CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-773

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

4/12/05

OFFICE OF CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW

NDA: 21-773. [redacted]	Submission Date: 06/29/2003
Brand Name	Byetta
Generic Name	Exenatide
Reviewer	Xiaoxiong (Jim) Wei, M.D., Ph.D.
Pharmacometrics Reviewers	Wei Qiu, Ph.D., Sang Chung, Ph.D.
Team Leader	Hae-Young Ahn, Ph.D.
OCPB Division	Division of Pharmaceutical Evaluation II
OND division	Division of Metabolic and Endocrine Drug Products (HFD-510)
Sponsor	Amylin Pharmaceuticals
Relevant IND(s)	57,725
Submission Type; Code	Original
Formulation; Strength(s)	Injection solution, [redacted]
Dosing regimen	5 or 10 μg, BID, s.c.
Indication	Type 2 diabetes mellitus

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1 Executive Summary

Amylin submitted a 505 (b) (1) NDA for marketing of [redacted] (exenatide). A total of seventeen human Phase 1 pharmacokinetic and pharmacodynamic studies and four Phase 2 clinical trials were submitted to support the section of Clinical Pharmacology and Biopharmaceutics.

1.1 Recommendation

The Office of Clinical Pharmacology and Biopharmaceutics/Division of Pharmaceutical Evaluation II (OCPB/DPE-2) has reviewed the information provided in the original NDA 21-773 for [redacted] in the section of human pharmacokinetics and biopharmaceutics. OCPB has found the application acceptable. This recommendation, the reviewer's comments, and Phase IV commitment below should be conveyed to the sponsor as appropriate.

Reviewer's comments:

Exenatide reduced lovastatin AUC by 40%, which can not be explained by delayed gastric emptying with exenatide. The Agency suggests that the sponsor characterize the mechanisms of lovastatin interaction with exenatide through in vitro and in vivo studies since it may apply to many other potential oral drug interactions. In addition, the sponsor should study how exenatide impacts on bioavailability of drugs that are instructed to be taken with food.

1.2 Phase IV Commitment

A single dose human in vivo drug interaction study between exenatide and oral contraceptive is recommended, where the effect of exenatide injection time on the bioavailability of oral contraceptives should be studied such as one hour before, 0 hour and one hour after exenatide injection. A combination oral contraceptive (COC) drug product, ethinyl estradiol + norethindrone (e.g., ortho-novum) is recommended for the study.

1.3 Summary of Clinical Pharmacology and Biopharmaceutics Findings

- Single-Dose Pharmacokinetics of Exenatide:

The mean single dose pharmacokinetic parameters of exenatide were estimated from the combined, single-dose database. Following SC administration, exenatide was rapidly absorbed and peak concentration was reached at 2.14 hour. Exenatide was rapidly eliminated with a mean terminal half-life of 2.4 hour. The mean apparent clearance (CL/F) was 9.1 L/h and the mean apparent volume of distribution (V/F) was 28.3 L.

- Relative bioavailability among injection sites:

An evaluation of the relative bioavailability of exenatide after subcutaneous administration at three anatomical sites (abdomen, arm, and thigh) showed that the site of injection did not substantially influence the pharmacokinetic profile of exenatide.

- Dose proportionality:

Doses ranging from 0.01 μg/kg to 0.4 μg/kg were evaluated in clinical studies with exenatide. The dose-proportionality was evaluated for Cmax and AUC0-inf over the therapeutic

range of 5 μg to 10 μg using a power model. The 90% confidence intervals (CI) for the exponents of the power models of AUC0-inf and Cmax were 0.8910 to 1.0261 and 0.7137 to 0.8716, respectively. Since the 90% CI with regards to AUC0-inf was within the range of 0.80 to 1.25, dose proportionality was concluded for AUC0-inf over the dose range of 5 μg to 10 μg. The Cmax values were less than proportional.

- Administration time relative to mealtime:

The optimal timing of exenatide administration is within 60 minutes prior to, or simultaneously with a meal. Administration after a meal should be avoided, as some patients may be at risk of hypoglycemia.

- First phase insulin release:

The intravenous infusion of exenatide resulted in restoration of impaired first-phase insulin secretion in patients with type 2 diabetes as evidenced by a four-fold increase in plasma insulin AUC (0 to 10 min) and a three-fold increase in insulin secretion rate compared to saline. First-phase insulin secretion during IV exenatide infusion was similar to or greater than that observed in healthy subjects administered saline infusions.

- Glucose dependent insulin release:

Continuous infusion of exenatide (0.066 pmol/kg/min; 0.4 μg/kg/day) demonstrated the glucose-dependent insulinotropic action of exenatide in healthy volunteers as evidenced by a 3 to 3.5-fold increase in the insulin secretion rate with exenatide treatment at glucose concentrations of 5 mmol/L. The insulin secretion rate decreased markedly at glucose concentrations of approximately 4.5 mmol/L. When plasma glucose concentrations were at or below 4 mmol/L, the insulinotropic effect of exenatide was negligible as compared with placebo. The counter regulatory response as measured by glucagon, epinephrine, norepinephrine, cortisol, and growth hormone concentrations remained intact during hypoglycemia with exenatide treatment. As a result, the recovery time from hypoglycemia was the same for each treatment indicating that exenatide does not impair the ability to reverse insulin induced hypoglycemia.

- Delayed gastric emptying:

Exenatide reduced the rate of absorption of acetaminophen by 56% and delayed its Tmax by 3.6 hours when acetaminophen as an indicator of gastric emptying was administered at +1 hour relative to exenatide administration in comparison to placebo.

- BID vs. TID regimen:

Exenatide 0.08 μg/kg administered subcutaneously two or three times a day for 28 days significantly improved glycemic control. Reductions in mean serum fructosamine concentrations from Day 1 to Day 28 were significantly greater for subjects receiving exenatide (range of means: -39.0 to -45.6 μmol/L) compared to placebo (-5.3 μmol/L). Reductions in mean postprandial plasma glucose concentrations from Day –1 to Day 28 were also significantly greater for subjects receiving exenatide (range of means: –79.1 to –56.9 mg/dL) compared to placebo (-11.3 mg/dL). The efficacy results from two or three times a day regimens are compatible.

- Exposure-Response:

Results of exposure-response (E-R) relationship was the essential data for the justification of dosage regimen transition from body weight adjusted dosing (0.02 - 0.4μg/kg) of the Phase II studies to fixed dosing (5 and 10μg) of the Phase III studies. Optimal target window of exenatide AUC was chosen as 600 pg•h/ml and 950 pg•h/ml. The lower window was from the threshold of acceptable glycemic benefits in efficacy (i.e., at least 30% reduction in postprandial glucose excursion), and the upper window was from the limit of dose limiting gastrointestinal adverse events in safety (e.g., nausea and vomiting). The population pharmacokinetic-pharmacodynamic (PPKPD) relationship was characterized with data of 4 Phase 2 studies, and simulation was conducted using the results of PPKPD analysis to evaluate the distribution of exenatide and postprandial glucose AUC with fixed doses (e.g., 5, 9, 10, and 12μg). Fixed dosing of 5μg or 10μg BID was proposed from the conclusion that two doses would have a favorable balance of glucose reduction and incidence of adverse events based on the results of simulation.

- Renal impairment:

Exenatide clearance in patients with mild to moderate renal impairment was similar to those in the healthy subject group. Exenatide clearance reduced from a mean estimate of 4.8 L/h in subjects with mild renal impairment to 0.9 L/h in subjects with ESRD. Exenatide clearance was significantly reduced in patients with ESRD, thus BID dosing of 5 μg in ESRD subjects would be associated with poor tolerability.

- Drug interactions:

Twice-daily subcutaneous administration of 10 μg exenatide did not produce a statistically significant change in steady state pharmacokinetic parameters of digoxin, Cmin,ss or AUCτ,ss. However, digoxin Tmax was delayed for a median value of 2.5 hours when administered concomitantly with exenatide.

Co-administration of exenatide caused statistically significant decreases in both mean lovastatin AUC0-∞and Cmax, of approximately 40% and 28%, respectively.

- Analytical assay:

The exenatide immunoenzymetric assay (IEMA) was used for the quantitation of exenatide in most nonclinical and clinical studies. The exenatide IEMA [redacted] detection method. The lower and upper limits of quantitation for the assay are [redacted] exenatide, respectively.

2. QUESTION BASED REVIEW (QBR)

2.1 GENERAL ATTRIBUTES OF THE DRUG

2.1.1 What are the highlights of the chemistry and physico-chemical properties of the drug substance, and the formulations of the drug product?

Exenatide (exendin-4, AC2993, LY2148568) is a 39-amino acid peptide (elemental composition: C184H282N50O60S, molecular weight: 4186.6 Daltons). The amino acid sequence for exenatide is as follows:

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-Trp-Leu-Lys-Asn-Gly-Gly-Pro-Ser-Ser-Gly-Ala-Pro-Pro-Pro-Ser-NH2

Exenatide is formulated as a sterile, preserved, isotonic solution for subcutaneous administration and is presented in a glass cartridge [redacted] assembled in a pen-injector (pen). The drug product consists of exenatide in a sodium acetate buffer containing the antimicrobial preservative, metacresol, and mannitol as a tonicity-adjusting agent.

2.1.2 What are the mechanism of action, therapeutic indication and dosage recommendations for exenatide?

Mechanism of Action

Exenatide is the first drug candidate in the class of agents known as incretin mimetics. The amino acid sequence of exenatide partially overlaps that of human glucagon-like peptide-1 (GLP-1). Exenatide has been shown to bind and activate the characterized human GLP-1 receptor in vitro, leading to an increase in both glucose-dependent synthesis and secretion of insulin from pancreatic beta cells. When administered in vivo, exenatide mimics certain antihyperglycemic actions of GLP-1. Endogenous incretins, such as GLP-1, improve glycemic control through multiple mechanisms of action, including enhancement of insulin secretion, following their release into circulation from the gut in response to food intake.

Actions of exenatide noted in vivo include sustained improvement in beta-cell function. This improvement is demonstrated by the re-establishment of the first-phase insulin response, the reduction in the proinsulin to insulin ratio. Glucose control is also enhanced via suppression of inappropriately elevated glucagon secretion, slowing of gastric emptying, and reduction in food intake with accompanying weight loss.

Proposed Indications:

To improve glycemic control in patients with type 2 diabetes mellitus [redacted] as an adjunctive therapy to metformin, a sulfonylurea, or a combination of metformin and a sulfonylurea.

Proposed Dosage Recommendation:

The proposed dosing recommendation is as follows: Exenatide therapy should be initiated at 5 µg per dose administered twice daily (BID) at any time within the 60-minute period before the morning and evening meals. Exenatide should not be administered after a meal. Based on clinical response, the dose of exenatide can be increased to 10 µg BID after 1 month of

therapy. Each dose should be administered as a subcutaneous (SC) injection in the thigh, abdomen, or upper arm.

2.1.3 What are the highlights of the formulation of drug product?

Eight formulations have been used in the development of exenatide (Table 1). The majority of clinical studies were conducted using the intended commercial formulation (AC2993-F8). All formulations contain [redacted] acetate buffer, [redacted] mannitol, and have a pH of pH 4.5. The formulations differ mainly in exenatide strength (ranging from [redacted] and preservative content. The commercial formulation (AC2993-F8) has been used in the most clinical pharmacology and all pivotal clinical trials.

Table 1. Composition of exenatide injection formulations

Formula No.	Concentration (mg/mL)					
	Exenatide (mg/mL)	Mannitol, USP (mg/mL)	Metacresol, USP (mg/mL)	Glacial Acetic Acid, USP (mg/mL)	Sodium Acetate Trihydrate, USP (mg/mL)	Water for Injection, USP
AC2993-F1[a]	[redacted]					
AC2993-F2[a]						
AC2993-F3[a]						
AC2993-F4[a]						
AC2993-F5[a]						
AC2993-F6[a]						
AC2993-F7[a]						
AC2993-F8[b]						

[a] Formulas AC2993-F1 through AC2993-F7 were manufactured at [redacted] and [redacted]. These formulas were packaged in vials and were used for early clinical and pre-clinical studies.

[b] Formula AC2993-F8 was manufactured at [redacted]. This formula was packaged in cartridges and used for phase 3 and other clinical studies. This is the intended commercial formulation.

2.2 General Clinical Pharmacology

2.2.1 What are the pharmacokinetic characteristics of a single dose of exenatide following subcutaneous (SC) administration in type 2 diabetes (by Dr. Wei Qiu)?

The mean single dose pharmacokinetic parameters of exenatide were estimated from the Combined, Single-dose database (TY2P12SD). Following SC administration, exenatide was rapidly absorbed and peak concentration was reached at 2.14 hour. Exenatide was rapidly eliminated with a mean terminal half-life of 2.4 hour. The mean apparent clearance (CL/F) was 9.1 L/h and the mean apparent volume of distribution (V/F) was 28.3 L.

Single-dose pharmacokinetic parameters of exenatide from six Phase 1 and Phase 2 studies including Studies 2993-102, -103 (Day 1), -104 (Part 2), -107 (Day 1), -110, and -118 (SC treatment arms) were combined into a Combined, Single-Dose database (TY2P12SD). Multiple parameter estimates from the same individual were considered discrete data in the analysis. Studies 2993-102, -103, -110, and -118 involved pharmacokinetic sampling for relative longer duration (8 to 15 hours post dose) compared with the other two studies 2993-104 (5-hour post dose) and 2993-107 (6-hour post dose). Therefore, the CL/F and V/F values were only calculated for these studies. Considering the relative short period of time of plasma sampling, the half-life values for studies 2003-104 and 2993-107 might not be determined as accurate as the studies

where sampling times were relatively longer. However, the half-life values obtained from these two studies were not quite different from the other studies. Therefore, the data from all six studies were used to estimate the mean half-life values. The study summary statistics including geometric mean (10^{th} to 90^{th} percentile) for single dose pharmacokinetic parameters of exenatide are presented in Table 2.

Table 2. Geometric Mean (10^{th} to 90^{th} percentile) of Pharmacokinetic Parameters of Single Dose Exenatide following SC Administration from Individual Studies (TY2P12SD)

Study	AUC0-inf ((pg.h/mL)/(ug/kg))	Cmax ((pg/mL)/(ug/kg))	Clearance (L/h)	Volume (L)	T1/2 (h)
102	9098 (6702-11526)	1618 (780-2277)	9.71 (7.85-12.38)	47.90 (32.12-81.72)	3.34 (2.33-5.29)
103	11367 (9001-13547)	2256 (1759-3026)	7.22 (5.33-9.48)	23.51 (16.96-35.57)	2.26 (1.61-3.53)
104	13203 (8831-19989)	2089 (1570-2910)	--	--	3.20 (1.68-6.33)
107	--	1904 (1168-3223)	--	--	2.40 (1.28-4.60)
110	8795 (6342-12360)	2067 (1380-3112)	10.20 (7.04-15.97)	22.54 (14.48-39.23)	1.53 (1.17-2.37)
118	10303 (6081-19114)	2097 (1052-3904)	9.66 (5.19-18.11)	27.51 (15.44-64.16)	1.97 (1.36-3.15)

The Proc Mixed procedure in SAS was used for the noncompartmental meta-analysis. A linear mixed effects model was fitted in which the study effect was modeled as a random effect. The within-study subject effect was also modeled as a random effect. Summary statistics are provided in Table 3.

