i.d. exenatide, respectively) and significant ( $P = 0.0006$ , linear contrast testing) reductions in fasting plasma glucose (+6.8 +/- 4.1, -20.1 +/- 5.2, -21.2 +/- 3.9, -17.7 +/- 4.8, and -17.3 +/- 4.4 mg/dL for placebo and 2.5, 5.0, 7.5, and 10.0 microg b.i.d. exenatide, respectively) by Day 28. These reductions were similar for patients treated with diet/exercise and those treated with metformin. In addition, patients receiving exenatide exhibited dose-dependent reductions in body weight (0.0 +/- 0.3, -0.7 +/- 0.3, -0.7 +/- 0.2, -1.4 +/- 0.3, and -1.8 +/- 0.3 kg for placebo and 2.5, 5.0, 7.5, and 10.0 microg b.i.d. exenatide, respectively;  $P < 0.01$  for 7.5 and 10.0 microg b.i.d. exenatide doses compared with placebo) at Day 28. The most common adverse event was mild-to-moderate nausea that was dose-dependent (seven of 123 patients randomized to exenatide withdrew from the study because of gastrointestinal effects). **CONCLUSIONS:** Exenatide dose-dependently improved glycemic control and reduced body weight over 28 days in patients with type 2 diabetes treated with diet/exercise or metformin.

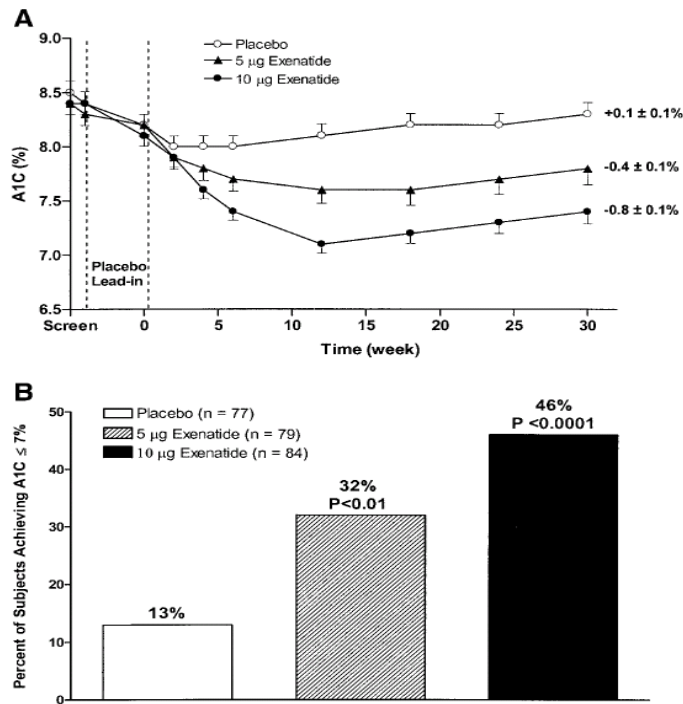
[Diabetes Care](#). 2005 May;28(5):1092-100.

**Effects of exenatide (exendin-4) on glycemic control and weight over 30 weeks in metformin-treated patients with type 2 diabetes.**

[DeFronzo RA](#), [Ratner RE](#), [Han J](#), [Kim DD](#), [Fineman MS](#), [Baron AD](#).

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**OBJECTIVE:** This study evaluates the ability of the incretin mimetic exenatide (exendin-4) to improve glycemic control in patients with type 2 diabetes failing to achieve glycemic control with maximally effective metformin doses. **RESEARCH DESIGN AND METHODS:** A triple-blind, placebo-controlled, 30-week study at 82 U.S. sites was performed with 336 randomized patients. In all, 272 patients completed the study. The intent-to-treat population baseline was 53 +/- 10 years with BMI of 34.2 +/- 5.9 kg/m<sup>2</sup> and HbA(1c) of 8.2 +/- 1.1%. After 4 weeks of placebo, subjects self-administered 5 microg exenatide or placebo subcutaneously twice daily for 4 weeks followed by 5 or 10 microg exenatide, or placebo subcutaneously twice daily for 26 weeks. All subjects continued metformin therapy. **RESULTS:** At week 30, HbA(1c) changes from baseline +/- SE for each group were -0.78 +/- 0.10% (10 microg), -0.40 +/- 0.11% (5 microg), and +0.08 +/- 0.10% (placebo; intent to treat; adjusted  $P < 0.002$ ). Of evaluable subjects, 46% (10 microg), 32% (5 microg), and 13% (placebo) achieved HbA(1c) < or =7% ( $P < 0.01$  vs. placebo). Exenatide-treated subjects displayed progressive dose-dependent weight loss (-2.8 +/- 0.5 kg [10 microg], -1.6 +/- 0.4 kg [5 microg];  $P < 0.001$  vs. placebo). The most frequent adverse events were gastrointestinal in nature and generally mild to moderate. Incidence of mild to moderate hypoglycemia was low and similar across treatment arms, with no severe hypoglycemia. **CONCLUSIONS:** Exenatide was generally well tolerated and reduced HbA(1c) with no weight gain and no increased incidence of hypoglycemia in patients with type 2 diabetes failing to achieve glycemic control with metformin.

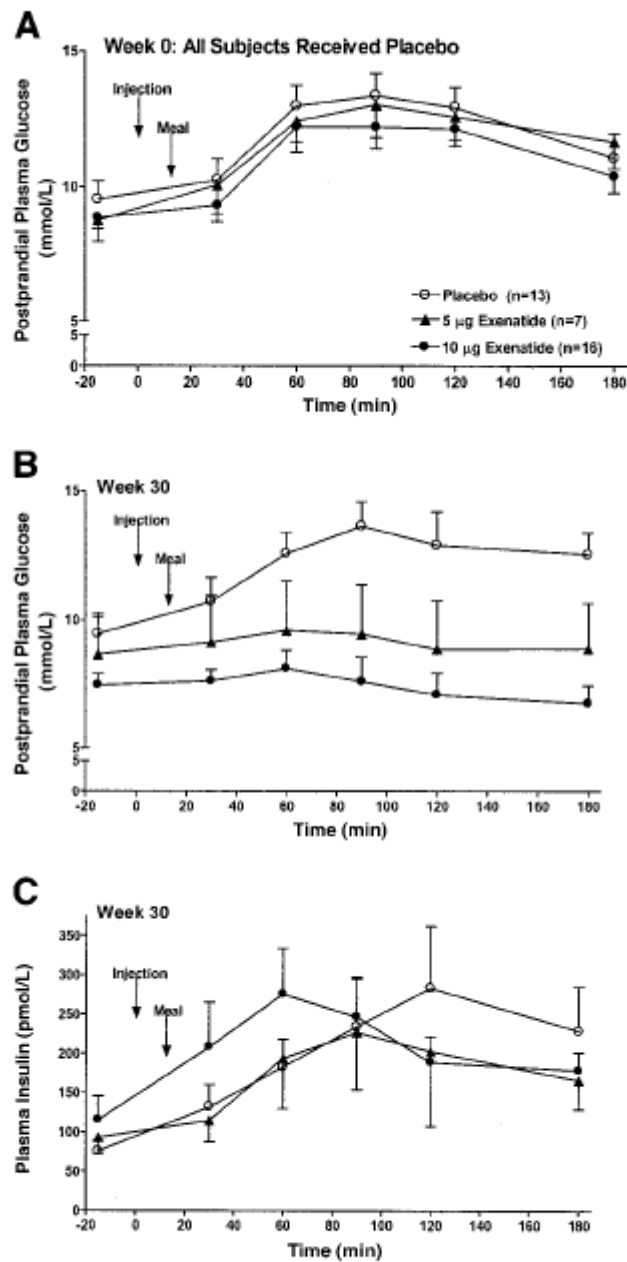


**Figure 2**—Glycemic control in subjects with type 2 diabetes treated with metformin and exenatide or placebo. A: HbA<sub>1c</sub> values over the course of the study in the intent-to-treat population. Baseline HbA<sub>1c</sub> values (mean ± SE) were 8.18 ± 0.09% in the 10-µg exenatide arm, 8.26 ± 0.11% in the 5-µg exenatide arm, and 8.20 ± 0.10% in the placebo arm. B: Percentage of evaluable subjects achieving HbA<sub>1c</sub> ≤ 7% at week 30. Subjects in the 10-µg exenatide arm received 5 µg exenatide twice daily during weeks 0–4. Subjects in all treatment arms were maintained on a stable metformin dose.

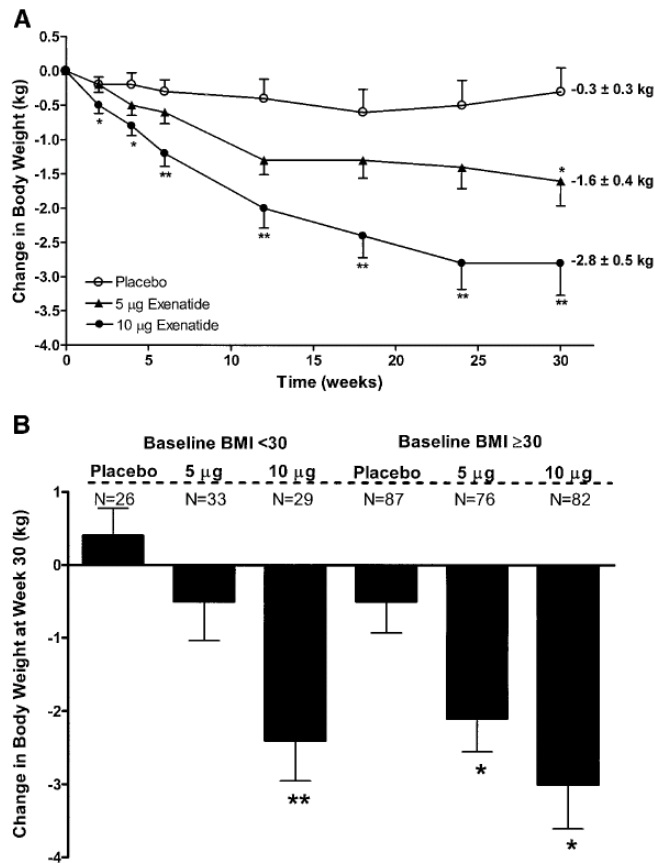
**Table 1**—Treatment-emergent adverse events

	Placebo	5-µg exenatide	10-µg exenatide
n	113	110	113
Nausea	26 (23)	40 (36)	51 (45)
Diarrhea	9 (8)	13 (12)	18 (16)
Upper respiratory tract infection	12 (11)	15 (14)	11 (10)
Vomiting	4 (4)	12 (11)	13 (12)
Dizziness	7 (6)	10 (9)	5 (4)
Sinusitis	6 (5)	5 (5)	7 (6)
Hypoglycemia	6 (5)	5 (5)	6 (5)
Back pain	3 (3)	3 (3)	7 (6)

Data are n (%). Adverse events had an overall incidence ≥ 5% in any treatment arm and a higher incidence in an exenatide arm for the intent-to-treat population.