Table 3. Summary of Exenatide Single Dose Pharmacokinetic Parameters: Geometric Mean (10^{th} to 90^{th} Percentiles) of Exenatide Following SC Administration (TY2P12SD)

Parameter	Geometric Mean	10^{th} to 90^{th} percentile	Interstudy CV%	Intrasubject CV%	Intersubject CV%
Tmax (hr)[2]	2.14	1.57-3.54	--	--	--
Vz/F (L)[1]	28.27	15.47-62.50	29.11	36.91	34.81
CL/F (L/hr)[1]	9.07	6.15-15.86	13.90	22.14	30.08
T1/2 (hr)[2]	2.35	1.35-4.52	27.87	42.45	21.14

[1] Four studies (2993-102, 2993-103, 2993-110, and 2993-118) were included in the analysis. Number of patients is 67.

[2] Number of patients is 118.

Results showed that the mean apparent volume of distribution of exenatide was 28.3 L. The mean apparent clearance was 9.1 L/h and the mean half-life was 2.4 h. The mean Tmax was 2.14 hr.

2.2.2 Was the dose-proportionality established for exenatide (by Dr. Wei Qiu)?

Dose-proportionality was established for AUC0-inf over the dose range of 5μg to 10 μg. The Cmax values were less than proportional.

Doses ranging from 0.01 μg/kg to 0.4 μg/kg were evaluated in clinical studies with exenatide. The dose-proportionality was evaluated for Cmax and AUC0-inf over the therapeutic range of 5 μg to 10 μg using a power model. Study and within-study subject were included in the model as random effects. The Combined, Single-dose Database (TY2P12SD) was used. The dose, in μg units, was used in this analysis. Results of the power model analysis are presented in Table 4.

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Table 4. Power model analysis of dose-proportionality of exenatide AUC0-inf and Cmax values over the range of 5 µg to 10 µg using TY2P12SD database.

PK Parameter	Dose (µg)	Power Model Equation	Predicted Geometric Mean PK Parameter Value	Ratio of Dose Normalized Geometric Means (90% CI) [c]	Conclusion Over Dose Range [d]
$AUC_{0-\infty}$ (pg-h/mL)	5	$(127.29 \times D^{0.96})$	595.41	0.97 (0.93, 1.02)	Yes
	10		1157.11		
C_{max} (pg/mL)	5	$(34.31 \times D^{0.79})$	122.88	0.87 (0.82, 0.91)	Yes
	10		212.86		

Abbreviations: $AUC_{0-\infty}$ = area under the concentration-time curve from 0 to infinity; CI = confidence interval, C_{max} = maximum concentration, D = dose, PK = pharmacokinetic

[a] Power Model from full dataset (Appendix 2.7.2.5.1).

[b] Dose-proportionality (predicted geometric means and ratios) assessed on 5-µg to 10-µg dose range.

[c] Ratio of model-predicted geometric mean values for high to low dose, normalized for dose.

[d] Dose-proportionality was concluded over the dose range if the 90% CI for ratio of dose normalized geometric means was entirely contained within 0.7 and 1.43.

Data Source: Combined Single-dose Database

The estimated exponents of the power model equations for AUC0-inf and Cmax were 0.96 and 0.79, respectively. The sponsor did not include the 90% CI in the original NDA submission. Via email (Feb. 14, 2005), the sponsor provided the 90% CI values that were 0.8910 to 1.0261 and 0.7137 to 0.8716, respectively, for the exponents of the power models of AUC0-inf and Cmax. Therefore, dose proportionality was concluded for AUC0-inf over the dose range of 5 µg to 10 µg. The Cmax values were less than proportional. The sponsor concluded dose proportionality for both AUC0-inf and Cmax based on the 90% CI for the ratios of dose-normalized geometric means being between 0.70 and 1.43, which was not acceptable.

2.2.3 What is the effect of exenatide on the first-phase and second phase insulin release in patients with type 2 diabetes?

Type 2 diabetes is characterized by diminished first-phase insulin release and abnormal second-phase insulin release. The sponsor conducted a phase 2, randomized, single-blind, single-center crossover study to assess the effects of exenatide on first-phase and second-phase insulin release in patients with type 2 diabetes mellitus (Study 2993-122).

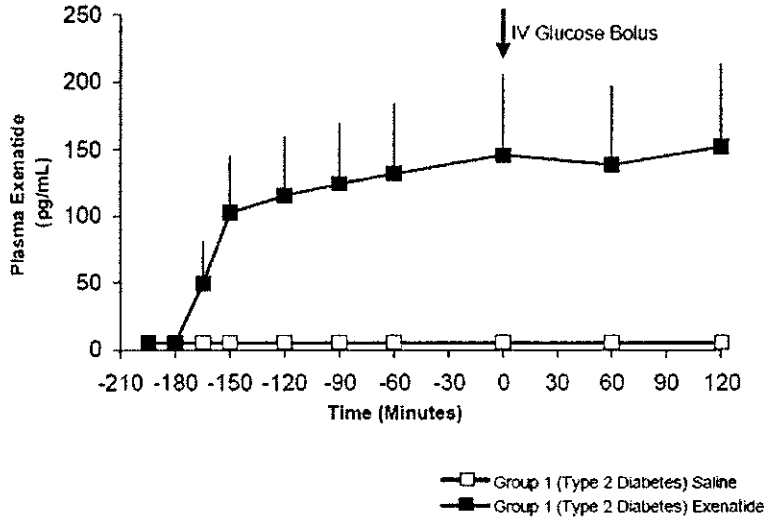
Following enrollment, Group 1 subjects (type 2 diabetes) were domiciled for 4 days/3 nights and Group 2 subjects (healthy controls; reference group) were domiciled for 2 days/1 night. Group 1 subjects were randomly assigned to one of two treatment sequences (AB or BA, where A = saline and B = exenatide). On separate days (Day 2 and Day 4), separated by a one-day wash-out period (Day 3), each Group 1 subject received an intravenous (IV) insulin infusion to reduce plasma glucose to euglycemic concentrations, followed by an infusion of either exenatide (0.05 µg/min for the first 30 min followed by 0.025 µg/min steady-state) or saline in a randomized order. Group 2 subjects received only saline infusions. An intravenous glucose tolerance test (IVGTT) was administered to subjects in both groups during the infusions of exenatide or saline to assess first- and second-phase insulin release in response to a glucose stimulus. A total of 26 subjects were enrolled: 14 Group 1 and 12 Group 2. Of those, 25 (96.2%) subjects completed the study and 1 (3.8%) was withdrawn early due to an adverse event.

The primary efficacy measure for examining the effect of exenatide was first-phase insulin release (FPIR). Secondary efficacy measures included second-phase insulin release

(SPIR), glucose disappearance constant (Kg), and insulin secretion rate (ISR). Blood samples were drawn for measurement of plasma exenatide on Day 2 and Day 4 for subjects in Group 1 only. Pharmacodynamic measures included insulin, C-peptide, glucose, proinsulin, and glucagon concentrations.

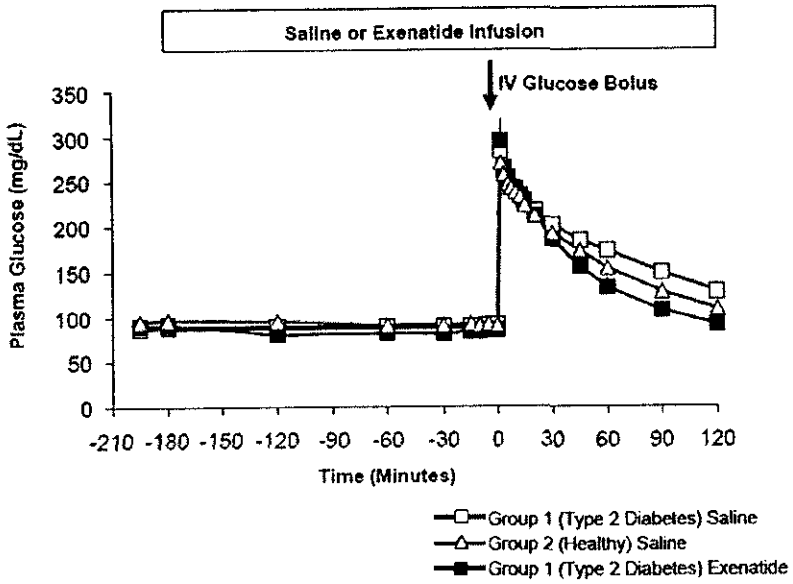
Mean plasma exenatide concentration rose rapidly and reached therapeutic levels (> 50 pg/mL) within 20 min after the start of the exenatide infusion and continued to increase for 30 min. Mean concentrations gradually increased to 131 pg/mL for 150 min until glucose stimulation and remained relatively constant (131 to 152 pg/mL) until cessation of exenatide infusion (Figure 1).

Figure 1. Mean (+SD) plasma exenatide concentration (population: evaluable Group 1 subjects in Study 2993-122 [N = 13])



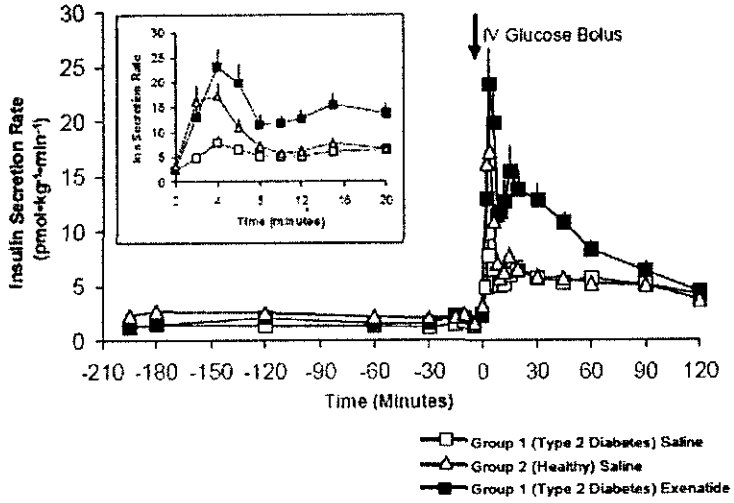
Pharmacodynamic results showed that the elevation of plasma exenatide concentrations to the therapeutic range (>50 pg/mL) produced a 4-fold increase in FPIR (0 to 10 min), restoring the impaired glucose-stimulated FPIR in subjects with type 2 diabetes. Exenatide concentrations maintained at the therapeutic range significantly improved glucose-stimulated FPIR in subjects with type 2 diabetes (LS mean: 675 mU•min/L [Group1 exenatide infusion] versus 164 mU•min/L [Group 1 saline infusion]; p = 0.0002) to levels observed in healthy subjects (675 mU•min/L [Group 1 exenatide infusion] versus 443 mU•min/L [Group 2 without exenatide], p = 0.1149). A significant increase in SPIR was also observed in type 2 diabetes subjects (6916 mU•min/L [Group 1 exenatide infusion] versus 2027 mU•min/L [Group 1 saline infusion], p = 0.0002) and when compared to healthy subjects (6916 mU•min/L [Group 1 exenatide infusion] versus 2055 mU•min/L [Group 2], p = 0.0029). Insulin Secretion Rate (ISR) and Glucose Disappearance Constant (Kg): Exenatide did not directly stimulate insulin secretion when glucose concentrations were in the euglycemic range during the 180 min infusion prior to IVGTT. Following IVGTT, the mean (SD) ISR at 4 min for Group 1 subjects during exenatide infusion peaked rapidly to 23.4 (11.73) pmol•kg-1•min-1 and was higher than Group 2 (17.2 (9.55) pmol•kg-1•min-1) subjects. Elevations in second-phase insulin release occurred primarily from 10 to 90 min. Plasma glucose concentrations were elevated following administration of the IV glucose bolus and then plasma glucose concentrations diminished over time.

Figure 2. Mean (SE) Plasma Glucose Concentration Time Curve by Group and Treatment [N = 13, Group 1; N = 12, Group 2])



Insulin secretion rates were derived from the standard parameters for C-peptide distribution and clearance from the C-peptide concentration profiles. During the 180 min infusion period prior to IVGTT, the mean insulin secretion rate was similar for Group 1 during infusions of exenatide and saline, but was slightly higher in Group 2 subjects. Following IVGTT, a rapid rise in insulin secretion rate was observed in all three groups. Insulin secretion rates initially peaked at 4 min to 23.4 (11.73) pmol•kg^{-1}•min^{-1} for Group 1 subjects during infusion of exenatide compared with 7.8 (5.21) pmol•kg^{-1}•min^{-1} for Group 1 during infusion of saline and 17.2 (9.55) pmol•kg^{-1}•min^{-1} for Group 2.

Figure 3. Mean (SE) Insulin Secretion Rate [N = 13, Group 1; N = 12, Group 2])

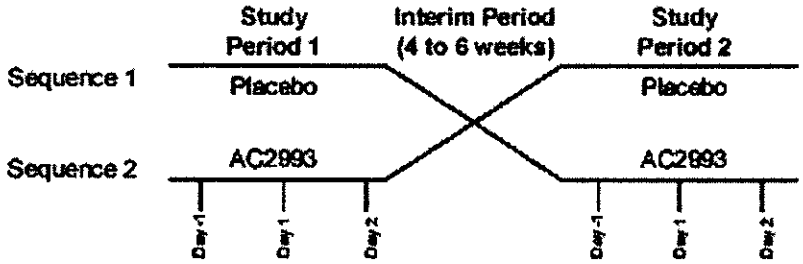


Therefore, the intravenous infusion of exenatide resulted in restoration of impaired first-phase insulin secretion in subjects with type 2 diabetes, as evidenced by a four-fold increase in plasma insulin AUC (0 to 10 min) and a three-fold increase in insulin secretion rate (at 4 min post glucose bolus) compared to saline. First-phase insulin secretion during IV exenatide infusion was similar to or greater than that observed in Group 2 subjects (healthy controls) administered saline infusions. The intravenous infusion of exenatide resulted in improvements in glucose-stimulated second-phase insulin secretion as evidenced by a 3.5-fold increase in plasma insulin AUC (10 to 120 min) and a 2.4-fold increase in peak insulin secretion rate (15 min post glucose bolus) compared to saline. These improvements resulted in higher second-phase insulin secretion than that observed in healthy control subjects receiving saline.