**Figure 3—Meal tolerance subgroups.** Postprandial plasma glucose concentrations after a standardized meal at week 0 (A) and at week 30 (B) and postprandial plasma insulin levels at week 30 (C). Exenatide or placebo were administered at time zero. Evaluable population: 10 μg exenatide, n = 16; 5 μg exenatide, n = 7; placebo, n = 13. Data are mean ± SE.



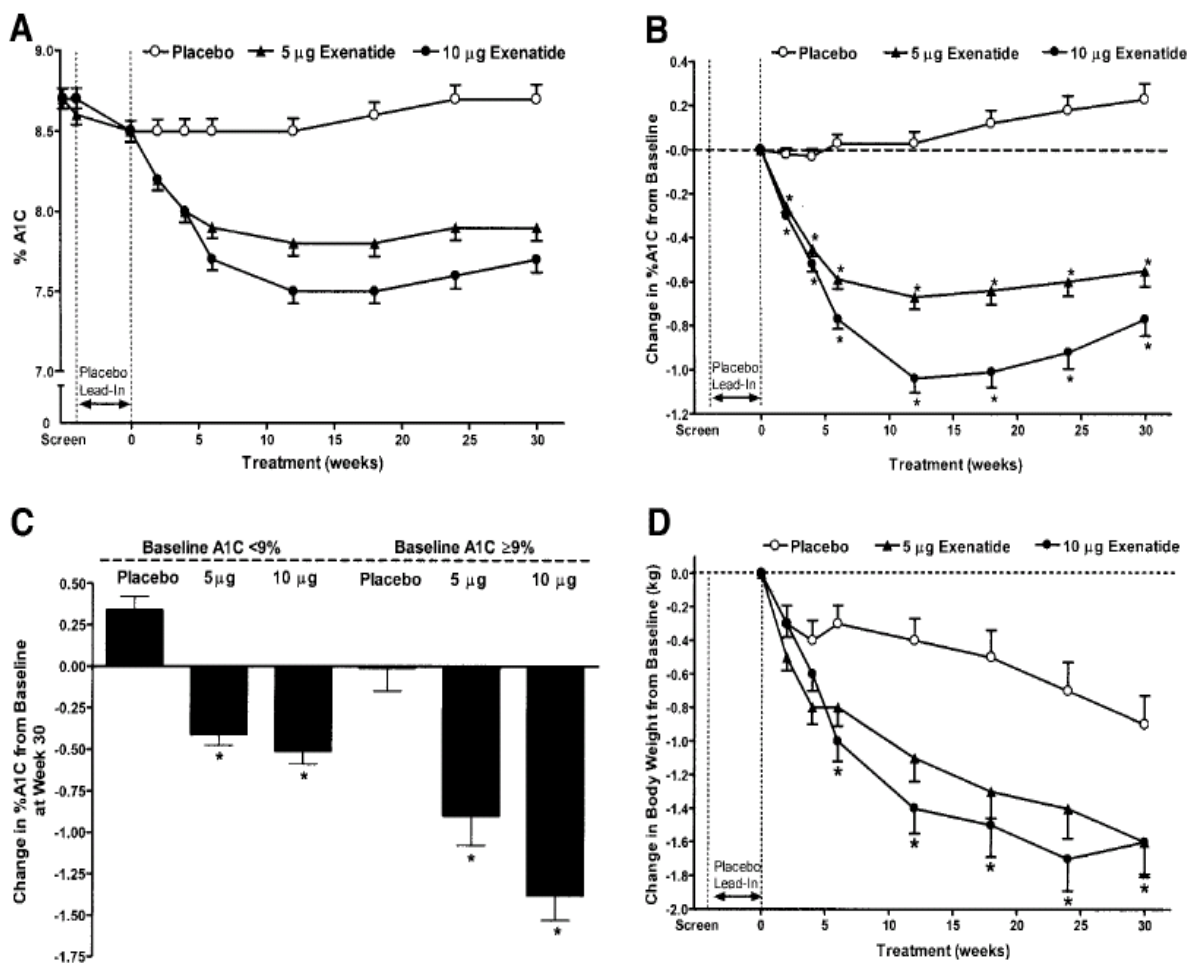
[Diabetes Care](#). 2005 May;28(5):1083-91.

**Effects of exenatide (exendin-4) on glycemic control over 30 weeks in patients with type 2 diabetes treated with metformin and a sulfonylurea.**

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**OBJECTIVE:** This study evaluated the effects of exenatide, a novel incretin mimetic, in hyperglycemic patients with type 2 diabetes unable to achieve glycemic control with metformin-sulfonylurea combination therapy. **RESEARCH DESIGN AND METHODS:** A 30-week, double-blind, placebo-controlled study was performed in 733 subjects (aged 55 +/- 10 years, BMI 33.6 +/- 5.7 kg/m<sup>2</sup>, A1C 8.5 +/- 1.0%; means +/- SD) randomized to 5 microg subcutaneous exenatide b.i.d. (arms A and B) or placebo for 4 weeks. Thereafter, arm A remained at 5 microg b.i.d. and arm B escalated to 10 microg b.i.d. Subjects continued taking their dose of metformin and were randomized to either maximally effective (MAX) or minimum recommended (MIN) doses of sulfonylurea. **RESULTS:** Week 30 A1C changes from baseline (+/-SE) were -0.8 +/- 0.1% (10 microg), -0.6 +/- 0.1% (5 microg), and +0.2 +/- 0.1% (placebo; adjusted P < 0.0001 vs. placebo), yielding placebo-adjusted reductions of -1.0% (10 microg) and -0.8% (5 microg). In the evaluable population, exenatide-treated subjects were more likely to achieve A1C < or =7% than placebo-treated subjects (34% [10 microg], 27% [5 microg], and 9% [placebo]; P < 0.0001). Both exenatide arms demonstrated significant weight loss (-1.6 +/- 0.2 kg from baseline each exenatide arm, -0.9 +/- 0.2 kg placebo; P < or = 0.01 vs. placebo). Mild or moderate nausea was the most frequent adverse event. The incidence of mild/moderate hypoglycemia was 28% (10 microg), 19% (5 microg), and 13% (placebo) and appeared lower with MIN than with MAX sulfonylurea treatment. **CONCLUSIONS:** Exenatide significantly reduced A1C in patients with type 2 diabetes unable to achieve adequate glycemic control with maximally effective doses of combined metformin-sulfonylurea therapy. This improvement in glycemic control was associated with no weight gain and was generally well tolerated.