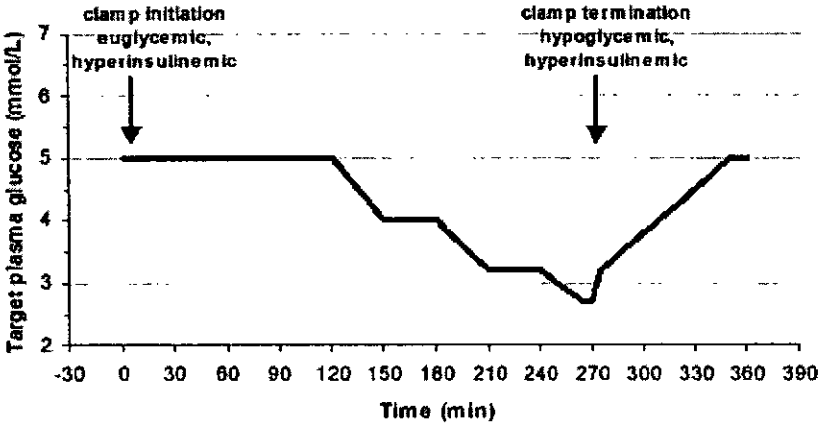
2.2.4 What is the effect of intravenously administered exenatide on insulin secretion and counter regulation in healthy subjects?

The sponsor conducted a triple-blind, placebo-controlled crossover study to assess the effects of exenatide delivered via continuous intravenous infusion on insulin secretion during euglycemia and various levels of hypoglycemia and to assess the effects of exenatide on the counter regulatory response to hypoglycemia in healthy subjects by quantitating changes in circulating concentrations of glucagon, growth hormone, cortisol, free fatty acids, epinephrine, and norepinephrine.

25 subjects were housed in the study unit for 3 days (2 nights) during each of the study periods and received the randomized study medication on Day 1 of each study period. Subjects were randomly assigned to one of two treatment sequences in this crossover study, each of which included a 360-minute infusion of exenatide, a 360-minute infusion of placebo, and a 4-to 6-week interim period as shown in the following diagram:

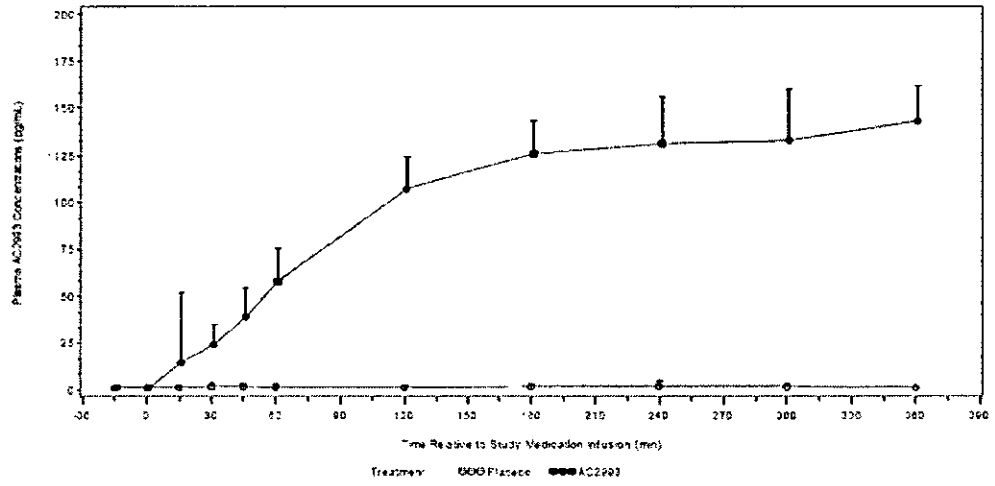


Exenatide or the equivalent volume of placebo was infused (0.066 pmol/kg/min) starting at time 0 and continued at a constant rate for 360 minutes. A euglycemic hyperinsulinemic clamp, followed by a stepwise hypoglycemic clamp was carried out from 0-270 minutes as demonstrated in the following schematic:



The plasma glucose concentration was targeted to ~ 5 mmol/L from time 60-120 minutes (euglycemic phase); and fall in progressive increments during the hypoglycemic phase; ~ 4 mmol/L from time 120-180 minutes, and ~3.2 mmol/L from time 180-240 minutes; the plasma glucose concentrations were maintained by the glucose clamp technique at the target concentration during the last 30 minutes of each step period. During the 240-270 minutes period, the plasma glucose concentration was targeted to ~2.7 mmol/L, where it was maintained for 5 minutes. At 270 minutes, insulin infusion and glucose clamp were terminated and plasma glucose was increased to 3.2 mmol/L to ensure subject safety; subsequent recovery from that point was assessed for a further 90 minutes. The time to achieve a plasma glucose concentration of at least 4 mmol/L was recorded. The variable glucose infusion may have been continued if needed to prevent the plasma glucose concentration from dropping below 3.2 mmol/L. Blood samples were collected throughout the 390-minute period (-30 minutes to 360 minutes) for determination of concentrations of circulating glucose, insulin, glucagon, growth hormone, cortisol, C-peptide, epinephrine, norepinephrine, free fatty acids, and exenatide.

Figure 4. Mean (SD) plasma exenatide concentration-time curve by treatment (evaluable subjects in Study 2993-111 [N=11])



Mean insulin concentrations were similar between the two treatments prior to infusion of study medication (-30 to 0 min). During time 0 through to 270 min, a fixed rate of insulin was infused for both treatments to maintain the hyperinsulinemic clamp. Significantly higher insulin concentrations were observed with exenatide treatment compared with placebo at glucose concentrations of approximately 5 mmol/L (90-120 min) (geometric LS mean of 413.48 pmol/L for exenatide treatment vs. 348.25 pmol/L for placebo treatment; with a geometric LS mean ratio of 1.19). The 95% confidence interval for the ratio did not include 1 (1.05, 1.34) demonstrating a statistically significant difference. In the presence of hypoglycemia (4 mmol/L to 3.2 mmol/L), insulin concentrations progressively declined with exenatide treatment reaching similar concentrations to those observed with placebo treatment. During the recovery period (270-360 min), after the insulin infusion was terminated, mean insulin concentrations declined rapidly and were similar for both treatments.

Continuous infusion of exenatide (0.066 pmol/kg/min; 0.4 μg/kg/day) was well tolerated in healthy volunteers. The study demonstrated the glucose-dependent insulinotropic action of exenatide in healthy volunteers as evidenced by a 3 to 3.5-fold increase in the insulin secretion rate with exenatide treatment at glucose concentrations of 5 mmol/L. The insulin secretion rate decreased markedly at glucose concentrations of approximately 4.5 mmol/L. When plasma glucose concentrations were at or below 4 mmol/L, the insulinotropic effect of exenatide was negligible as compared with placebo. The counter regulatory response as measured by glucagon, epinephrine, norepinephrine, cortisol, and growth hormone concentrations remained intact during hypoglycemia with exenatide treatment. As a result, the recovery time from hypoglycemia was the same for each treatment indicating that exenatide does not impair the ability to reverse insulin induced hypoglycemia.

2.2.5 Is two times a day (BID) regimen superior or compatible to three times a day (TID) regimen for exenatide treatment of type 2 diabetes?

The sponsor conducted a Phase 2, randomized, double-blind, placebo-controlled, multi-center study to examine the effect on glucose control of exenatide (0.08 μg/kg) given two times a day versus three times a day for 28 days in patients with type 2 diabetes treated with sulfonylureas and/or metformin. 109 patients were randomized to the four groups: BID (bd) (breakfast and dinner), BID (bs) (breakfast and bedtime), TID (breakfast, dinner, bedtime) injection of exenatide 0.08 μg/kg; or TID (breakfast, dinner, bedtime) injections of placebo. Patients randomized to the BID regimens received a third injection of placebo in order to preserve the blind.

The primary efficacy endpoints were the change in serum fructosamine concentrations from Day 1 to Day 28 and the change in time-weighted average postprandial plasma glucose concentrations from Day -1 to Day 1 and Day 28. Changes were computed as follow-up day minus baseline day. A one-way ANOVA was used to test the null hypotheses of no difference among treatment groups versus the alternative hypothesis of a difference among treatment groups. Pairwise comparisons of interest included comparing each of the three exenatide treatment groups to the placebo group. Both the unadjusted p-values and the Dunnett adjusted p-values are calculated and presented. 97 subjects (89%) completed the study and 12 (11%) subjects withdrew. Seven (6%) subjects withdrew from the study due to an adverse event. Efficacy results are summarized in Table 6.

Table 5. Primary and Key Secondary Efficacy Parameters: Comparisons to Placebo (Population: Intent-to-Treat)

	Placebo (N=28)	Exenatide BID (bd) (N=26)	Exenatide BID (bs) (N=27)	Exenatide TID (N=28)
Primary Efficacy Parameters				
Serum Fructosamine (µmol/L)				
Mean Change From Day 1 to Day 28	-5.3	-45.1	-39.0	-45.6
Unadjusted p-value		<0.001	0.004	<0.001
Postprandial Plasma Glucose (mg/dL)				
Mean Change From Day-1 to Day 28	–11.3	–79.1	–56.9	–60.4
Unadjusted p-value		<0.001	0.004	0.002
Key Secondary Efficacy Parameters				
HbA1c (%)				
Mean Change From Day 1 to Day 28	–0.25	–1.08	–0.70	-1.02
Unadjusted p-value		<0.001	0.006	<0.001

Exenatide BID (bd)= twice daily at breakfast and dinner; Exenatide BID (bs)= twice daily at breakfast and bedtime; Exenatide TID= three times daily at breakfast, dinner, and bedtime.

A one-way ANOVA also showed no statistically significant change in mean fasting lipid (LDL cholesterol, HDL cholesterol, LDL/HDL cholesterol ratio, triglyceride, and Apo B) concentrations among the treatment groups.

Fifteen subjects (20% of those with Week 28 data) receiving exenatide and zero placebo subject generated treatment-emergent positive antibody responses by Day 28. Five subjects had a low titer (1:5) antibody response at baseline (2 placebo/3 active) that did not increase in titer during the study.

Exenatide 0.08 µg/kg administered subcutaneously two or three times a day for 28 days significantly improved glycemic control. Reductions in mean serum fructosamine concentrations from Day 1 to Day 28 were significantly greater for subjects receiving exenatide (range of means: -39.0 to -45.6 µmol/L) compared to placebo (-5.3 µmol/L). Reductions in mean postprandial plasma glucose concentrations from Day –1 to Day 28 were also significantly greater for subjects receiving exenatide (range of means: –79.1 to –56.9 mg/dL) compared to placebo (-11.3 mg/dL). The efficacy results from two or three times a day regimens are compatible.

2.2.6 Does exenatide impact the absorption of oral drugs by time dependent manner?

Since exenatide delays gastric emptying, the absorption rate of orally administered medications taken concomitantly may be altered. Acetaminophen was used as a representative oral drug because it is predominantly absorbed from the small intestine, has a well characterized PK profile. The acetaminophen dose (1000 mg) utilized in this study is a commonly administered dose. A 10 µg dose of exenatide was selected for this study, because 10 µg is the highest dose proposed for commercialization. The sponsor conducted a randomized, single-blind, placebo-controlled, six-way crossover study to define the time window (in relation to exenatide dosing) during which the pharmacokinetics of orally administered drugs may be altered. On 6 consecutive study days, healthy subjects received one of six treatments in random order. Each

treatment (A, B, C, D, E, and F) was defined by the study medication administered (exenatide 10 μg or placebo) and the timing of oral acetaminophen elixir administration relative to the time at which study medication (exenatide 10 μg or placebo) was administered (0 h). On each study day, subjects received a single injection of study medication (exenatide 10 μg or placebo) 15 minutes prior to breakfast. The standardized breakfast consisted of cereal, milk (8 oz.), toast, butter, jelly, and decaffeinated coffee or tea. Results are presented in Figure 6 and PK parameters are summarized in Table 7.

Figure 5. Mean (+SD) plasma acetaminophen concentration-time curve by treatment (N=39)

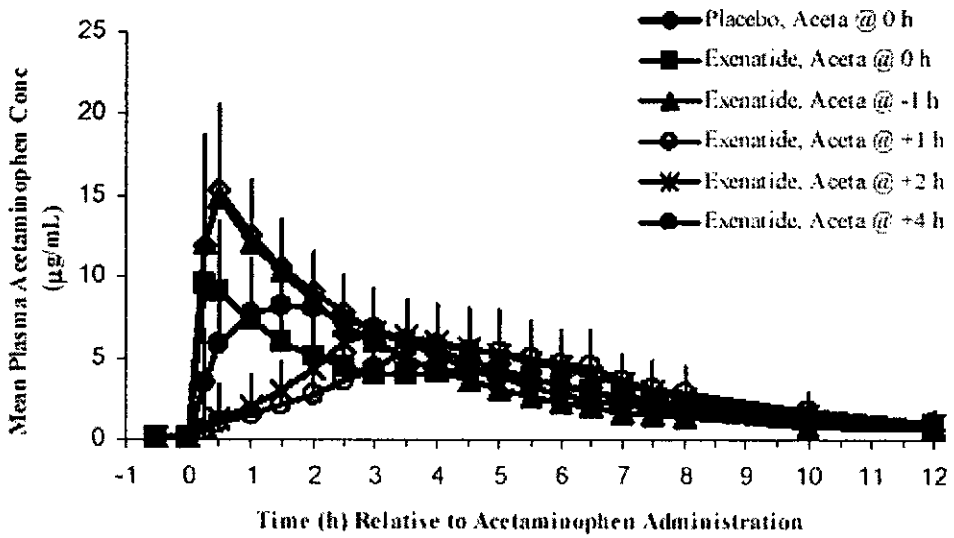


Table 6. Plasma acetaminophen pharmacokinetic parameters by treatment population (mean ±SD, N=39)

Parameter	Placebo Aceta 0 h	Exenatide Aceta -1 h	Exenatide Aceta 0 h	Exenatide Aceta +1 h	Exenatide Aceta +2 h	Exenatide Aceta +4 h
AUC(0-12 h) (μg•h/mL)	52.6 (14.4)	47.0 (13.0)	41.6 (14.0)	40.6 (12.0)	39.8 (12.4)	45.0 (13.8)
Cmax (μg/mL)	16.7 (4.9)	16.0 (4.8)	10.6 (4.6)	7.3 (2.5)	7.7 (2.5)	9.8 (3.0)
Tmax (h)	0.6 (0.3)	0.6 (0.3)	0.9 (1.6)	4.2 (1.2)	3.3 (1.2)	1.6 (1.0)
t1/2 (h)	2.5 (0.5)	2.9 (1.1)	3.0 (1.1)	2.6 (0.9)	2.5 (0.6)	2.9 (1.0)

The maximal effect of exenatide on mean plasma acetaminophen Cmax and Tmax were observed when acetaminophen was administered at +1 hour relative to exenatide administration. In comparison to placebo, mean plasma acetaminophen Cmax was reduced by 56.3% and Tmax was prolonged 3.6 h. When acetaminophen was administered at +2 hour relative to exenatide dosing, the magnitude of reduction in Cmax and prolongation of Tmax was slightly smaller in comparison to values obtained with acetaminophen administration at +1 hour. The reduction in acetaminophen AUC at 0, +1, +2 hours relative to exenatide administration is 21%, 23% and 24%, respectively. The extent of change in Cmax is much greater than the change in AUC by concurrent administration of exenatide.

The reviewer agrees with the sponsor that the results of this study could be extended to other orally administered medications taken by patients with type 2 diabetes concomitantly with exenatide. Patients should be advised to take oral drugs at least one hour before exenatide use.

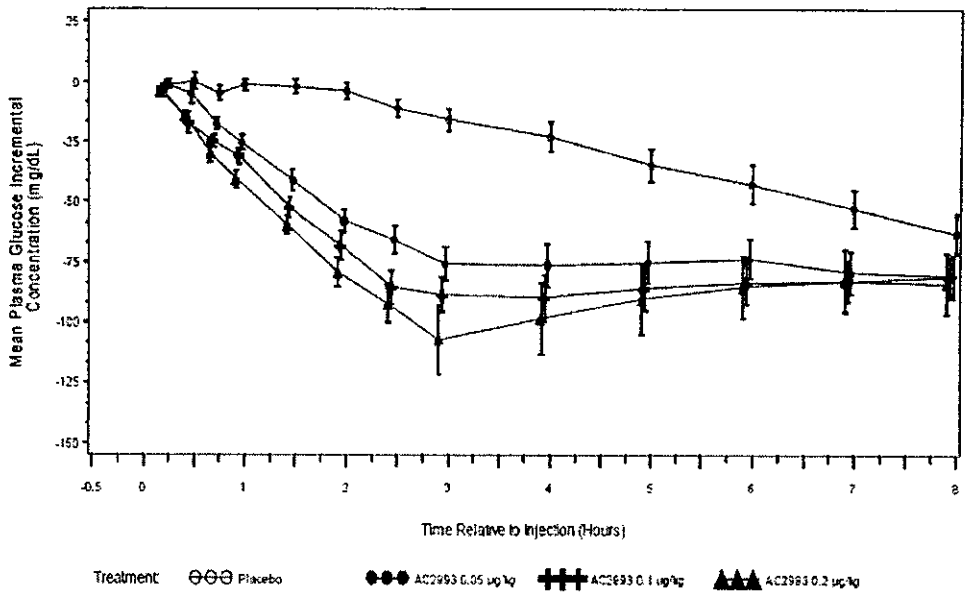
2.2.7 What is the effect of exenatide on plasma glucose concentrations in fasting patients with type 2 diabetes?

The sponsor conducted a double-blind, placebo-controlled crossover study to examine the effect of subcutaneously injected exenatide on plasma glucose concentrations for 8 hours in 14 fasting subjects with type 2 diabetes. Subjects were randomly assigned to one of four treatment sequences (Treatment Sequence: 1 = ADBC, 2 = BACD, 3 = CBDA, 4 = DCAB; Treatment: A = Placebo, B = 0.05 μg/kg exenatide, C = 0.1 μg/kg exenatide, D = 0.2 μg/kg exenatide). Subjects were to fast from 2200 hours on Day –1, Day 2, Day 4, and Day 6. On Day 1, Day 3, Day 5, and Day 7, subjects received a single subcutaneous injection of study medication (exenatide or placebo) at time = 0 (approximately 0700 hours) according to the assigned treatment sequence. No treatment was given on Day –1, Day 2, Day 4, Day 6, or at study termination. During the 8 hours following study medication injection, blood samples were collected at timed intervals to measure plasma glucose, serum insulin, plasma epinephrine, plasma norepinephrine, plasma glucagon, serum cortisol, serum growth hormone, and plasma exenatide. Serum prolactin was assessed at 1 hour after dosing. 12 subjects completed at least two treatment periods.

Mean plasma exenatide concentrations increased in relation to dose from baseline to a maximum concentration at 2 hours for all exenatide doses. At the 2-hour time point, mean exenatide concentrations were 100.8 pg/mL, 205.2 pg/mL, and 359.2 pg/mL, for the 0.05 μg/kg, 0.1 μg/kg and 0.2 μg/kg doses, respectively, compared to placebo at 1.3 pg/mL. Pharmacokinetic plots for individual subjects were consistent with the mean curves with a clear dose-dependent pattern apparent for every subject.

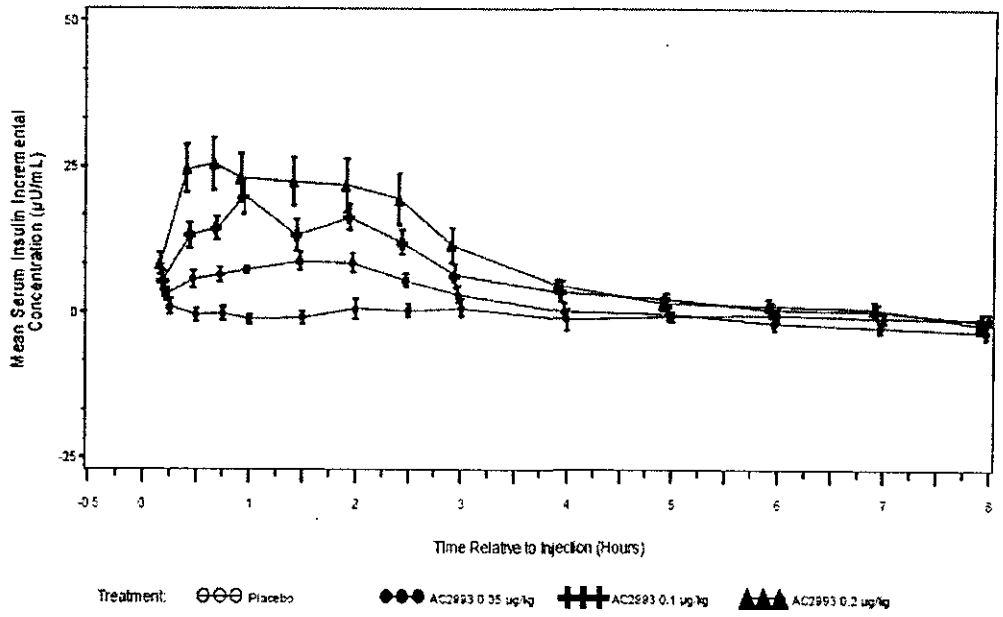
All three doses of exenatide (0.05 μg/kg, 0.1 μg/kg, and 0.2 μg/kg) markedly reduced fasting plasma glucose concentrations in a dose-dependent manner during the 8-hour time period (Figure 6). With exenatide treatment, there was a 38 mg/dL to 55 mg/dL greater reduction in baseline corrected average fasting plasma glucose concentrations compared to the decrease observed with placebo treatment. The mean fasting plasma glucose nadir occurred between 3 and 4 hours after administration of exenatide. At 3 hours postdose, mean incremental fasting plasma glucose concentrations were –75.7 mg/dL, -88.6 mg/dL, and -107.0 mg/dL for exenatide doses 0.05 μg/kg, 0.1 μg/kg, and 0.2 μg/kg, respectively. Similar values were observed at 4 hours postdose with mean incremental fasting glucose concentrations of -76.2 mg/dL, -89.7 mg/dL, and –98.5 mg/dL for exenatide doses 0.05 μg/kg, 0.1 μg/kg, and 0.2 μg/kg, respectively. For placebo, the mean incremental fasting plasma glucose concentrations were -15.9 mg/dL at 3 hours and -23.0 mg/dL at 4 hours. Fasting plasma glucose concentrations remained below baseline at 8 hours postdose. Fasting plasma glucose pharmacodynamic parameters AUC(0-8 h), Cave, Cmax, and Cmin decreased in a dose-dependent manner for exenatide treatments compared to placebo.

Figure 6. Mean (±SE) incremental fasting plasma glucose concentration-time curve by treatment [N = 12])



There was a dose-dependent increase in mean incremental fasting serum insulin concentrations for the three exenatide treatments (0.05 µg/kg, 0.1 µg/kg, and 0.2 µg/kg) compared to placebo within the first few hours after dosing (Figure 7). By 2 hours postdose, mean fasting incremental serum insulin concentrations for all exenatide treatments had peaked. Thereafter, mean fasting incremental serum insulin concentrations began to decrease, and by 4 hours postdose they approached baseline for all exenatide treatments. The time frame of the observed peak and subsequent decrease of fasting serum insulin concentrations coincided with the time frame of the nadir for fasting glucose concentrations. After 4 hours postdose, little difference was observed between mean incremental fasting serum insulin concentrations for the exenatide treatments and placebo. However, the glucose-dependent insulinotropic nature of exenatide was still apparent because similar serum insulin concentrations were maintained in response to significantly lower plasma glucose concentrations compared to those seen with placebo. Mean incremental serum insulin concentrations peaked earlier for higher doses. Mean incremental serum insulin concentrations peaked at 45 minutes, 1 hour, and 1.5 hours for exenatide doses 0.2 µg/kg, 0.1 µg/kg, and 0.05 µg/kg, respectively. Corresponding mean incremental serum insulin concentrations at these time points were 25.6 µU/mL, 20.0 µU/mL, and 8.8 µU/mL, for the 0.2 µg/kg, 0.1 µg/kg, and 0.05 µg/kg doses, respectively. Fasting serum insulin pharmacodynamic parameters AUC(0-8 h), Cave, and Cmax increased in a dose dependent manner for exenatide treatments compared to placebo.

Figure 7. Mean (±SE) incremental fasting serum insulin concentration-time curve by treatment [N=12])



Exenatide (0.05 µg/kg, 0.1 µg/kg, and 0.2 µg/kg) effectively lowered fasting plasma glucose concentrations in a dose-dependent manner over 8 hours. With exenatide treatment, there was a 38 mg/dL to 55 mg/dL reduction in baseline corrected average fasting plasma glucose concentrations compared to the decrease observed with placebo treatment. The period of greatest glucose reduction coincided with peak serum insulin concentrations.

An apparent dose-dependent increase in mean fasting incremental plasma epinephrine and serum growth hormone concentrations was observed for the exenatide treatments. An apparent increase in mean incremental fasting norepinephrine was observed for the 0.1 µg/kg and 0.2 µg/kg doses. No trends were observed for serum prolactin concentrations.

2.2.8 What is the effect of time of administration of subcutaneous exenatide relative to a meal on post-prandial glycemic control in patients with Type 2 diabetes?

Previous clinical studies with exenatide have largely been conducted with subcutaneous exenatide administration occurring within 15 minutes prior to a meal. It is important to know when the exenatide administration will reach optimal effectiveness to control post prandial glucose and avoid potential for hypoglycemia. The sponsor conducted an exploratory study to investigate the clinical implications of the administration of exenatide at various times relative to a meal. This was an open-label, placebo-controlled, randomized, fixed sequence, six-way crossover study. Only pharmacodynamic parameters were analyzed. Each subject was to receive 5 subcutaneous single doses of 10µg exenatide (administered at -60, -15, 0, 30 and 60 minutes relative to the start of a standard breakfast), and one subcutaneous dose of placebo administered 15 minutes prior to the start time of a standard breakfast over six consecutive days (Days 1 to 6). Results showed that each of the exenatide treatments demonstrated improved glycemic control compared to placebo. For the exenatide treatments, the peak post-prandial glucose concentration

was lower following administration prior to the meal or at the time of the meal, compared to administration after the meal.

Figure 8. Comparison of mean post-prandial absolute plasma glucose profiles across treatments.

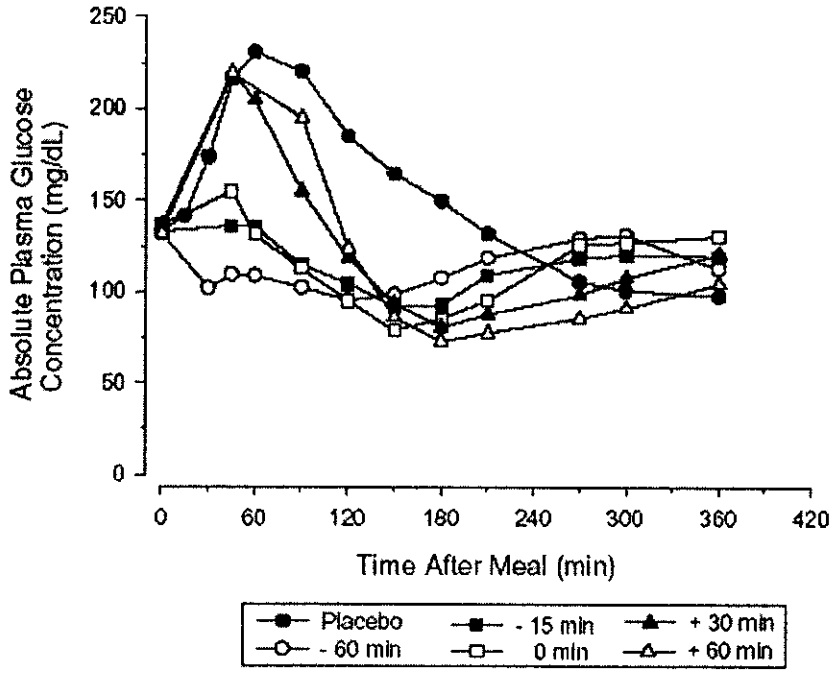


Table 7. Absolute plasma glucose pharmacodynamic parameters by treatment (mean ±SD)

Parameter	Treatment					
	Placebo	**-60 min**	**-15 min**	**0 min**	**30 min**	**60 min**
N	16	15	16	15	16	16
AUC0-6h (mg.min/dL)	52800 (13200)	40300 (7120)	40800 (8250)	41300 (7420)	43700 (9520)	42200 (9780)
Cmax (mg/dL)	237 (50.7)	158 (31.4)	161 (32.1)	169 (40.9)	219 (47.9)	225 (52.9)
Cmin (mg/dL)	91.9 (21.8)	75.5 (16.2)	70.7 (19.6)	67.2 (15.2)	61.9 (18.7)	55.4 (12.7)

Based on the results of this study, particularly the data relating to low plasma glucose values and symptoms of hypoglycemia, the optimal timing of exenatide administration is within 60 minutes prior to, or simultaneously with a meal. Administration after a meal should be avoided, as some subjects may be at risk of low blood glucose.