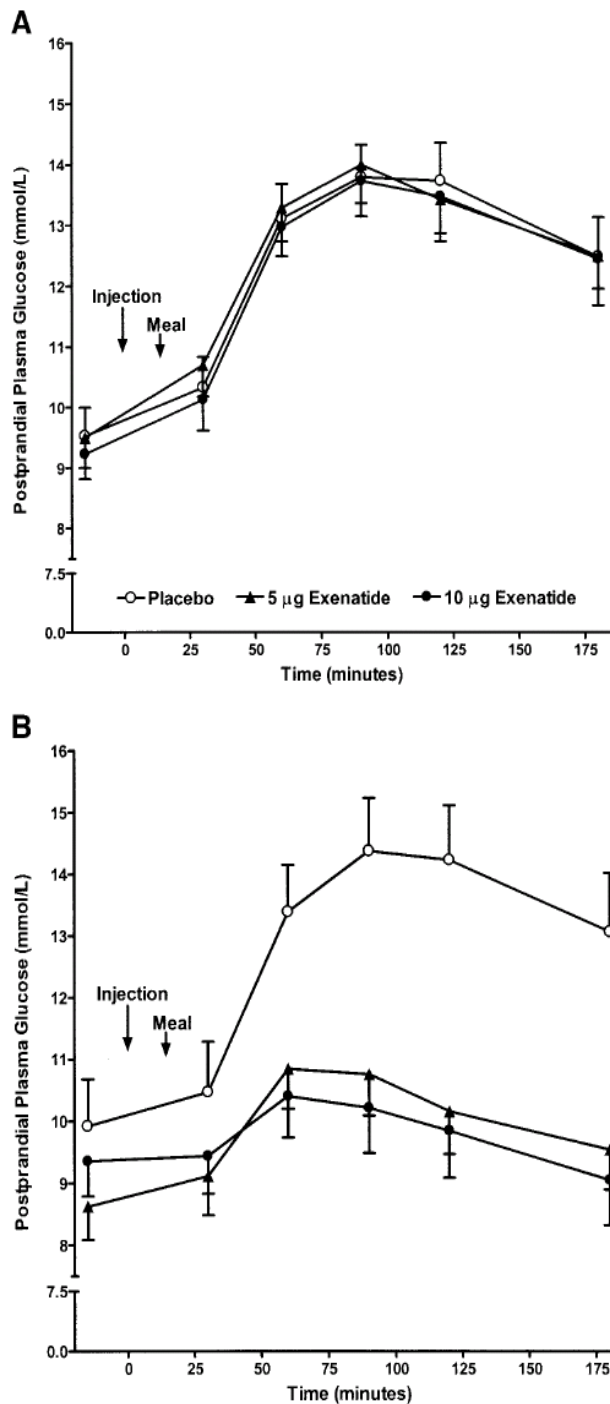


**Figure 2**—Glycemic control in subjects with type 2 diabetes treated with metformin and a sulfonylurea plus exenatide or placebo (ITT population) A: A1C values over the course of the study (raw data). B: Change in A1C over 30 weeks. \*Adjusted  $P < 0.0001$  compared with placebo. Week 30 changes in A1C values from baseline were  $-0.77 \pm 0.08\%$  (10- $\mu\text{g}$  arm; adjusted  $P < 0.0001$  vs. placebo),  $-0.55 \pm 0.07\%$  (5- $\mu\text{g}$  arm; adjusted  $P < 0.0001$  vs. placebo), and  $+0.23 \pm 0.07\%$  (placebo arm). C: Week 30 change in A1C stratified by baseline A1C. For subjects with baseline A1C  $<9\%$ , baseline A1C values were  $7.92 \pm 0.04\%$  ( $n = 169$ ),  $7.91 \pm 0.04\%$  ( $n = 172$ ), and  $7.94 \pm 0.04\%$  ( $n = 172$ ) for the 10- $\mu\text{g}$  exenatide, 5- $\mu\text{g}$  exenatide, and placebo arms, respectively. The corresponding values for subjects with baseline A1C  $\geq 9\%$  were  $9.86 \pm 0.07\%$  ( $n = 72$ ),  $9.75 \pm 0.07\%$  ( $n = 73$ ), and  $9.75 \pm 0.07\%$  ( $n = 75$ ). D: Effects of exenatide on body weight. Subjects in the 10- $\mu\text{g}$  exenatide b.i.d. treatment arm received 5  $\mu\text{g}$  exenatide b.i.d. during weeks 0–4. Subjects in all treatment arms were maintained on metformin-sulfonylurea therapy. \* $P \leq 0.001$  compared with placebo treatment. Data are means  $\pm$  SE.

**Table 1** —Most frequent adverse events with incidence  $\geq 10\%$  in any treatment arm (ITT)\*

Preferred term	Placebo	5 $\mu\text{g}$ exenatide	10 $\mu\text{g}$ exenatide
n	247	245	241
Nausea	51 (20.6)	96 (39.2)	117 (48.5)
Hypoglycemia	31 (12.6)	47 (19.2)	67 (27.8)
Upper respiratory tract infection	48 (19.4)	28 (11.4)	42 (17.4)
Vomiting	11 (4.5)	36 (14.7)	33 (13.7)
Diarrhea	16 (6.5)	25 (10.2)	42 (17.4)
Feeling jittery	17 (6.9)	21 (8.6)	28 (11.6)
Headache	12 (4.9)	27 (11.0)	18 (7.5)

Data are n (%). \*Treatment emergent.



**Figure 3**—Postprandial plasma glucose concentrations in the meal tolerance test subpopulation. **A:** Postprandial plasma glucose concentrations after a standardized meal at day 1. Subjects in all treatment arms received placebo. Postprandial plasma glucose geometric mean  $AUC_{(15-180 \text{ min})}$  values were  $2,033 \text{ mmol} \cdot \text{min} \cdot \text{l}^{-1}$  in the  $10\text{-}\mu\text{g}$  exenatide arm,  $2,089 \text{ mmol} \cdot \text{min} \cdot \text{l}^{-1}$  in the  $5\text{-}\mu\text{g}$  exenatide arm, and  $2,090 \text{ mmol} \cdot \text{min} \cdot \text{l}^{-1}$  in the placebo arm. **B:** Postprandial plasma glucose concentrations after a standardized meal at week 30. Geometric mean  $AUC_{(15-180 \text{ min})}$  values were  $1,539 \text{ mmol} \cdot \text{min} \cdot \text{l}^{-1}$  in the  $10\text{-}\mu\text{g}$  exenatide arm ( $P = 0.0004$  vs. placebo),  $1,584 \text{ mmol} \cdot \text{min} \cdot \text{l}^{-1}$  in the  $5\text{-}\mu\text{g}$  exenatide arm ( $P = 0.0009$  vs. placebo), and  $2,087 \text{ mmol} \cdot \text{min} \cdot \text{l}^{-1}$  in the placebo arm. Exenatide or placebo were administered at time zero. Evaluable population:  $10\text{-}\mu\text{g}$  exenatide,  $n = 27$ ;  $5\text{-}\mu\text{g}$  exenatide,  $n = 27$ ; placebo,  $n = 23$ . Subjects in the  $10\text{-}\mu\text{g}$  exenatide b.i.d. arm received  $5\text{-}\mu\text{g}$  exenatide b.i.d. during weeks 0–4. Subjects in all treatment arms were maintained on metformin-sulfonylurea therapy. Data are means  $\pm$  SE.

**Table 2**—Change in A1C from baseline to week 30 and incidence of hypoglycemia stratified by sulfonylurea management group (ITT)

Sulfonylurea management group	Change in A1C (%)			Incidence of hypoglycemia (%)		
	Placebo	$5\text{-}\mu\text{g}$ exenatide	$10\text{-}\mu\text{g}$ exenatide	Placebo	$5\text{-}\mu\text{g}$ exenatide	$10\text{-}\mu\text{g}$ exenatide
MAX	$+0.2 \pm 0.1$	$-0.7 \pm 0.1$ ; $P < 0.0001^*$	$-0.9 \pm 0.1$ ; $P < 0.0001^*$	15%	22%	35%
MIN	$+0.3 \pm 0.1$	$-0.4 \pm 0.1$ ; $P < 0.0001^*$	$-0.6 \pm 0.1$ ; $P < 0.0001^*$	10%	16%	21%

Data are means  $\pm$  SE, unless otherwise noted. \*A1C change comparison for exenatide treatment versus placebo.

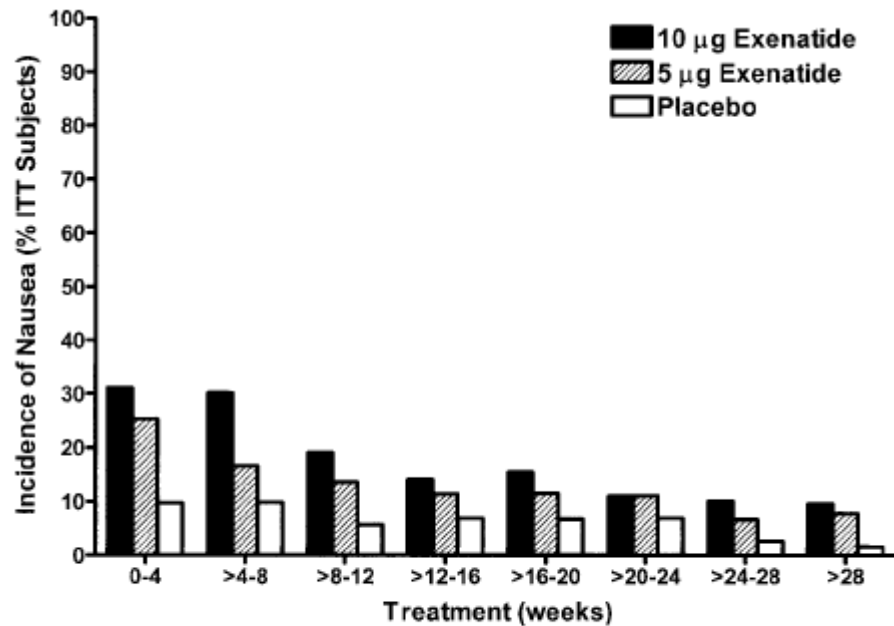


Figure 4—Time-dependent incidence of subjects experiencing treatment-emergent nausea (ITT population).

[J Clin Pharmacol](#). 2005 May;45(5):570-7.

**Pharmacokinetics of an oral drug (acetaminophen) administered at various times in relation to subcutaneous injection of exenatide (exendin-4) in healthy subjects.**

[Blase E](#), [Taylor K](#), [Gao HY](#), [Wintle M](#), [Fineman M](#).

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Exenatide is an incretin mimetic with potential glucoregulatory activity in type 2 diabetes. This randomized, single-blind, placebo-controlled 6-way crossover study assessed exenatide's effect on acetaminophen pharmacokinetics. Of 40 randomized healthy subjects, 39 completed the study. On the placebo day, acetaminophen (1000 mg) was ingested and placebo injected subcutaneously at 0 hours. On exenatide days, acetaminophen was ingested at -1, 0, +1, +2, and +4 hours, relative to the 10 mug exenatide injected subcutaneously at 0 hours. With exenatide injection, mean plasma acetaminophen AUC(0-12 h) values were reduced by 11% to 24% (vs placebo). Peak plasma acetaminophen concentrations were similar for the -1-hour and placebo groups and reduced by 37% to 56% at other times. The most frequent adverse events were generally mild to moderate nausea and vomiting. Exenatide treatment concurrent with or preceding acetaminophen ingestion slowed acetaminophen absorption but had minimal effect on the extent of absorption.

[Clin Ther](#). 2005 Feb;27(2):210-5.