2.2.9 What are characteristics of exenatide metabolism and elimination?

No significant fragments of exenatide were found in plasma following IV or SC injection in rats. The role of the liver in exenatide degradation and clearance was studied by comparing PK parameters between liver injured and control rats and found to not contribute significantly if at all, to the clearance of exenatide. Experiments were also carried out in renal-ligated rats to assess

the involvement of the kidney in clearance of exenatide. Three metabolites were present at very low levels in renal-ligated rats that could not be identified in control rats suggesting that exenatide and or exenatide metabolites were cleared from the system by the kidney before they could accumulate. From animal studies, it appears to be that exenatide is metabolized in the kidney following renal filtration so that exenatide does not appear in the urine in significant amounts. The characterization of exenatide metabolites from human plasma or urine was not performed.

2.2.10 What was the justification on dosing transition from body weight adjusted dosing in the Phase II studies to the fixed dosage regimens in the Phase 3 studies (by Dr. Sang Chung)*?*

The sponsor proposed the fixed dosage regimen for the Phase 3 studies using the modeling and simulation results with data from the Phase 2 studies, which were based on the body weight adjusted dosing. Justification of the fixed dosing regimens was consisted of mainly four steps: 1) selection of a target window for exenatide AUC, 2) simulation using the PPKPD relationship for distribution of exenatide AUC after body weight adjusted dosing to measure range of fixed dosed within the target window (Simulation Study 1), 3) simulation for distribution of exenatide AUC after the fixed doses (Simulation Study 2), and 4) selection of the proposed fixed doses based on the results of simulation studies.

At least 30% reduction in postprandial glucose excursion was selected as the threshold as acceptable glycemic benefits in efficacy, and the incidence of dose limiting gastrointestinal adverse events in safety (e.g., nausea and vomiting) was decided as the factor determining the upper target window. Optimal target window of exenatide AUC was chosen as between 600 pg h/ml and 950 pg h/ml based on the acceptable efficacy threshold and the dose limiting adverse events.

The PPKPD analysis using a sigmoid inhibitor E_{max} model was conducted to evaluate exposure-response relationship with total 195 data from 50 patients in the four Phase 2 studies. Exenatide AUC and postprandial glucose AUC up to 5 hours postdose were the parameters for the PPKPD analysis. Data distribution was showed in the Figure 11, and the estimates of the final model were summarized in the Table 9.

Figure 9. Relationship between exenatide AUC and postprandial glucose AUC (Red lines represent the optimal target window)

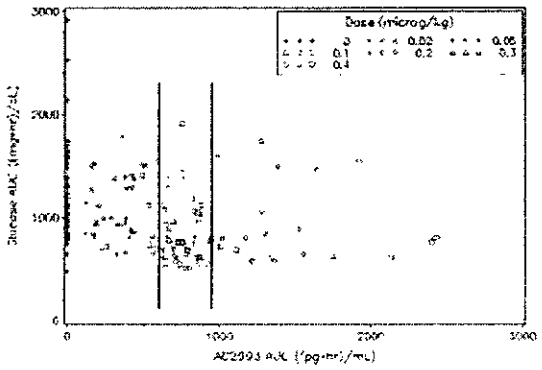


Table 8. Estimates and SE for the structural model*

Parameter	Population mean		Inter-subjects variability (%CV)	
	Final estimate	%SEM	Final estimate	% SEM
AUC_{50} (pg h/ml)	444	29.3	29.3	29.3
E_{max} (fraction of baseline glucose AUC)	0.515	6.6		
Residual variability (SD)	100.0	19.6		

*: $AUC_{glc,0-5} = E_0 - \left[\frac{E_{max} \times AUC_{exe,0-5}}{AUC_{50} + AUC_{exe,0-5}}\right]$

where, E_0 = measured baseline glucose AUC when administered placebo (mg h/dL)
E_{max} = the maximum reduction in glucose ACU_{0-5} from placebo (mg h/dL)
AUC_{50} = the exenatide AUC at which 50% of the maximum reduction in glucose AUC occurs
An exponential and an additive error model was introduced for AUC_{50} and residual error, respectively.

The exenatide exposure up to 5 hours postdose ($AUC_{exe,0-5}$) were simulated using the Bayesian parameter estimates in the final PK model with doses of 0.1, 0.15, 0.175, and 0.2 μg/kg (Simulation Study 1). Total doses ranging from 5μg to 16μg with median value of 9μg showed exenatide exposure within the target window according to the results of Simulation Study 1. Doses of 5, 9, 10, and 12μg were selected to simulate the exenatide exposure range ($AUC_{exe,0-5}$) and % postprandial glucose reduction under fixed dosage regimens (Simulation Study 2), and primary results were summarized in the Table 10.

Table 9. Distribution of exenatide AUC and % glucose AUC reduction from placebo

Dose (μg)	Exenatide AUC			Glucose AUC		
	% of subjects <600	% of subjects 600-950	% of subjects > 950	% of subjects <20% reduction	% of subjects 20-40% reduction	% of subjects >40% reduction
5	91.7	8.2	0.1	39	47.5	13.5
9	19.8	65.7	14.5	24.5	55.9	19.8
10	13	63.9	23.1	23.4	54.8	21.8
12	6.6	42.2	51.2	20.1	55.5	24.4

Fixed dosing of 5μg or 10μg BID was proposed from the conclusion that two doses would have a favorable balance of glucose reduction and incidence of adverse events based on the results of Simulation Study 2. The results were presented at the End-of-Phase 2 (EOP2) meeting between the sponsor and the Agency.

Reviewer's Comments:

The results of modeling and simulation were generally acceptable. However, there were several issues related to modeling, and thus it should be cautious in the interpretation of results.

First, the estimate of E_{max} was not reliable because of two issues. One was that E_{max} was a constant fraction of baseline glucose AUC according to the sponsor's model (i.e., E_{max} = 0.5146* (baseline glucose AUC)). The results appeared to be overly simplified. For example, magnitude of drug effect can be proportional or inversely proportional to the baseline glucose AUC in addition to a constant fraction of the baseline value. Therefore, the relationship between the magnitude of drug effect and the baseline condition is to be estimated based on data, not estimated based on assumption. The other one was that the apparent E_{max} was observed in only

about 6% of patients according to the exploratory analysis (i.e., 3 patients out of total 50 patients), and thus the estimate seems to be not reliable measure.

Second, there was no predictor for dose limiting adverse events (e.g., gastrointestinal side effects), and thus the proposed doses were chosen primarily based on results of efficacy distributions. However, glucose AUC in conjunction with minimum concentration under a threshold for hypoglycemic events (e.g., below 60 mg/dL) can be a potential predictor for the dose limiting adverse events. In this regard, it is recommended considering a predictor for the adverse events for E-R in the future studies.

2.3 INTRINSIC FACTORS

2.3.1 Age, Gender, Race:

- ***Do age, gender, and race impact the pharmacokinetics of exenatide (by Dr. Wei Qiu)?***

The influence of age, gender, and race factors on the pharmacokinetic behaviour of exenatide were evaluated by analyzing data from ten trials using population pharmacokinetic modelling approach (NONMEM) (see Appendix). A total of 4870 exenatide concentrations obtained from 242 subjects were included in the analysis. The mean age of the population was 54 years ranging from 22 to 73 years. Sixty-five percent of the patients were male. In addition, 53%, 14%, and 30% of the population was Caucasian, Black, and Hispanic, respectively.

The population pharmacokinetic modelling started with the development of a structural model. The one-compartment PK model with linear elimination and a combination of linear and non-linear absorption was selected based on the goodness-of-fit (GOF) plots.

Since anti-exenatide antibody developed after a period of time in some patients, the influence of anti-exenatide antibody on the pharmacokinetics of exenatide was evaluated first using a forward selection approach ($\alpha = 0.05$) and backward elimination process ($\alpha = 0.001$). The impact of anti-exenatide antibody absence on apparent clearance (CL/F) and the effect of titer ratio as a piece-wise linear function on apparent volume of distribution (V/F) were incorporated based on significant decrease in Minimum Value of the Objective Function (MVOF) as well as decrease in the inter-individual variability (IIV) in the parameter of interest.

Following the evaluation of the influence of anti-exenatide antibody presence, empirical Bayesian estimates of linear absorption rate (KaL), CL/F, and V/F were generated. The differences between the Bayesian parameter estimates and the population parameter estimates were plotted against all covariates including age, gender, race, and others (e.g., weight (WTKG), height, ideal body weight (IBW), percent of ideal body weight (%IBW), body mass index (BMI), and body surface area (BSA), serum creatinine (SCr), alkaline phosphatase (ALP), alanine aminotransferase (ALT), albumin (ALB), gamma-glutamyl transferase (GGT), total bilirubin (TBIL), aspartate aminotransferase (AST), and creatinine clearance (CrCL)). Based upon the patterns exhibited in the plots, regression analyses were initially performed using SAS to identify parameters with trends.

Age, gender, race and other demographics factors were tested for significance using forward selection ($\alpha = 0.05$) and backward elimination process ($\alpha = 0.001$).

The findings on the effects of age, gender, and race on exenatide PK are discussed below.

Age

Age demonstrated a statistically significant relationship to CL/F ($\alpha = 0.05$) in the regression analyses. In the univariate analyses conducted using NONMEM ($\alpha = 0.05$), the effect of age on CL/F was significant ($p = 0.005$). However, after including the most significant covariates, body weight and anti-exenatide antibody in the model, age was not found to be statistically significant predictor of CL/F or V/F.

Gender

Gender demonstrated a statistically significant relationship to KaL, CL/F and V/F ($\alpha = 0.05$) in the regression analyses. In the univariate analyses, the effect of gender on KaL ($p < 0.00001$) and CL/F ($p = 0.002$) were significant while the effect of gender on V/F was not significant ($p = 0.07$). In the forward selection process, gender was found to be a significant covariate for KaL. After backward elimination process, the effect of gender on KaL remained to be significant covariate. Gender was not found to be a statistically significant predictor of CL/F or V/F.

Race

Race demonstrated a statistically significant relationship to V/F ($\alpha = 0.05$) in the regression analyses. In the univariate analyses, the effect of race on V/F was highly significant ($p < 0.00001$). Due to the increase in IIV of V/F, CL/F and KaL, the effect of race was not selected in the forward selection process. Therefore, race was not found to be a statistically significant predictor of exenatide PK.

2.3.2 Renal impairment:

- ***What is the effect of renal impairment on exenatide pharmacokinetics?***

The sponsor conducted a single dose study to evaluate the pharmacokinetics of exenatide in patients with mild or moderate renal dysfunction or end-stage renal disease (ESRD), compared to healthy subjects with normal renal function. This was an open-label, parallel study. Subjects in Group 1 (healthy, estimated creatinine clearance: >80 mL/min) were age- and gender-matched to subjects in Groups 2 to 4 (mild: 51 to 80 mL/min; moderate: 31 to 50 mL/min; and ESRD under hemodialysis) as far as was practically possible. A single dose of 5 µg (Group 3 [5 subjects] and Group 4) or 10 µg (Group 1, Group 2, and Group 3 [2 subjects]) exenatide were given. A single subcutaneous dose of exenatide was administered on Day 1 approximately 15 minutes prior to a standardized breakfast. Results are summarized in Table 10. The statistical analysis is summarized in Table xx.

Table 10. Mean noncompartmental pharmacokinetic parameters for plasma exenatide by treatment group

	Geometric Mean (CV%)				
Parameter	**Healthy**	**Mild impairment**	**Moderate impairment**		**ESRD**
N	8	8	5	1	8
Dose (µg)	10	10	5	10	5
Creatinine	83-156	60-78	34-50		4-11

Clearance [b] (mL/min)					
Tmax [c] (h)	2.0 (1.0 – 3.0)	2.0 (0.52 – 3.0)	2.50 (1.0 – 3.0)		2.0 (1.0 – 4.0)
Cmax (pg/mL)	821 (61.0)	470 (24.6)	202 (19.9)	352.6	601 (69.4)
(pg/mL)/(µg/kg) [d]	5940 (50.4)	3560 (12.9)	3100 (15.0)	3100 (15.0)	7600 (55.5)
AUC0-t [e] (pg·h/mL)	2880 (32.0)	2030 (19.4)	1070 (12.6)	1960	5060 (43.9)
(pg·h/mL)/(µg/kg) [d]	20800 (22.8)	15400 (26.4)	16500 (11.4)	16500 (11.4)	64000 (31.3)
CLp/F(L/h)	3.41 (31.4)	4.80 (17.4)	4.35 (15.2)	4.79	0.929 (42.2)
(L/h/kg)	0.0471 (22.1)	0.0634 (25.9)	0.0563 (8.98)	0.0563 (8.98)	0.0147 (28.8)
Vz/F(L)	7.11 (40.2)	14.7 (21.9)	19.5 (49.8)	24.1	7.97 (43.9)
(L/kg)	0.0983 (30.5)	0.194 (14.9)	0.257 (49.4)	0.257 (49.4)	0.126 (37.0)
t1/2 f (h)	1.45 (0.944 to 2.02)	2.12 (1.56 to 3.36)	3.16 (1.82 to 7.01)		5.95 (4.27 to 7.58)

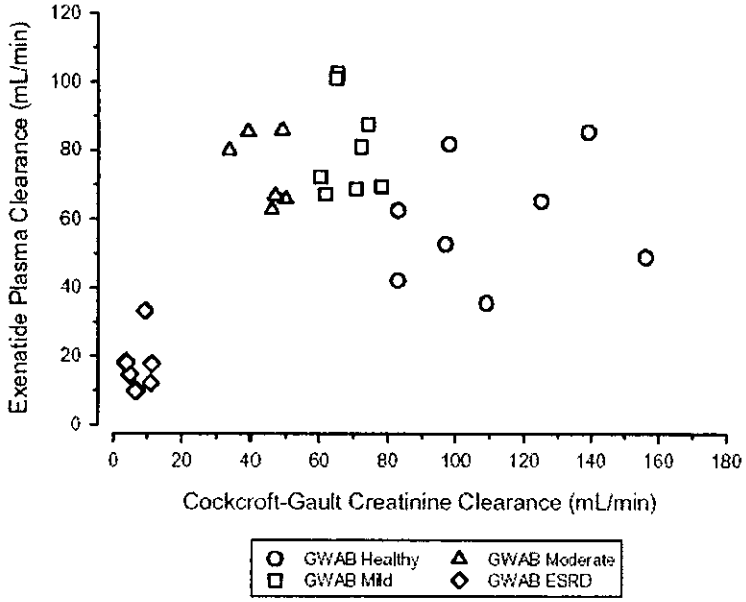
N = number of subjects included in means; ESRD = End-Stage Renal Disease; [a] Subject 222 was excluded as an outlier from all statistical evaluations; [b] Cockroft-Gault creatinine clearance at screening (range); [c] Median (range); [d] Dose-weight normalized parameter; [e] Sample collection intervals were up to 12 hours for Healthy, up to 18 hours for Mild and Moderate, and up to 60 hours for ESRD subjects; [f] Mean (range).