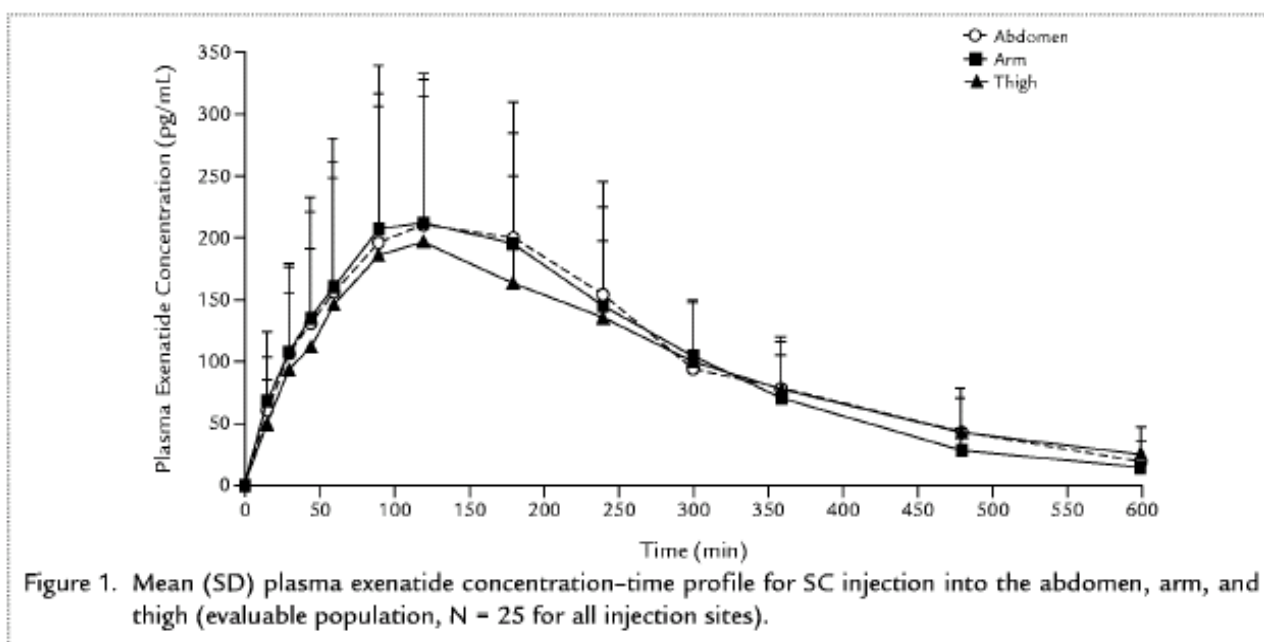
**A randomized, open-label, crossover study examining the effect of injection site on bioavailability of exenatide (synthetic exendin-4).**

[Calara F](#), [Taylor K](#), [Han J](#), [Zabala E](#), [Carr EM](#), [Wintle M](#), [Fineman M](#).

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BACKGROUND: Exenatide (synthetic exendin-4;AC2993) is a 39-amino acid peptide in the new class of antidiabetic agents known as incretin mimetics. In clinical trials, exenatide exhibited glucoregulatory effects (glucose-dependent stimulation of insulin secretion, suppression of inappropriately elevated glucagon secretion, slowing of gastric emptying) in patients with type 2 diabetes mellitus (DM). OBJECTIVE: The goal of this study was to determine the relative bioavailability of exenatide

injected subcutaneously into the abdomen, arm, or thigh. METHODS: Patients with type 2 DM were randomized in an open-label, crossover study to assess relative bioavailability of exenatide (10 microg) injected into the arm and thigh versus injection into the abdomen. Serial plasma exenatide concentrations were measured for 10 hours after injection. A sample size of >24 patients provided approximately 80% power to ensure that 90% CIs were within the 80% to 125% interval for the ratios (geometric least squares [LS] means) of AUC(0-infinity). RESULTS: Twenty-eight patients were randomized into the study (mean age, 56 [8] years; glycosylated hemoglobin, 8.0 [1.7]%; body mass index, 33 [5] kg/m<sup>2</sup>; all values given as mean [SD]). AUC(0-infinity) values (geometric LS mean SE for SC injections into the abdomen arm and thigh were 63,935 (6608), 59,573 (6157), and 62,148 (6424) pg./mL, respectively. The AUC (geometric LS mean ratio for relative bioavailability) for arm versus abdomen was 0.93 (geometric 90% CI, 0.82-1.05); for thigh versus abdomen it was 0.97 (geometric 90% CI, 0.86-1.10). Consistent with the observed data, intrasubject variability of AUC(0-infinity) was low among the 3 treatments (coefficient of variation, 26%). C(max) values (geometric LS mean [SE]) were 220 (24) pg/mL, abdomen; 218 (23) pg/mL, arm; and 193 (21) pg/mL, thigh. The C(max) (geometric LS mean ratio) for arm versus abdomen was 0.99 (geometric 90% CI, 0.85-1.15), and for thigh versus abdomen it was 0.88 (geometric 90% CI, 0.75-1.02). The most common treatment-emergent adverse events were mild to moderate nausea (36%), headache (25%), vomiting (21%), and dizziness (18%). Three patients received an inadvertent 10-fold overdose and were withdrawn from the study immediately. All experienced severe nausea and vomiting, and 1 patient experienced severe hypoglycemia requiring aid. All recovered without mishap and were excluded from statistical and tolerability results. There were no adverse events related to the injection or the injection site. CONCLUSION: In this study of patients with type 2DM, SC administration of exenatide into the abdomen, arm, or thigh resulted in comparable bioavailability.



[Am J Health Syst Pharm.](#) 2005 Jan 15;62(2):173-81.

**Pharmacokinetics, pharmacodynamics, and safety of exenatide in patients with type 2 diabetes mellitus.**

[Kolterman OG](#), [Kim DD](#), [Shen L](#), [Ruggles JA](#), [Nielsen LL](#), [Fineman MS](#), [Baron AD](#).

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PURPOSE: The pharmacology and tolerability of exenatide in patients with type 2 diabetes mellitus were studied.

METHODS: Two randomized, single-blind, placebo-controlled studies were conducted. Treatment with oral antidiabetic agents was stopped 14 days before study initiation. In the first study (study A), eight subjects received placebo, 0.1-, 0.2-, 0.3-, and either 0.4-microg/kg exenatide or placebo five minutes before a meal combined with liquid acetaminophen (to assess the rate of gastric emptying) on days 1, 3, 5, 7, and 9. In the second study (study B), subjects received a single s.c. dose of exenatide or placebo on consecutive days. Part 1 of study B used exenatide doses of 0.01 and 0.1 microg/ kg; 0.02-,

0.05-, and 0.1-microg/kg doses were given in part 2. After an overnight fast, the study drug was injected 15 minutes before a meal (part 1) and before a meal and acetaminophen (part 2). Parts 1 and 2 of study B enrolled six and eight patients, respectively. RESULTS: In both studies, plasma exenatide pharmacokinetic profiles appeared dose proportional. Exenatide doses of 0.02-0.2 microg/kg dose-dependently lowered postprandial glucose excursions. Exenatide suppressed postprandial plasma glucagon and slowed gastric emptying. There were no serious adverse events and no patient withdrawals related to treatment. Nausea and vomiting were the most common adverse events and were mild to moderate in severity at doses ranging from 0.02 to 0.2 microg/kg. CONCLUSION: Administration of preprandial exenatide by s.c. injection resulted in dose-proportional exenatide pharmacokinetics and antidiabetic pharmacodynamic activity. At doses ranging from 0.02 to 0.2 microg/kg, exenatide dose-dependently reduced postprandial plasma glucose excursion by insulinotropism, suppression of plasma glucagon, and slowing of gastric emptying.

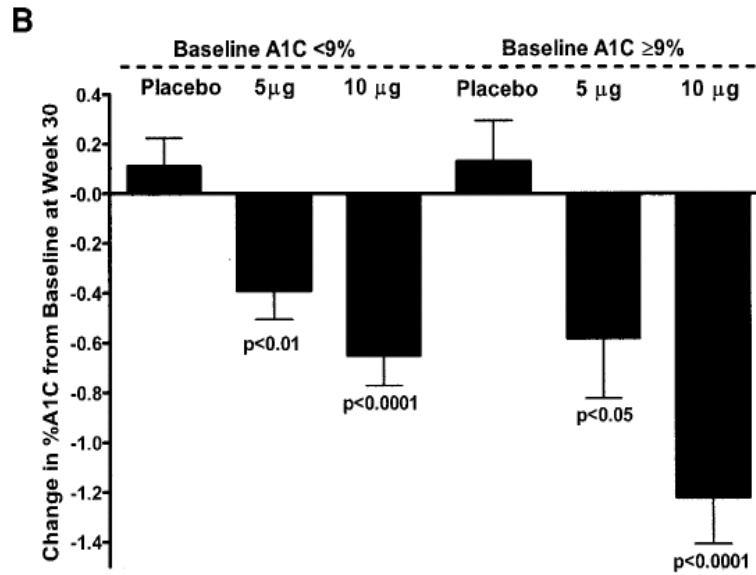
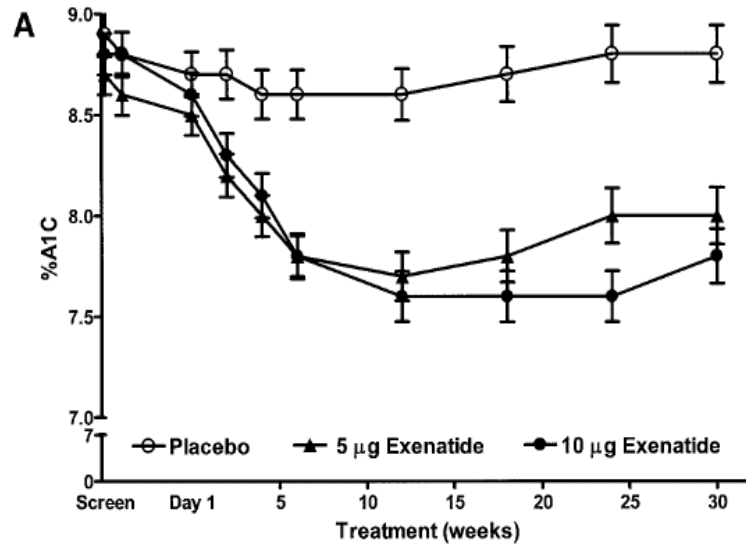
[Diabetes Care](#). 2004 Nov;27(11):2628-35.

**Effects of exenatide (exendin-4) on glycemic control over 30 weeks in sulfonylurea-treated patients with type 2 diabetes.**

**[Buse JB](#), [Henry RR](#), [Han J](#), [Kim DD](#), [Fineman MS](#), [Baron AD](#); [Exenatide-113 Clinical Study Group](#).**

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OBJECTIVE: This study evaluated the ability of the incretin mimetic exenatide (exendin-4) to improve glycemic control in patients with type 2 diabetes failing maximally effective doses of a sulfonylurea as monotherapy. RESEARCH DESIGN AND METHODS: This was a triple-blind, placebo-controlled, 30-week study conducted at 101 sites in the U.S. After a 4-week, single-blind, placebo lead-in period, 377 subjects were randomized (60% men, age 55 +/- 11 years, BMI 33 +/- 6 kg/m<sup>2</sup>), HbA(1c) 8.6 +/- 1.2% [+/SD]) and began 4 weeks at 5 microg subcutaneous exenatide twice daily (before breakfast and dinner; arms A and B) or placebo. Subsequently, subjects in arm B were escalated to 10 microg b.i.d. exenatide. All subjects continued sulfonylurea therapy. RESULTS: At week 30, HbA(1c) changes from baseline were -0.86 +/- 0.11, -0.46 +/- 0.12, and 0.12 +/- 0.09% (+/-SE) in the 10-microg, 5-microg, and placebo arms, respectively (adjusted P < 0.001). Of evaluable subjects with baseline HbA(1c) > 7% (n = 237), 41% (10 microg), 33% (5 microg), and 9% (placebo) achieved HbA(1c) <= 7% (P < 0.001). Fasting plasma glucose concentrations decreased in the 10-microg arm compared with placebo (P < 0.05). Subjects in the exenatide arms had dose-dependent progressive weight loss, with an end-of-study loss in the 10-microg exenatide arm of -1.6 +/- 0.3 kg from baseline (P < 0.05 vs. placebo). The most frequent adverse events were generally mild or moderate and gastrointestinal in nature. No severe hypoglycemia was observed. CONCLUSIONS: Exenatide significantly reduced HbA(1c) in patients with type 2 diabetes failing maximally effective doses of a sulfonylurea. Exenatide was generally well tolerated and was associated with weight loss.



**Figure 2—** Glycemic control in subjects with type 2 diabetes treated with a sulfonylurea and exenatide or placebo. A: HbA<sub>1c</sub> values over the course of the study (ITT population). Baseline HbA<sub>1c</sub> values were 8.6 ± 0.1% in the 10-µg exenatide arm (●, n = 129), 8.5 ± 0.1% in the 5-µg exenatide arm (▲, n = 125), and 8.7 ± 0.1% in the placebo arm (○, n = 123). Data are means ± SE. B: Change in HbA<sub>1c</sub> values at week 30 stratified by baseline HbA<sub>1c</sub> (ITT population). Baseline HbA<sub>1c</sub> values were 7.9 ± 0.1% (10 µg), 7.8 ± 0.1% (5 µg), and 7.9 ± 0.1% (placebo) in subjects with baseline HbA<sub>1c</sub> <9%. Baseline HbA<sub>1c</sub> values were 10.0 ± 0.1% (10 µg), 9.7 ± 0.1% (5 µg), and 10.1 ± 0.1% (placebo) in subjects with baseline HbA<sub>1c</sub> ≥9%. Data are means ± SE. The adjusted P values shown are with placebo as the reference arm. Subjects in the 10-µg b.i.d. exenatide treatment arm received 5 µg b.i.d. exenatide during weeks 0–4. Subjects in all treatment arms were maintained on a sulfonylurea.

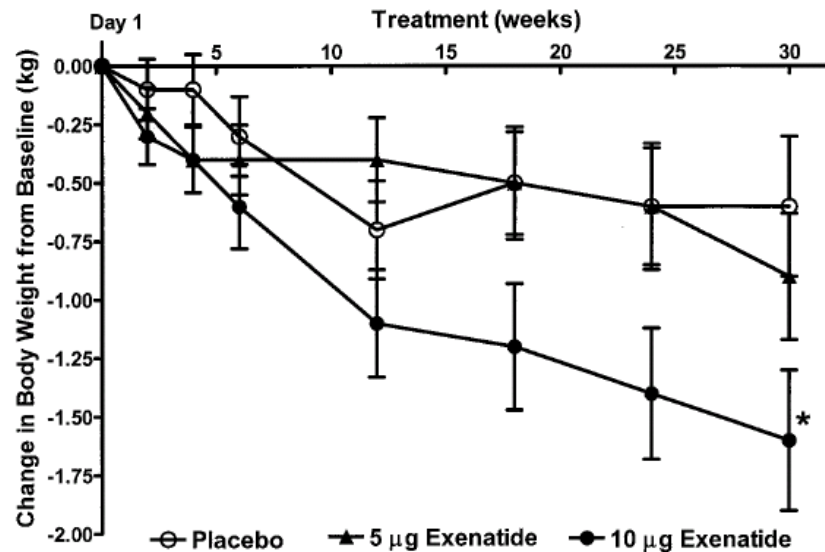


Figure 3— Change in body weight from baseline over time in ITT subjects with type 2 diabetes treated with a sulfonylurea and exenatide or placebo. Baseline weights were  $95.2 \pm 1.6$  kg in the 10- $\mu$ g exenatide arm (●, n = 129),  $94.9 \pm 1.9$  kg in the 5- $\mu$ g exenatide arm (▲, n = 125), and  $99.1 \pm 1.7$  kg in the placebo arm (○, n = 123). Subjects in the 10- $\mu$ g b.i.d. exenatide treatment arm received 5  $\mu$ g b.i.d. exenatide during weeks 0–4. Subjects in all treatment arms were maintained on a sulfonylurea. Data are means  $\pm$  SE. \*P  $\leq$  0.05 compared with placebo treatment.

Table 1—Treatment-emergent adverse events related to the gastrointestinal tract and hypoglycemia

Adverse event	Placebo	Exenatide		
		5 $\mu$ g	10 $\mu$ g	All
n	123	125	129	254
Nausea	9 (7)	49 (39)	66 (51)	115 (45)
Hypoglycemia	4 (3)	18 (14)	46 (36)	64 (25)
Dizziness	8 (7)	19 (15)	19 (15)	38 (15)
Feeling jittery	2 (2)	15 (12)	19 (15)	34 (13)
Vomiting	3 (2)	12 (10)	17 (13)	29 (11)
Diarrhea	5 (4)	14 (11)	11 (9)	25 (10)
Headache	8 (7)	11 (9)	10 (8)	21 (8)
Constipation	4 (3)	2 (2)	12 (9)	14 (6)
Sweating increased	1 (1)	3 (2)	10 (8)	13 (5)
Weakness	4 (3)	7 (6)	2 (2)	9 (4)

Data are n (%).

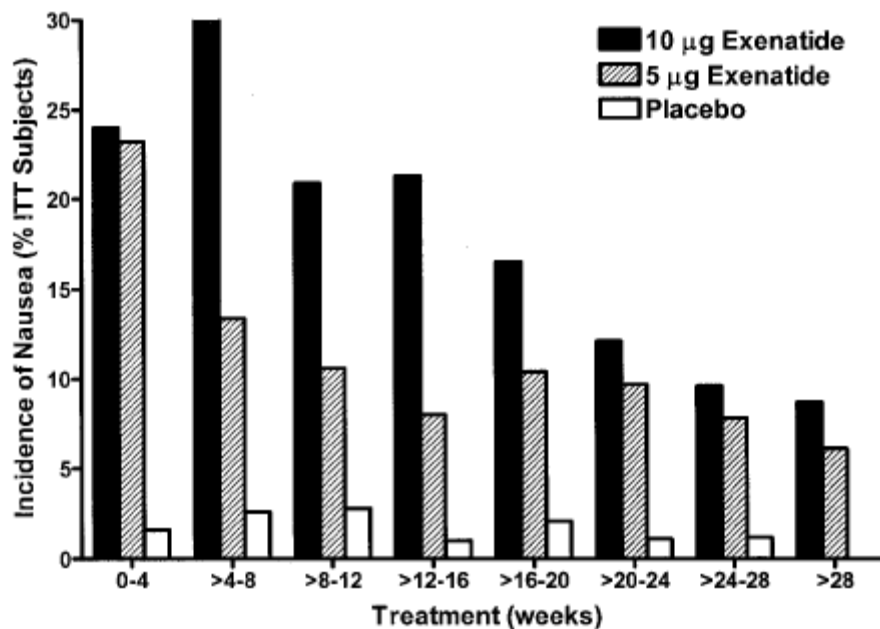


Figure 4—Time-dependent incidence of subjects experiencing treatment-emergent nausea (ITT population).

Table 2—Post-hoc analysis of weight change in subjects with or without at least one episode of nausea

Subject group	Placebo	5 µg exenatide	10 µg exenatide
Never had nausea (kg)	-0.7 ± 3.1 (110)	-0.6 ± 3.0 (75)	-1.4 ± 3.6 (61)
At least one episode of nausea (kg)	0.6 ± 4.7 (9)	-1.3 ± 2.9 (48)	-1.7 ± 3.2 (65)

Data are means ± SD (n).

[Diabetes Metab Res Rev.](#) 2004 Sep-Oct;20(5):411-7.

**Effectiveness of progressive dose-escalation of exenatide (exendin-4) in reducing dose-limiting side effects in subjects with type 2 diabetes.**

[Fineman MS](#), [Shen LZ](#), [Taylor K](#), [Kim DD](#), [Baron AD](#).

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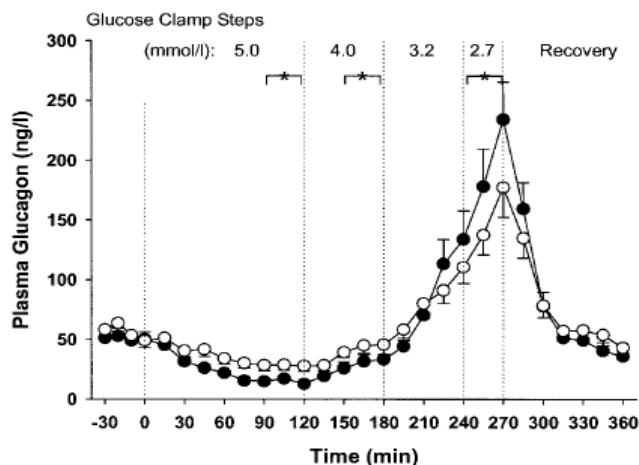
BACKGROUND: Exenatide (exendin-4) exhibits dose-dependent glucoregulatory activity, but causes dose-limiting nausea and vomiting. This study was designed to formally assess the possibility of inducing tolerance to the side effects of nausea and vomiting at therapeutic doses of exenatide, using a dose-escalation methodology. METHODS: In this two-arm, triple-blind, multicenter study, 123 subjects with type 2 diabetes were enrolled and randomized; 99 (80.5%) of them completed the study. Subjects in the exenatide-primed arm received subcutaneous exenatide, starting at 0.02 micro g/kg three times a day (TID) and increasing in 0.02 micro g/kg per dose increments every 3 days for 35 days. Subjects in the exenatide-naive arm received placebo TID for 35 days. At the end of this 35-day regimen, subjects in both arms received the same highest dose of exenatide (0.24 micro g/kg TID) for 3 days. Thus, the exenatide-naive arm received exenatide for the first time on Day 35. RESULTS: The exenatide-primed arm had a lower proportion of subjects experiencing nausea and vomiting in response to exposure to the highest dose of exenatide (27 vs 56% in the exenatide-naive arm;  $p = 0.0018$ ). Kaplan-Meier estimates of cumulative incidence were 0.28 in the exenatide-primed arm, compared with 0.68 in the exenatide-naive arm ( $p \leq 0.001$ ). As predicted by the study design, fewer subjects in the exenatide-primed arm reported severe nausea (29%) and vomiting (10%) than those in the exenatide-naive arm (48 and 31%, respectively). In the exenatide-primed arm, fasting serum glucose progressively declined over the first 35 days of dosing, but was unchanged in the exenatide-naive arm (placebo phase) during the same interval. CONCLUSION: Gradual dose-escalation of exenatide successfully reduced the proportion of subjects experiencing dose-limiting nausea and vomiting, with no loss of glucoregulatory activity, thus demonstrating the value of gradual dose-escalation in mitigating the gastrointestinal side effects of exenatide. Copyright 2004 John Wiley & Sons, Ltd.