Table 11. Comparison of dose-weight normalized AUC0-∞ and Cmax between healthy control group and mild, moderate and ESRD groups

Dose-Weight Normalized Parameter	Group	LS Gmean	Ratio of LS GMean Group (2, 3 or 4)/Healthy	90% CI on Ratio
AUC0-∞ (pg·h/mL)/(mg/kg)	Healthy	19917.11		
	Mild	16036.41	0.81	(0.66, 0.98)
	Moderate	19258.16	0.97	(0.77, 1.21)
	ESRD	67101.74	3.37	(2.80, 4.06)
Cmax (pg/mL)/(mg/kg)	Healthy	5392.13		
	Mild	3649.98	0.68	(0.49, 0.93)
	Moderate	3507.42	0.65	(0.45, 0.94)
	ESRD	7433.74	1.38	(1.01, 1.88)

The ratios of the geometric means of dose-weight normalized AUC0-∞ between the healthy group and the mild, moderate and ESRD groups were 0.81, 0.97 and 3.37, respectively, and the ratios for dose-normalized Cmax were 0.68, 0.65 and 1.38, respectively. The 90% CIs for the ratios indicate that the increase in AUC0-∞ and Cmax in the ESRD group were statistically significant. AUC0-∞ in the mild and moderate groups was similar to the healthy subject group though Cmaxs were lower. This is consistent with the graphical analyses that indicated a substantial change in clearance only in the ESRD group (Figure 10)

Figure 10. Relationship between plasma exenatide clearance and creatinine clearance.



Overall, these analyses suggest that exenatide clearance estimates in subjects with mild to moderate renal impairment were similar to those in the healthy subject group. Exenatide clearance reduced from a mean estimate of 4.8 L/h in subjects with mild renal impairment to 0.9 L/h in subjects with ESRD. Exenatide clearance was significantly reduced in subjects with ESRD, thus BID dosing of 5 µg in ESRD subjects would be associated with poor tolerability.

2.3.3 Hepatic impairment, Pediatric:

No studies were conducted with exenatide.

2.4 Extrinsic Factors:

2.4.1 Does exenatide administration alter the pharmacokinetics of digoxin?

The sponsor conducted an open-label, fixed sequence, drug interaction study to determine the effects of chronic exenatide dosing on the pharmacokinetics of digoxin at steady-state in healthy male subjects. A total of 23 subjects were enrolled in the study and 21 subjects completed the study. Exenatide 10 µg BID was given on Days 8 to 12 for 5 consecutive days. Digoxin 0.5 mg BID was given on Day 1 and 0.25 mg QD was given on Days 2 to 12. Blood samples were collected on Days 7 and 12 over a 24-hour period for the measurement of plasma digoxin concentrations. Urine was collected over a 24-hour period on Days 7 and 12 for the measurement of digoxin amounts. Blood samples were collected on Days 11 and 12 for the measurement of plasma exenatide concentrations approximately 2 hours following the exenatide dose. Noncompartmental analysis methods were used to determine standard pharmacokinetic parameters of digoxin when administered alone and concomitantly with exenatide. Results are shown in Figure 11 and Table 12.

Figure 11. Arithmetic mean (±SE) digoxin plasma concentration-time profiles following steady-state dosing of 0.25 mg QD digoxin alone or in the presence of steady-state dosing of 10 μg exenatide BID administered subcutaneously.

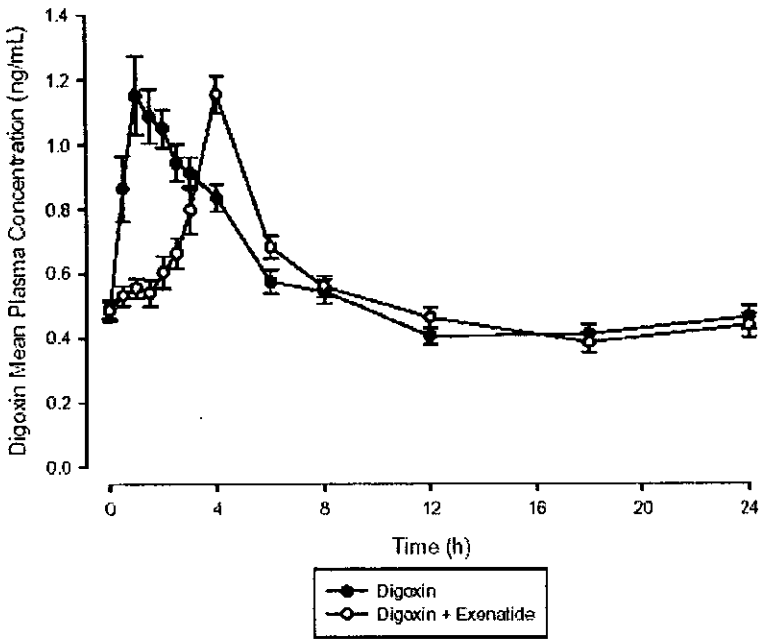


Table 12. Statistical comparison of digoxin AUCτ,ss, Cmin,ss and Cmax,ss for digoxin + exenatide (Day 12) and digoxin (Day 7)

Parameter	LS Geometric Mean		LS Geometric Mean Ratio	90% CI
	Digoxin + exenatide	Digoxin	Digoxin + exenatide/ Digoxin	
AUCτ,ss (ng·h/mL)	12.11	12.78	0.95	(0.90, 1.00)
Cmin (ng/mL)	0.32	0.34	0.94	(0.87, 1.03)
Cmax (ng/mL)	1.15	1.40	0.82	(0.75, 0.89)

Twice-daily subcutaneous administration of 10 μg exenatide did not produce a statistically significant change in digoxin Cmin,ss or AUCτ,ss. The 90% CI for the geometric mean ratio of Cmax,ss ranged from 0.75 to 0.89, with the estimated ratio 0.82, and was therefore slightly below the prospectively defined equivalence range of (0.8, 1.25). However, digoxin Tmax was delayed for a median value of 2.5 hours when administered concomitantly with exenatide.

Therefore, exenatide may not produce clinically relevant drug interaction with digoxin.

2.4.2 Does exenatide administration alter the pharmacokinetics of lovastatin?

The sponsor conducted an open-label, fixed sequence, drug interaction study to evaluate the effect of exenatide on the single dose pharmacokinetics of lovastatin in healthy subjects. A total of 22 subjects were enrolled in the study and 20 subjects completed the study. Exenatide 10

μg BID was given on Days 2, 3 and 4 for 3 consecutive days. Lovastatin: 40 mg was given on Days 1 and 4. Blood samples were collected on Days 1 and 4 for the measurement of plasma lovastatin concentrations. Non-compartmental analysis methods were used to determine standard pharmacokinetic parameters of lovastatin when administered alone and concomitantly with exenatide (Day 1 and Day 4, respectively). Cmax and AUC0-∞were log-transformed and analyzed using a linear mixed effects model. Ninety % confidence intervals of the ratio between two treatments were calculated. Results are shown in Figure 12 and Table 13.

Figure 12. Lovastatin plasma concentration vs. time profiles (arithmetic mean ± SE) after administration of a single dose of lovastatin (40 mg) given alone (Day 1) or concomitantly with exenatide (Day 4) (Panel A: linear scale; Panel B: semi logarithmic scale).

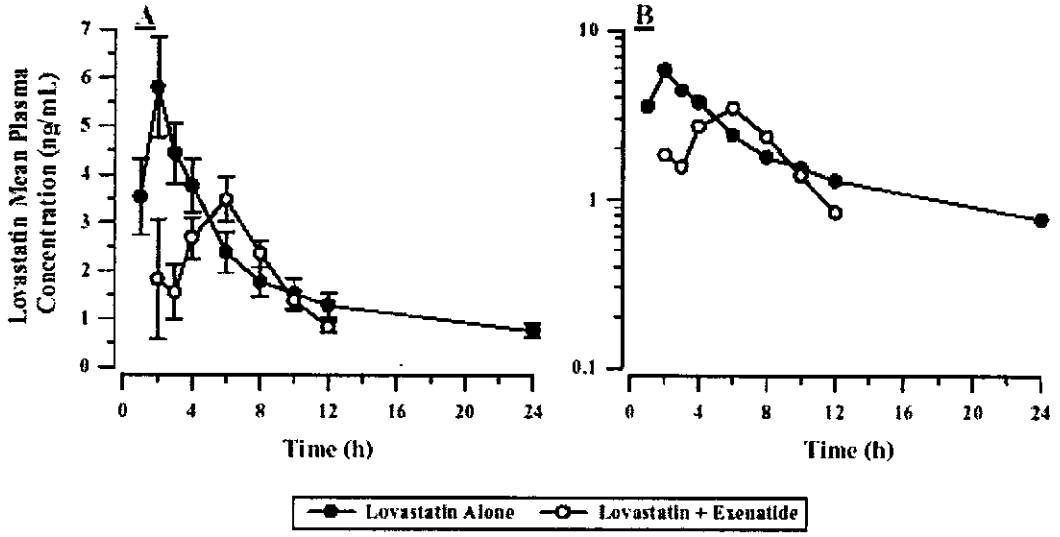


Table 13. Comparison of AUC0-∞ and Cmax for lovastatin + exenatide (Day 4) and lovastatin (Day 1)

Parameter	LS Geometric Mean		LS Geometric Mean Ratio	
	Lovastatin + exenatide	Lovastatin	Lovastatin + exenatide/ Lovastatin	90% CI
AUC 0-∞ (ng·h/mL)	25.32 (11.57%)	42.22 (10.85%)	0.60	(0.50, 0.71)
Cmax (ng/mL)	3.91 (12.33%)	5.42 (11.25%)	0.72	(0.57, 0.91)

Co-administration of exenatide caused statistically significant decreases in both mean lovastatin AUC0-∞and Cmax, of approximately 40% and 28%, respectively. This reviewer thinks that patients who are treated with lovastatin should be aware that lovastatin AUC and Cmax will be reduced by 40% and 28% when exenatide is added on in therapy. Dose adjustment of lovastatin should be considered.

2.4.3 What is the effect of exenatide on the pharmacokinetics and pharmacodynamics of Lisinopril?

The sponsor conducted a pharmacodynamic interaction study to evaluate the influence of exenatide on the plasma pharmacokinetics of Lisinopril and the effect of exenatide on the blood pressure response to Lisinopril in subjects with mild to moderate hypertension. This was a subject- and investigator-blind, placebo-controlled, randomized, two-period, two-sequence crossover, drug interaction study. A total of 22 subjects entered the study and 19 subjects completed the study. Three subjects were withdrawn after completing Treatment Period 1.

All subjects were to receive 10 µg BID exenatide on Day 1. Subjects who entered the study were already stabilized on a regular daily dose of Lisinopril (for at least 30 days prior to the study with daily dose of 5 to 20 mg) and continued to receive their usual dose of Lisinopril for the duration of the study. Exenatide or placebo was administered exactly 15 minutes prior to the standard breakfast or evening meal on Day 1 of each treatment period.

Results show that the concomitant administration of exenatide produced a slight decrease in mean Cmax,ss and a minor delay in the appearance of peak plasma concentrations of Lisinopril.

Figure 13. Mean (±SD) dose-weight normalized plasma lisinopril concentration versus time profiles by treatment (Panel A: linear scale; Panel B: semi logarithmic scale).

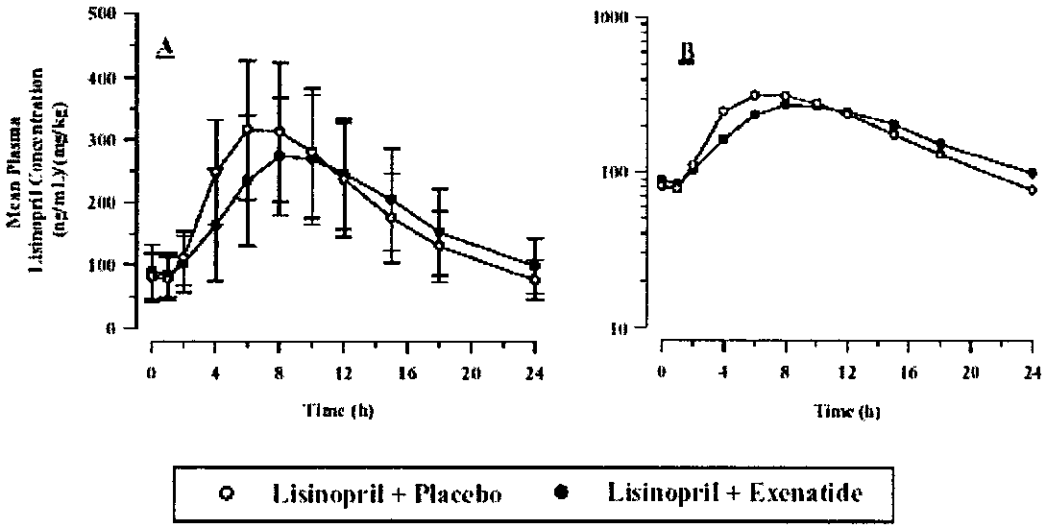


Table 14. Statistical comparison of dose-weight normalized pharmacokinetic parameters by treatment

Parameter	LS Geometric Mean		LS Geometric Mean Ratio	
	Lisinopril & 10μg BID exenatide	**Lisinopril & BID placebo**	**(Lisinopril +Exenatide)/ (Lisinopril + Placebo)**	**90% CI**
AUCτ,ss (ng·h/mL)/(mg/kg)	4150	4260	0.965	(0.895, 1.041)
Cmax ss (ng/mL)/ (mg/kg)	287	307	0.932	(0.855, 1.017)

In each treatment period, ambulatory blood pressure and heart rate monitoring was conducted for 24 hours post exenatide/placebo dosing. The 24-hour means for diastolic and systolic blood pressure were computed. The two treatments were compared using a linear mixed effects model. LS mean differences between treatments were calculated along with the 95% CIs. Results of the statistical analyses comparing the two treatments are shown in Table 15. Two primary variables, mean diastolic and systolic blood pressure (over 24 hours), and two secondary variables, weighted mean of diastolic and systolic blood pressure (over 24 hours), were analyzed. All the variables are adjusted for the baseline. Concomitant administration of exenatide did not cause a statistically significant change in any of the variables and the differences of LS means between the two treatments were between 1.38 and 2 mmHg across the four parameters.

Since the upper limits of 95% CIs for all the parameters were below 8 mmHg (as pre-specified in protocol), no clinically relevant effect of co-administration of exenatide on systolic and diastolic blood pressure was indicated in hypertensive subjects stabilized on lisinopril.