**Effect of intravenous infusion of exenatide (synthetic exendin-4) on glucose-dependent insulin secretion and counterregulation during hypoglycemia.**

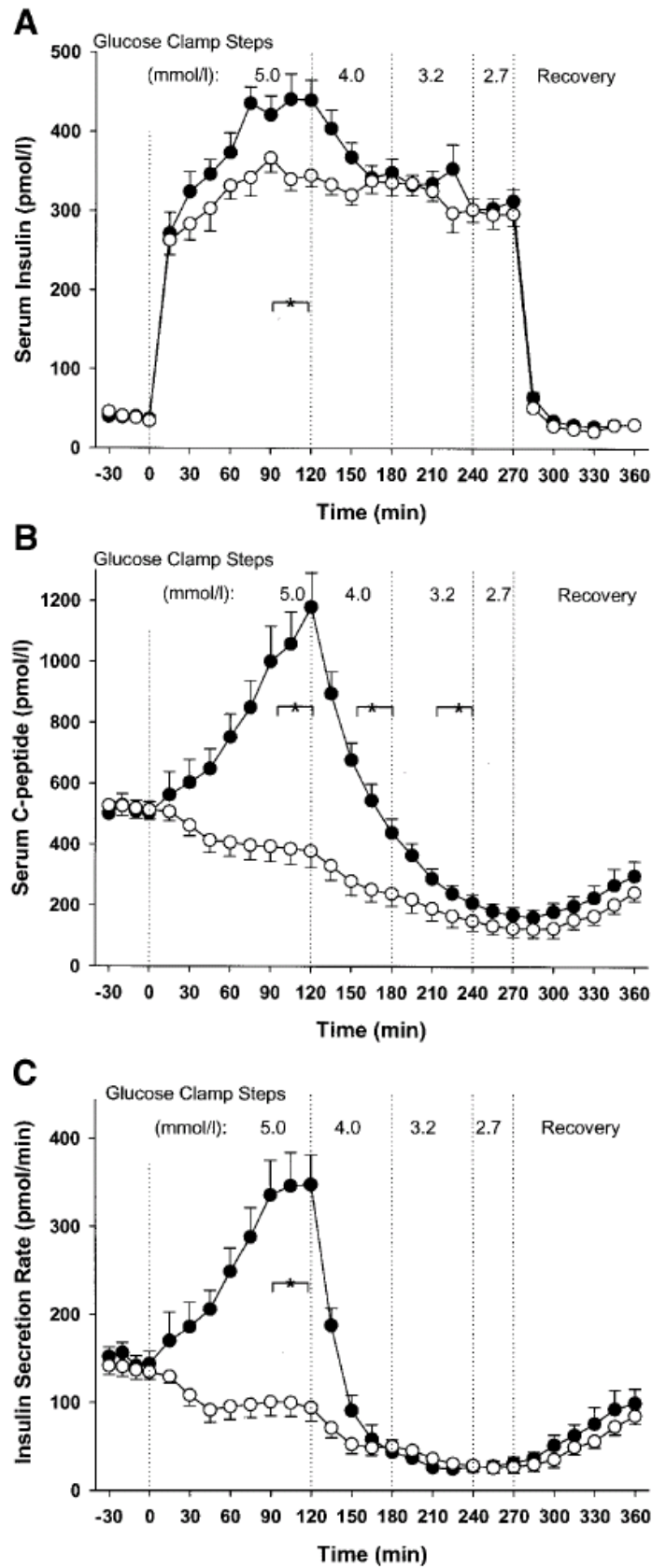
**Dejn KB, Brock B, Juhl CB, Djurhuus CB, Grubert J, Kim D, Han J, Taylor K, Fineman M, Schmitz O.**

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This study assessed whether glucose-dependent insulin secretion and overall counterregulatory response are preserved during hypoglycemia in the presence of exenatide. Twelve healthy fasted volunteers were randomized in a triple-blind crossover study to receive either intravenous exenatide (0.066 pmol. kg(-1). min(-1)) or placebo during a 270-min stepwise hyperinsulinemic-hypoglycemic clamp (insulin infusion 0.8 mU. kg(-1). min(-1)). Plasma glucose was clamped sequentially at 5.0 (0-120 min), 4.0 (120-180 min), 3.2 (180-240 min), and 2.7 mmol/l (240-270 min). At 270 min, insulin infusion was terminated and plasma glucose increased to approximately 3.2 mmol/l. The time to achieve plasma glucose  $\geq$ 4 mmol/l thereafter was recorded. Insulin secretory rates (ISRs) and counterregulatory hormones were measured throughout. Glucose profiles were superimposable between the exenatide and placebo arms. In the presence of euglycemic hyperinsulinemia, ISRs in the exenatide arm were approximately 3.5-fold higher than in the placebo arm (353  $\pm$  29 vs. 100  $\pm$  29 pmol/min [least-square means  $\pm$  SE]). However, ISRs declined similarly and rapidly at all hypoglycemic steps ( $\leq$ 4 mmol/l) in both groups. Glucagon was suppressed in the exenatide arm during euglycemia and higher than placebo during hypoglycemia. Plasma glucose recovery time was equivalent for both treatments. The areas under the concentration-time curve from 270 to 360 min for cortisol, epinephrine, norepinephrine, and growth hormone were similar between treatment arms. There were no differences in adverse events. In the presence of exenatide, there was a preserved, glucose-dependent insulin secretory response and counterregulatory response during hypoglycemia.



**FIG. 3. Glucagon counterregulatory hormone response. Basal period: -30 to 0 min. Infusion of exenatide or placebo commenced at 0 min. Glycemic steps: 0-120 min, euglycemia with plasma glucose at ~5.0 mmol/l; 120-180 min, hypoglycemia with plasma glucose at ~4.0 mmol/l; 180-240 min, hypoglycemia with plasma glucose at ~3.2 mmol/l ending in nadir of ~2.8 mmol/l; 270-360 min, recovery phase. ○, placebo treatment arm; ●, exenatide treatment arm. Data are means  $\pm$  SE;  $n = 11$  per treatment arm. \* $P < 0.05$ , exenatide vs. placebo during steady state of a glycemic interval.**



**FIG. 2.** Insulin secretory response. Basal period: -30 to 0 min. Infusion of exenatide or placebo commenced at 0 min. Glycemic steps: 0-120 min, euglycemia with plasma glucose at ~5.0 mmol/l; 120-180 min, hypoglycemia with plasma glucose at ~4.0 mmol/l; 180-240 min, hypoglycemia with plasma glucose at ~3.2 mmol/l ending in nadir of ~2.8 mmol/l; 270-360 min, recovery phase. ○, placebo treatment arm; ●, exenatide treatment arm. Data are means  $\pm$  SE;  $n = 11$  per treatment arm. \* $P < 0.05$ , exenatide vs. placebo during steady state of a glycemic interval.

[J Clin Endocrinol Metab.](#) 2004 Jul;89(7):3469-73.

**Exendin-4 normalized postcibal glycaemic excursions in type 1 diabetes.**

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Exendin-4 is a reptilian peptide that activates the mammalian receptor for truncated glucagon-like peptide 1 (tGLP-1) with relatively prolonged actions. Exendin-4 and tGLP-1 can reduce blood glucose levels by stimulating insulin secretion, inhibiting glucagon secretion, and delaying gastric emptying. We tested a range of doses of exendin-4 on postcibal glycaemic excursions in nine volunteers with type 1 diabetes, all with negligible endogenous insulin secretion, in paired comparisons with vehicle in at least six volunteers with each of six doses. We established a side effect-free dose and an appropriate antecibal time for sc administration of exendin-4. Subsequently, exendin-4 was administered 15 min before breakfast, with usual insulin, to eight of the volunteers. Acetaminophen was ingested with the meal as an indicator of gastric emptying. The mean plasma glucose excursion was reduced by 90%, falling into the normal range, after breakfast, whereas plasma pancreatic polypeptide, glucagon, and acetaminophen levels were reduced, and insulin levels were not affected. Thus, normalization of postcibal glycaemia was associated with delayed gastric emptying and suppression of glucagon secretion, without increased secretion or blood levels of insulin. We suggest that tGLP-1 agonists have therapeutic potential as congeners with insulin in C-peptide-negative type 1 diabetes.

[Diabetes Care.](#) 2003 Aug;26(8):2370-7.

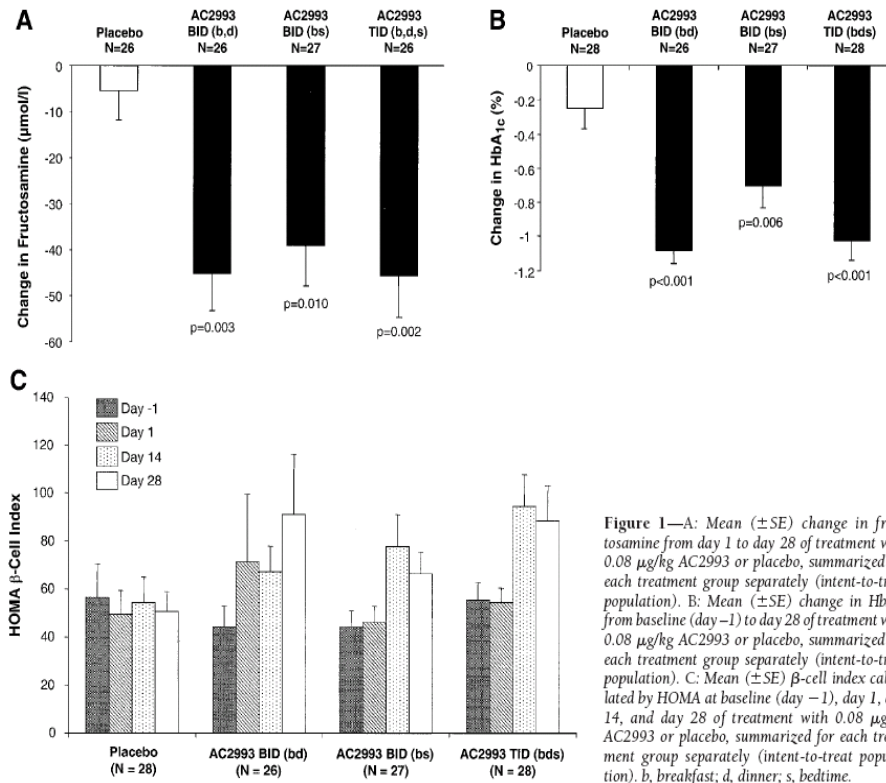
**Effect on glycaemic control of exenatide (synthetic exendin-4) additive to existing metformin and/or sulfonylurea treatment in patients with type 2 diabetes (triple-blind).**

[Fineman MS](#), [Bicsak TA](#), [Shen LZ](#), [Taylor K](#), [Gaines E](#), [Varns A](#), [Kim D](#), [Baron AD](#).

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**OBJECTIVE:** AC2993 (synthetic exendin-4; exenatide) is a peptide that enhances glucose-dependent insulin secretion, suppresses inappropriately elevated glucagon secretion, and slows gastric emptying. AC2993 also promotes beta-cell proliferation and neogenesis in vitro and in animal models. This study examines the activity and safety of subcutaneously injected AC2993 in patients with type 2 diabetes currently treated with diet and/or oral antidiabetic agents (OAs).

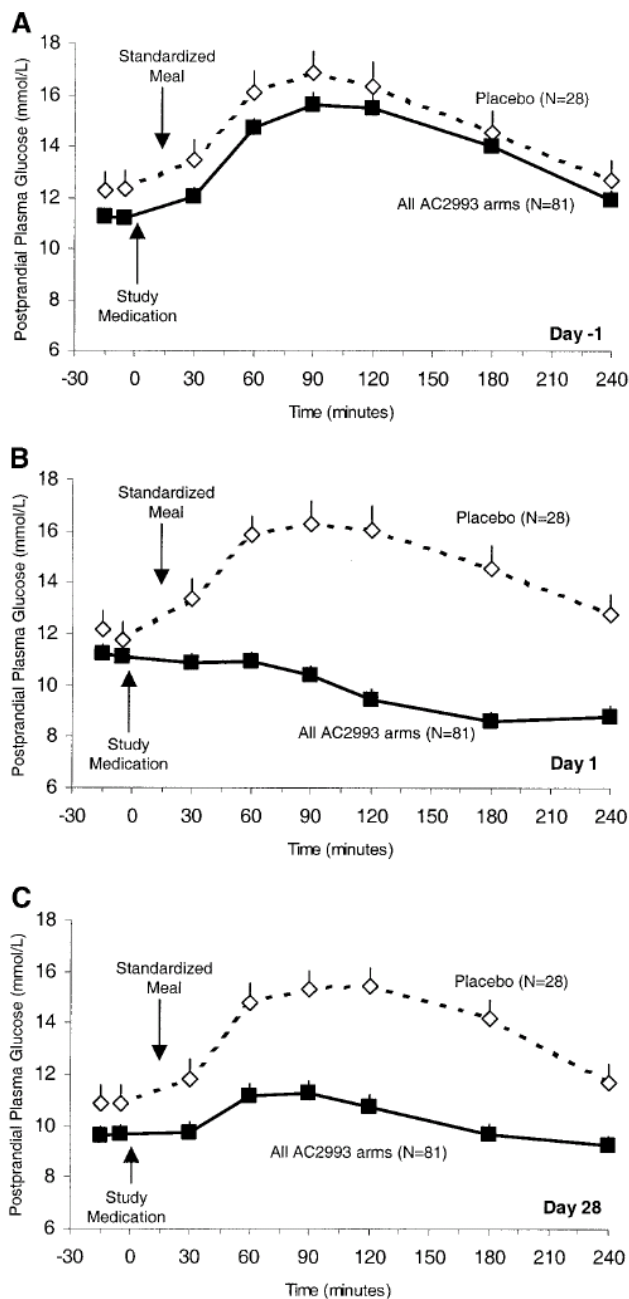
**RESEARCH DESIGN AND METHODS:** A total of 109 patients treated with diet and a sulfonylurea and/or metformin were enrolled in a blinded study. Patients were randomly assigned to one of three subcutaneously (SC) injected regimens of AC2993 (0.08 micro g/kg) or placebo for 28 days. **RESULTS:** All three AC2993 regimens led to significant reductions in serum fructosamine relative to placebo ( $P \leq 0.004$ ). Mean reductions ranged from 39 to 46 micro mol/l. All AC2993 groups had reductions in HbA(1c) ranging from 0.7 to 1.1% ( $P \leq 0.006$ ). An end-of-study HbA(1c) <7% was achieved by 15% of AC2993 patients versus 4% of placebo patients, confirming AC2993 effects on fasting and postprandial glycaemia. On days 14 and 28, the beta-cell index (homeostasis model assessment) for patients treated with AC2993 was 50-100% higher than baseline, contrasting with unchanged levels for placebo. The most common adverse event was transient mild-to-moderate nausea. **CONCLUSIONS:** AC2993 is a promising therapeutic for patients with type 2 diabetes. In this study, it had significant effects on HbA(1c) levels in patients not currently achieving optimal glucose control with diet and/or OAs.



**Figure 1**—A: Mean (±SE) change in fructosamine from day 1 to day 28 of treatment with 0.08 μg/kg AC2993 or placebo, summarized for each treatment group separately (intent-to-treat population). B: Mean (±SE) change in HbA<sub>1c</sub> from baseline (day -1) to day 28 of treatment with 0.08 μg/kg AC2993 or placebo, summarized for each treatment group separately (intent-to-treat population). C: Mean (±SE) β-cell index calculated by HOMA at baseline (day -1), day 1, day 14, and day 28 of treatment with 0.08 μg/kg AC2993 or placebo, summarized for each treatment group separately (intent-to-treat population). b, breakfast; d, dinner; s, bedtime.

Homeostasis model assessment (HOMA) (23) was conducted to assess β-cell function at baseline and at days 14 and 28. The HOMA scores (24) were calculated as follows:

$$\text{HOMA } \beta\text{-cell index} = \frac{20 \times \text{fasting insulin } (\mu\text{U/ml})}{\text{fasting glucose (mmol/l)} - 3.5}$$



**Figure 2**—Mean ( $\pm$ SE) postprandial plasma glucose concentration profile at baseline day -1 (A), day 1 (B), and day 28 (C) of treatment with 0.08  $\mu$ g/kg AC2993 (all arms combined) or placebo (intent-to-treat population).

[J Clin Endocrinol Metab.](#) 2003 Jul;88(7):3082-9.

**Synthetic exendin-4 (exenatide) significantly reduces postprandial and fasting plasma glucose in subjects with type 2 diabetes.**

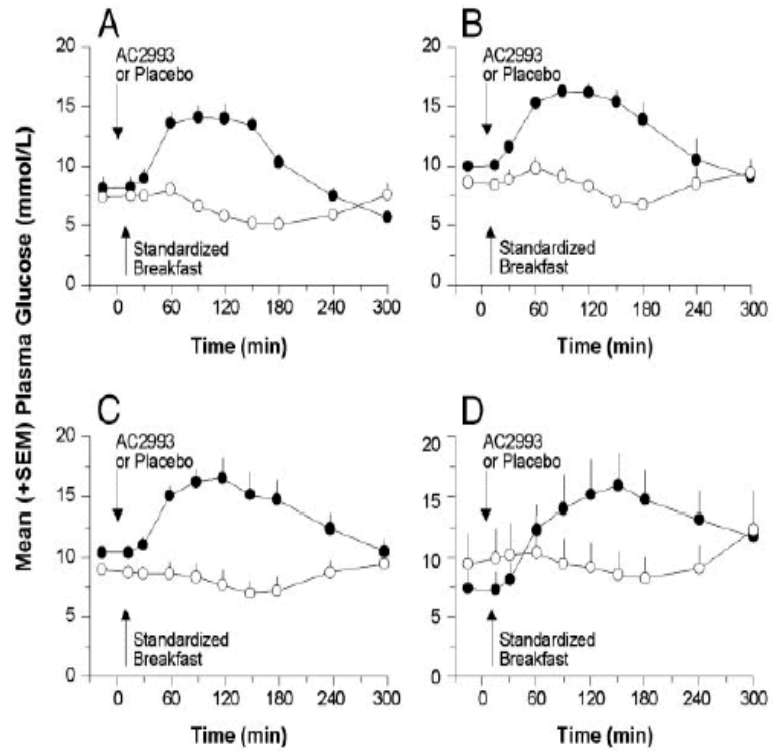
[Kolterman OG](#), [Buse JB](#), [Fineman MS](#), [Gaines E](#), [Heintz S](#), [Bicsak TA](#), [Taylor K](#), [Kim D](#), [Aisporna M](#), [Wang Y](#), [Baron AD](#).