Table 15. Comparison of 24-hour mean and weighed-mean diastolic and systolic blood pressure for lisinopril given with placebo or exenatide

Blood pressure parameter (mmHg)	LS-Mean		Difference of LS means (Lisinopril & exenatide - lisinopril & placebo)	95% CI for difference (lower, upper)
	Lisinopril & 10 μg BID exenatide	Lisinopril & BID placebo		
Diastolic	-6.97	-8.35	1.38	(-1.41, 4.17)
Systolic	-8.07	-9.45	1.38	(-1.95, 4.71)
Weighted-Diastolic	-15.97	-17.45	1.48	(-2.21, 5.17)
Weighted-Systolic	-22.46	-24.47	2.00	(-3.07, 7.08)

Therefore, 10 μg exenatide BID did not alter the pharmacokinetics and pharmacodynamics of Lisinopril in patients with hypertension.

2.5 General Biopharmaceutics

2.5.1 What is the difference between phase 3 clinical drug products and the commercial drug products?

For clinical studies, exenatide injection was filled into 3.0-mL cartridges that were used with commercially available reusable variable dosing pen-injectors. The drug product presentation planned for commercial use is similar to that used in the Phase 3 long-term controlled clinical studies. The only differences are that a fixed-dose disposable pen-injector, rather than a reusable pen-injector, will be used and the cartridge sizes will be different. The formulation and the composition of the product contact materials in the cartridges will remain the same. The commercial presentations are intended to provide more patient convenience. Descriptions of the formulation, pen-injectors, volume of drug solution supplied in the cartridges, and manufacturer(s) of the drug product are summarized in Table 16.

Table 16: Drug Product Presentations

Completed Phase 3 and Ongoing Clinical Studies[a]	
Exenatide Formulation	AC2993-F8
Pen-injector*	[redacted]
Delivery Volume	
Product Contact Materials	
Volume Supplied in Cartridge	
Manufacturers**	
Proposed Commercial Product	
Exenatide Formulation	AC2993-F8
Pen-injector*	Disposable Pen-injector (Amylin Pharmaceuticals, San Diego, CA)
Delivery Volume	20 µL (5 µg dose) 40 µL (10 µg dose)
Product Contact Materials	Round, clear, USP Type I glass
Volume Supplied in Cartridge	5-µg Dosing: 1.2 mL 10-µg Dosing: 2.4
Manufacturers**	[redacted] (additional drug product manufacturer)

* FDA approved commercial devices; Serial 059, 15 Nov 2001 [redacted] Serial 147, 09 May 2003 [redacted]

** Description of cartridge manufactures was submitted to the Agency in Serial 059, 15 November 2001 [redacted] and Serial 103, 30 August 2002 [redacted]

a Ongoing studies are 2993-112E, 2993-113E, 2993-115E, 2993-117, 2993-119, H8O-MC-GWAA, H8O-MC-GWAD

2.5.2 What is the effect of injection sites on the bioavailability of exenatide?

The sponsor conducted a randomized, open-label, four-way crossover study to examine the bioavailability of exenatide injected subcutaneously at three anatomical sites in patients with type 2 diabetes mellitus. Each day during the 4-day treatment period of this inpatient study, subjects were to receive one of four treatments: a SC injection of exenatide (10 μg) in the abdomen, arm, or thigh; or an intravenous (IV) bolus dose of exenatide (1 μg). The exenatide 10 μg SC treatment in the abdomen was used as the reference treatment to determine the relative bioavailability of exenatide 10 μg SC treatments in the arm and thigh. The IV bolus dose was used as the reference treatment to determine the absolute bioavailability of the SC treatments. Subjects were randomly assigned to one of four treatment sequences, and received treatments in the order specified by their assigned sequence. Twenty-eight subjects were enrolled 25 subjects completed all 4 days of the 4-day treatment period. Plasma exenatide concentrations were assessed at selected time points during a 10-hour period following each treatment. Estimates of relative bioavailability for SC treatments are provided in Table 17.

Table 17. Relative bioavailability of exenatide 10 μg subcutaneous treatments (N = 25)

Parameter/Statistics [1]	Injection site	
	Arm	Thigh
AUC(0-inf)		
Geometric LS Mean Ratio	0.93	0.97
Geometric 90% CI Ratio	(0.819, 1.048)	(1.857, 1.096)
Cmax		
Geometric LS Mean Ratio	0.99	0.88
Geometric 90% CI Ratio	(0.849, 1.152)	(0.752, 1.020)

[1] Reference treatment: exenatide 10 μg SC (abdomen)

An evaluation of the relative bioavailability of exenatide after subcutaneous administration at three anatomical sites (abdomen, arm, and thigh) showed that the site of injection did not substantially influence the pharmacokinetic profile of exenatide though Cmax for thigh injection is slightly off the lower limit of 90% BE criteria.

For absolute bioavailability, the results suggested an absolute bioavailability of over 100% (121%, 113% and 118% for abdomen, arm and thigh, respectively). The sponsor has indicated that such variability in the IV bolus data is likely attributable to methodological issues related to administration of the IV dose; therefore, the sponsor did not draw any conclusion for absolute bioavailability.

2.6 Analytical Section

2.6.1 What is the property of analytical method?

Analytical methods were developed and validated for the quantitation of plasma exenatide in mouse, rat, rabbit, dog, monkey, and human plasma to support nonclinical and clinical pharmacokinetic studies. The exenatide immunoradiometric assay (IRMA) was used in initial nonclinical studies and one clinical study (2993-101). The exenatide IRMA was replaced by the exenatide immunoenzymetric assay (IEMA) to increase assay sensitivity. The exenatide IEMA was used for the quantitation of exenatide in most nonclinical and clinical studies.

2.6.1.1 Detection of exenatide concentrations in plasma by IRMA

The exenatide IRMA is a two-site sandwich assay that uses two monoclonal antibodies. The capture antibody EXE4:2-8 specifically recognizes a C-terminal epitope of exenatide and does not cross-react with GLP-1(7-36) or glucagon. The detecting antibody GLP1:3-3 recognizes a common N-terminal epitope on exenatide which is common to GLP-1(7-36) and glucagon. The assay is specific for exenatide due to the selectivity of the capture antibody. Since both antibodies need to bind to the peptide in order to generate an assay signal, cross-reactivity with other peptides or metabolites is minimized. The lower and upper limits of quantitation for the assay are [redacted] exenatide, respectively.

2.6.1.2 Detection of exenatide concentrations in plasma by IEMA

The exenatide IEMA, based in principle upon the exenatide IRMA, was developed and validated for increased assay sensitivity and to eliminate the use of radioactive materials required in the IRMA. The exenatide IEMA has been used to evaluate specimens for nonclinical and clinical studies (all clinical studies except 2993-101). The exenatide IEMA is a [redacted] As for the IRMA, the IEMA is specific for exenatide due to the selectivity of the capture antibody. The accuracy of the assay, assessed by adding known amounts of exenatide to plasma specimens, ranged from [redacted] of the expected values. Dilution linearity was demonstrated by a plot of calculated concentrations of plasma samples diluted with exenatide-free plasma or plasma mimic against the expected values. Slopes of the resulting lines ranged from [redacted] with a mean slope of 1.0 representing a perfect correlation. Peptides exhibiting sequence similarity with exenatide: exendin-4(2-39), exendin-4(3-39), GLP-1(7-36), and glucagon were assayed at [redacted] (5 times the high standard) and no cross-reactivity was observed indicating high assay specificity. Insulin at [redacted] was also tested with no cross-reactivity. Assay sensitivity was defined by measuring the lower limit of quantitation (LLOQ). The lower and upper limits of quantitation for the assay are [redacted] exenatide, respectively. Only values between [redacted] were reported for clinical samples.

2.6.2 Is there any interfering effect of exenatide antibody in patients' plasma on exenatide measurement?

Throughout drug development program, it has been noticed that up to 44% patients receiving exenatide with long tern use such as during 28 days clinical trials, have generated antibody against exenatide in plasma. Interestingly, patients with positive antibody showed a higher exposure of exenatide with reduced exenatide clearance though efficacy was compromised to some extent. The case below is one example from these clinical trials.

In the Phase 2 Study 107a, fifteen subjects receiving exenatide for 28 days and zero placebo subject generated treatment-emergent positive antibody responses by Day 28. Five subjects had a low titer (1:5) antibody response at baseline (2 placebo/3 active) that did not increase in titer during the study.

Figure 14. Mean pooled plasma exenatide concentration-time curves for Day 1 and Day 28 (population: intent-to-treat subjects in Study 2993-107 [N=81])

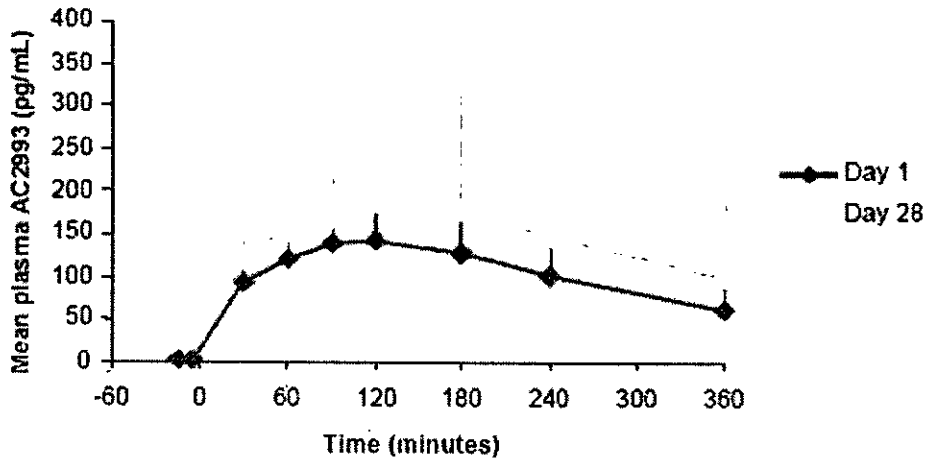


Figure 15. Mean pooled plasma exenatide concentration-time curves for Day 1 and Day 28 excluding subjects who were positive for anti-exenatide antibodies (population: intent-to-treat subjects in Study 2993-107 [N=63])

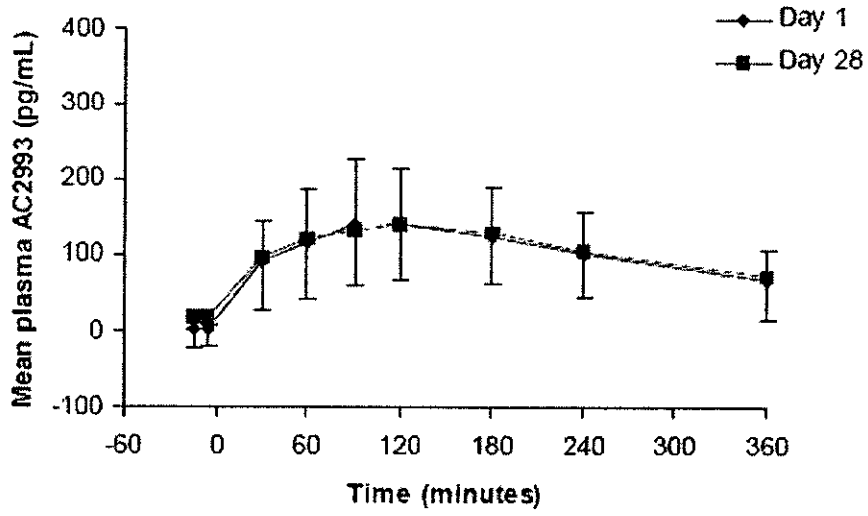
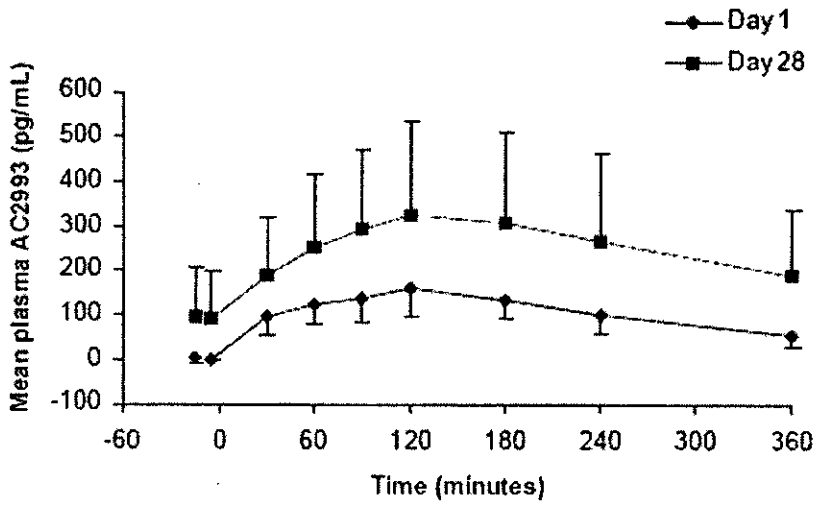


Figure 16. Mean pooled plasma exenatide concentration-time curves for Day 1 and Day 28 for subjects with positive anti-exenatide antibodies at any visit (population: intent-to-treat subjects in Study 2993-107 [N=18])



The sponsor did not conduct any studies to examine the potentially interfering effect of exenatide antibody in patients' plasma on the exenatide measurement during assay development. We can't conclude whether the difference in pharmacokinetics between antibody positive and negative patients is attributed to the interfering effect of exenatide antibody in assays or exenatide antibody altering the pharmacokinetics of exenatide in human. The sponsor should conduct such a study to clarify the cause of pharmacokinetic difference regarding exenatide antibody.