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Despite the advent of new treatments, glucose control in the type 2 diabetes population is unsatisfactory. AC2993 (synthetic exendin-4; exenatide), a novel glucose-dependent insulinotropic agent, exhibited notable antidiabetic potential in two clinical studies in patients with type 2 diabetes. In study A, 24 subjects received sc injections of study medication (0.1 micro g/kg

AC2993 or placebo) twice daily with meals for 5 d. Statistically significant reductions in mean postprandial circulating concentrations of glucose, insulin, and glucagon occurred following treatment with AC2993. In study B, 13 subjects receiving a single dose of study medication (0.05, 0.1, or 0.2 micro g/kg AC2993 or placebo) following an overnight fast had reduced fasting plasma glucose concentrations during the subsequent 8-h period. The relative glucose and insulin concentration profiles were consistent with glucose-dependent insulinotropism. AC2993 was well tolerated. Mild transient headache, nausea, and vomiting were the main adverse events. In conclusion, AC2993 acutely and markedly reduces fasting and postprandial glucose concentrations in patients with type 2 diabetes. During fasting, glucose-dependent enhancement of insulin secretion and suppression of glucagon secretion are the predominant mechanisms, and postprandially, slowing of gastric emptying is additionally operative. This robust antidiabetic effect warrants further evaluation of AC2993.

FIG. 2. Mean (+SEM) postprandial plasma glucose concentration profiles following a single dose of placebo (●) or 0.1 µg/kg AC2993 (○) on d 5 for groups of subjects with a range of severity of type 2 diabetes. A, Group 1, diet only, n = 4; B, group 2, OAA, HbA<sub>1c</sub> < 8%, n = 6; C, group 3, OAA, HbA<sub>1c</sub> 8% or greater, n = 8; D, group 4, insulin with or without OAA, n = 6. Conversion factor: mmol/liter = 0.05555 mg/dl.



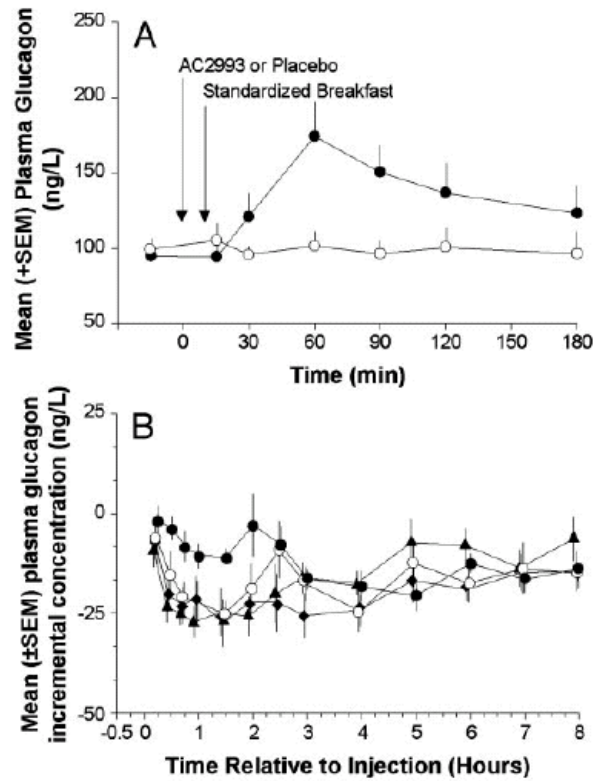


FIG. 4. A, Mean (+SEM) postprandial plasma glucagon concentration profiles following a single dose of placebo (●) or 0.1 µg/kg AC2993 (○) on d 5 (n = 20). B, Mean (+SEM) fasting plasma glucagon concentration profiles following a single dose of placebo (●), 0.05 µg/kg AC2993 (○), 0.1 µg/kg AC2993 (◆), or 0.2 µg/kg AC2993 (▲) on d 5 (n = 12). Conversion factor: ng/liter = pg/ml.

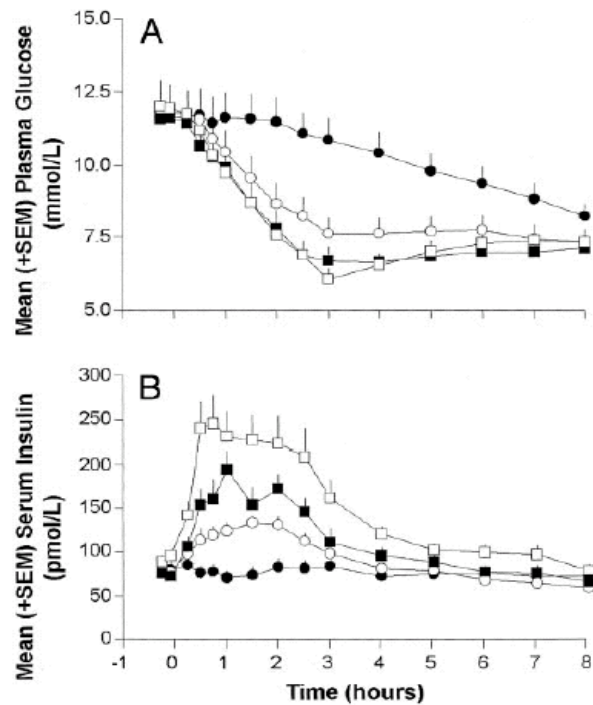


FIG. 5. Mean (+SEM) fasting plasma glucose (A) and serum insulin (B) concentration profile during the 8 h following a single dose of placebo (●), 0.05 µg/kg AC2993 (○), 0.1 µg/kg AC2993 (■), or 0.2 µg/kg AC2993 (□) administered at t = 0 (n = 12). Conversion factors: glucose: mmol/liter = 0.05555 mg/dl; insulin: pmol/liter = 6.945 µU/ml.

Effects of 1-mo bolus subcutaneous administration of exendin-4 in type 2 diabetes.

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A gut insulinotropic peptide, glucagon-like peptide-1 (GLP-1), when given continuously subcutaneously, has been shown to be an effective agent to treat type 2 diabetes. Because of inactivation by dipeptidyl peptidase IV (DPP IV), it has a very short half-life (90-120 s), hence the need for continuous administration. Exendin-4 is an agonist of the GLP-1 receptor. It is not a substrate for DPP IV, and we previously demonstrated that intravenous administration has potent insulinotropic properties in type 2 diabetic volunteers. We evaluated the efficacy of bolus subcutaneous exendin-4 in insulin-naive type 2 diabetic volunteers. Ten patients aged 44-72 yr with mean fasting glucose levels of 11.4  $\pm$  0.9 mmol/l were enrolled, and daily or twice-daily bolus subcutaneous exendin-4 was self-administered for 1 mo. Glycosylated hemoglobin, multiple daily capillary blood glucose, beta-cell sensitivity to glucose, and peripheral tissue sensitivity to insulin were compared before and after treatment. The greatest decline in capillary blood glucose was seen before bed, with a drop from 15.5 to 9.2 mmol/l ( $P < 0.0001$ ). Glycosylated hemoglobin improved significantly with treatment, from 9.1 to 8.3% ( $P = 0.009$ ). beta-Cell sensitivity to glucose was improved, as assessed by C-peptide levels during a hyperglycemic clamp. No significant adverse effects were noted or reported. Our data suggest that, even with this short duration of therapy, exendin-4 treatment had a significant effect on glucose homeostasis.

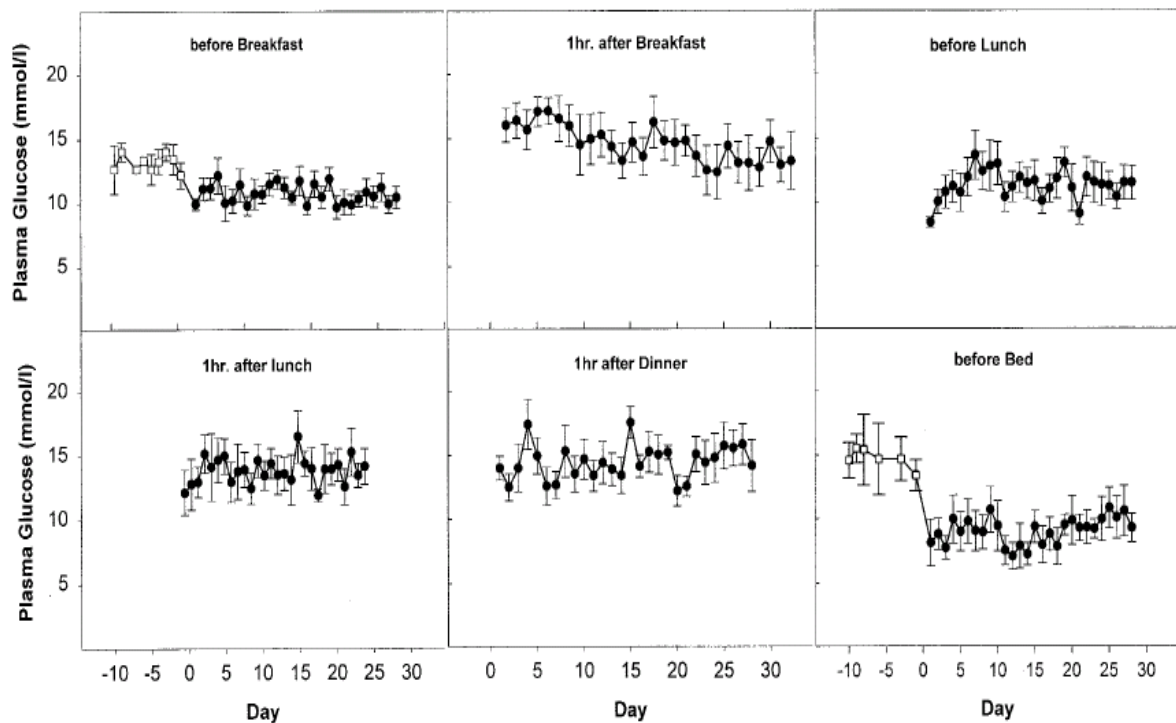


Fig. 1. Capillary blood glucose levels at designated times during exendin-4 therapy. In before Breakfast and before Bed,  $\square$  represents values before therapy was initiated and  $\bullet$  values after initiation of therapy. Data are means  $\pm$  SE.