3. DETAILED LABELING RECOMMENDATIONS

LABELING COMMENTS:

[redacted]

3 Page(s) Withheld

_____ § 552(b)(4) Trade Secret / Confidential

_____ § 552(b)(5) Deliberative Process

✓ § 552(b)(5) Draft Labeling

Withheld Track Number: Clin Pharm/Bio-1

4. Appendices:

4.1 OCPB Filing/Review Form

Office of Clinical Pharmacology and Biopharmaceutics

New Drug Application Filing and Review Form

General Information About the Submission

NDA Number	**21-773**	**Brand Name**	[redacted]
OCPB Division (I, II, III)	**DPE II**	**Generic Name**	**Exenatide**
Medical Division	**HFD-510**	**Drug Class**	**New class of anti-diabetic**
OCPB Reviewer	**Xiaoxiong (Jim) Wei**	**Indication(s)**	**Type 2 Diabetes Mellitus**
OCPB Team Leader	**Hae-Young Ahn**	**Dosage Form**	**0.25 mg/mL solution**
		Dosing Regimen	**5 - 10µg BID**
Date of Submission	**06-30-04**	**Route of Administration**	**S.C.**
Estimated Due Date of OCPB Review	**03-10-05**	**Sponsor**	**Amylin**
PDUFA Due Date	**04-30-05**	**Priority Classification**	**S1**
Division Due Date	**04-08-05**		

Clin. Pharm. and Biopharm. Information

	"X" if included at filing	Number of studies submitted	Number of studies reviewed	Critical Comments If any
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data, etc.	X			
Tabular Listing of All Human Studies	X			
HPK Summary	X			
Labeling	X			
Reference Bioanalytical and Analytical Methods	X			
I. Clinical Pharmacology				
Mass balance:				
Isozyme characterization:				
Blood/plasma ratio:				
Plasma protein binding:	X	1		
Pharmacokinetics (e.g., Phase I) -				
Healthy Volunteers-				
single dose:	X	2		
multiple dose:				
Patients-				
single dose:	X	2		
multiple dose:	X	11		
Dose proportionality -				
fasting / non-fasting single dose:	X			
fasting / non-fasting multiple dose:				
Drug-drug interaction studies -				
In-vivo effects on primary drug:				
In-vivo effects of primary drug:	X	4		
In-vitro:	X	2		
Subpopulation studies -				
ethnicity:				
gender:				
pediatrics:				
geriatrics:				

renal impairment:	X	1		
hepatic impairment:				
PD:				
Phase 2:				
Phase 3:				
PK/PD:				
Phase 1 and/or 2, proof of concept:	X	2		
Phase 3 clinical trial:				
Population Analyses -				
Data rich:	X	1		
Data sparse:	X			
II. Biopharmaceutics				
Absolute bioavailability:	X	(1)		
Relative bioavailability -	[redacted]	[redacted]		
solution as reference:				
alternate formulation as reference:				
Bioequivalence studies -				
traditional design; single / multi dose:				
replicate design; single / multi dose:				
Food-drug interaction studies:				
Dissolution:				
(IVIVC):				
Bio-wavier request based on BCS				
BCS class				
III. Other CPB Studies				
Genotype/phenotype studies:				
Chronopharmacokinetics				
Pediatric development plan				
Literature References				
Total Number of Studies		26		

Filability and QBR comments

	"X" if yes	Comments
Application filable ?	YES	
Comments sent to firm ?	NO	

Briefing in Content:

[redacted] (Exenatide) is the first drug in a new drug class as an incretin mimetic to improve glycemic control in people with type 2 diabetes mellitus. Exenatide is a 39-amino acid peptide amide. Exenatide is rapidly absorbed with Tmax of 2.1 hrs following SC administration. Exenatide is predominantly eliminated through the kidney. The mean exenatide clearance is reduced to 0.9 L/h (compared with 9.1 L/h in healthy subjects) in patients with end-stage renal disease receiving dialysis.

The commercial formulation was used in pivotal clinical trials. PK and PD data were evaluated using population methods to characterize the exposure-response relationship. Total ten PK, PK/PD and clinical efficacy studies were used for population modeling.

4.2 Proposed Package Insert (separate file)

4.3 Individual Study Review (see Addenndum as a separate file)

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/s/

Xiao-xiong Wei
4/12/05 10:44:37 AM
BIOPHARMACEUTICS

QBR, the body of primary review

Hae-Young Ahn
4/12/05 11:55:47 AM
BIOPHARMACEUTICS

4/12/05

Appendices
4.3 Individual Study Review

NDA: 21-773 / 21-919 (N-000)
Drug name: [redacted] (Exenatide injection solution)
Indication: Treatment of type 2 diabetes
Submission date: 06-30-2004
Reviewer: Xiaoxiong (Jim) Wei
Pharmacometrics Reviewers: Wei Qiu, Sang Chung
Team Leader: Hae-Young Ahn
OCPB: DPE2
OND: DMEDP (Division of Metabolic and Endocrine Drug Products, HFD-510)

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Study #: 2933-101

Title: A rising single dose, double blind, placebo controlled study examining the pharmacokinetics and tolerability of AC2993 given by the subcutaneous route in healthy volunteers

Studied period:
Date of first enrolment: 9th August 1998
Date of last completed: 13th September 1998

Objectives:
- To examine the safety and tolerability of AC2993 given by the subcutaneous route
- To investigate the pharmacokinetics of AC2993 given by the subcutaneous route

Methodology
This was a rising single dose, double blind, placebo controlled pharmacokinetic and tolerability study involving the subcutaneous injection of AC2993 at five different doses in five groups of male subjects studied in the fasting state. Within each group, six subjects were randomized to receive AC2993 and two were randomized to placebo.

Selection of Doses in the Study

On the basis of the pre-clinical and clinical data available at study initiation, the investigation of AC2993 in the dose range 0.1 μg/kg to 10.0 μg/kg in male, healthy volunteers was considered to be appropriate. Following an increase in the incidence of nausea and vomiting at the 0.3 μg/kg dose, further dose escalation was stopped and doses of 0.01 μg/kg, 0.05 μg/kg and 0.2 μg/kg were administered in place of 1.0 μg/kg , 3.0 μg/kg and 10.0 μg/kg dose.

Selection arid Timing of Dose for Each Subject

The medication was to be administered on the morning of Day I, after overnight fast as a single subcutaneous injection into the anterolateral aspect of the left thigh. Subjects were to remain fasted until four hours post-dose and from one hour pre-dose until four hours post-dose subjects were to remain semi-recumbent (except to pass urine and for blood pressure measurements). Administration of the medication was to be performed by the investigator or designated deputy.

Table. Subject disposition

Group	Treatment	Number of subjects
1	0.1 μg/kg	6
	Placebo	2
2	0. 3 μg/kg	6
	Placebo	2
3	0.2 μg/kg	6
	Placebo	2
4	0.01 μg/kg	6
	Placebo	2
5	0.05 μg/kg	6
	Placebo	2

Number of subjects (planned and analyzed):
Number of subjects (planned and analyzed): Forty (40) male subjects were planned and enrolled. All subjects were analyzed for safety parameters.

Test product: AC2993

Dose: 0.01 µg/kg, 0.05 µg/kg, 0.1 µg/kg, 0.2 µg/kg or 0.3 µg/kg by subcutaneous injection Administration Route: Subcutaneous injection

Batch numbers:
AC2993 [redacted] Lot No. 98-0401SP
AC2993 Lot No. 98-0403SP

Reference Therapy: Placebo
Placebo Lot No. 98-0404SE

Criteria for evaluation:
Pharmacokinetics:
Blood sampling for assay of AC2993
Pre-dose and at 10, 20, 30 min, 1, 1.5, 2, 3, 4, 5, 6, 7, 8, 10, 12, 14, 17, 20, 24, 48 hours and 7 days post-dose.

Safety:
Monitoring of adverse events.
Hematology, plasma chemistry and urinalysis.
Plasma glucose, insulin lactate, glucagon and C-peptide.
Urinary electrolytes and osmolality

Vital signs (supine blood pressure, pulse rate and oral temperature).
12-lead ECO (Rhythm, heart rate, PR interval, QRS interval, QT interval and QTc interval).
Physical examination.
Concomitant medication.
Fluid balance

STATISTICAL METHODS:
Pharmacokinetic parameters For AC2993
Cmax and tmax were calculated from the observed plasma concentration-time data. Descriptive statistics were produced for these parameters.

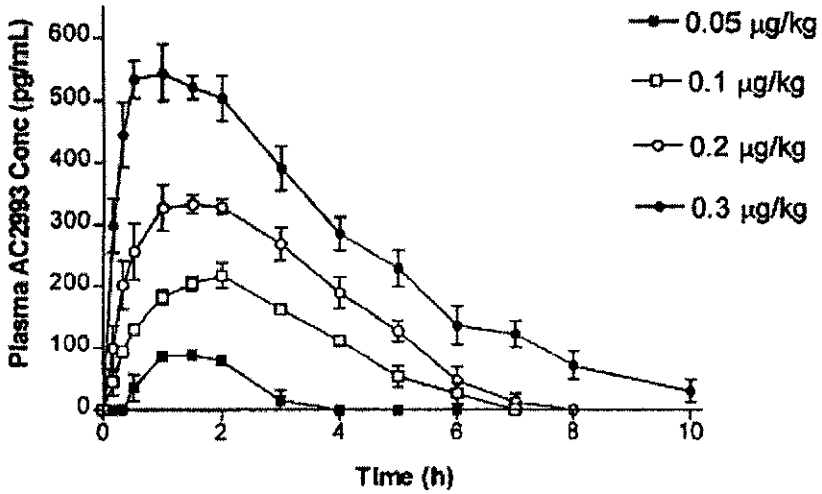
Safety parameters
Safety data were analyzed and evaluated through a summary of the incidence of adverse events and of vital signs electrocardiograms, hematology and plasma chemistry results, plasma glucose, insulin, lactate, glucagon and C-peptide, urine electrolytes mid osmolality and urinary volumes.

PHARMACOKINETIC RESULTS:
Formal pharmacokinetic analysis was limited to Cmax and tmax due to the limited number of concentration-time points for the raw plasma data.
Plasma AC2993 Cmax and tmax were calculated from the baseline subtracted data.
Maximum plasma concentrations were achieved between I and 2 hours post-dose with little difference in tmax among the doses examined, Examination of the data indicates a dose dependent increase for Cmax.

Treatment (µg/kg)	N	Cmax (pg/mL) (mean)	Tmax (h)
0.01	6	N/A	N/A†
0.05	4*	90.25 ± 9.30	1.25
0.1	6	223.85 ± 47.74	2.00
0.2	6	369.83 ± 59.04	1.75
0.3	6	586.89 ± 48.38	1.00

†Plasma samples from 0.01 µg/kg treatment group were not assayed due to the lower limit of quantitation
*Two subjects were omitted from the calculation as AC2993 concentrations were below the lower limit of quantitation

Figure. Mean (±SEM) plasma exenatide concentration-time profiles



SAFETY RESULTS:

There were no deaths or serious adverse events reported in this study. A total of 55 treatment emergent adverse events were reported by subjects receiving AC2993 and 13 by subjects receiving placebo. The majority of treatment emergent adverse events were mild in severity. Only two adverse events were considered to be of moderate severity (2 episodes of vomiting at the 0.2 µg/kg dose level). The most commonly reported adverse events were headache, nausea, vomiting, dizziness and postural hypotension. Nausea and vomiting were only reported by subjects receiving AC2993 at the two highest dose levels of 0.2 µg/kg and 0.3 µg/kg. Although no adverse events required treatment, subjects that received the 0.3 pg/kg dose level and exhibited symptoms of nausea and dizziness were given Ribena? (a carbohydrate drink) lo offset any potential for hypoglycemia. In general there was a trend suggesting that the frequency of adverse events increased with increasing doses o1AC2993. There were no clinically significant abnormalities noted in vital signs. 12-lead ECG, ECG monitoring, laboratory safety parameters, urinalysis or physical examination. There was no observable change in plasma glucose for placebo and 0.01 µg/kg AC2993 treated subjects, whereas at dose levels of 0.05 µg/kg and above a decrease in plasma glucose was observed within 20 minutes of drug administration. The maximum decrease was generally observed at 30 or 60 minutes post-dose and was approximately dose proportional.

A clear increase in plasma insulin concentration was observed with a time course con-elated with the changes observed in plasma glucose concentration, Plasma lactate, C-peptide and glucagon were unremarkable and showed no dose-related changes, although the post-dose C-peptide values tended to be higher than the pie-dose values.

CONCLUSION:

In the healthy male volunteers that participated in this study, AC2993 was well tolerated at subcutaneous doses up to and including 0.1 µg/kg. A fall in plasma glucose was also observed at this dose level. At doses of 0.2 µg/kg and above the most commonly observed adverse events were headache, nausea, vomiting, dizziness and postural hypotension. There was a transient fall in plasma glucose following dosing. The lowest measured plasma glucose concentration was 3.4 mmol/L.

Reviewer's comments:

Study #: 2993-102

Title: A Single-Blind, Rising Dose, Placebo-Controlled Study to Evaluate the Safety, Tolerability and Effects of Multiple Doses of AC2993 Given by the Subcutaneous Route to Subjects with Type 2 Diabetes Mellitus

Investigators and Study Centers: [redacted]

Objectives: Primary Objectives: To examine the safety and tolerability of AC2993 given by the subcutaneous (SC) route to subjects with type 2 diabetes mellitus. To examine the effect of AC2993 given by the SC route on plasma glucose in subjects with type 2 diabetes mellitus. Secondary Objectives: To investigate the pharmacokinetics of AC2993 given by the SC route to subjects with type 2 diabetes mellitus. To investigate the effect of AC2993 on plasma insulin and glucagon. To investigate the effect of AC2993 on satiety. To investigate the effect of AC2993 on gastric emptying.

Methodology:
This was a single-center, single-blind, placebo-controlled, rising dose study designed to compare four different doses of AC2993 and placebo. Eight subjects who satisfied the inclusion and exclusion criteria and had successfully completed the screening requirements were to receive a single dose of each of the following: placebo, AC2993 0.1 µg/kg, 0.2 µg/kg, 0.3 µg/kg, and either 0.4 µg/kg or an additional dose of placebo, depending on the tolerability of the three lower doses. Each dose was to be administered subcutaneously following an overnight fast. Immediately following injection of study medication, a standardized liquid meal (Sustacal√7 kcal/kg and acetaminophen 20 mg/kg) was to be given to subjects to drink completely within 5 minutes of dosing. A minimum of 48 hours was to separate each dosing period.

Number of Subjects: Eight male subjects with type 2 diabetes mellitus were enrolled in this study.

Key Demographics: Subjects were primarily Hispanic (75.0%) with a mean age of 52.7 years. Seven (87.5%) subjects were receiving oral hypoglycemic agents (OHA) therapy prior to screening. All OHA therapy was successfully discontinued by baseline (Day 0).

Subject Disposition: Of the eight subjects enrolled in this study, seven (87.5%) completed the study. Subject 008 withdrew prematurely due to a severe grand mal seizure (probably not related to study medication) on Day 2 of the study, one day after receiving a single dose of 0.1 µg/kg (Day 1).

Diagnosis and Main Criteria for Inclusion: Male subjects with type 2 diabetes mellitus, treated with diet and/or with OHA therapy and with an HbA1c concentration ≥ 8.0% but ≤ 10.0% at screening were enrolled in this study.

Test Product, Dose, and Mode of Administration, Batch No.: AC2993 [redacted], 0.1 µg/kg, 0.2 µg/kg, 0.3 µg/kg, and 0.4 µg/kg per subject, SC injection, Lot number: (AC-2993-F1) 98-0401SP.

Duration of Treatment: Five single-dose periods with at least a 48-hour washout period between dosing.

Reference Therapy, Dose, and Mode of Administration, Batch No: Placebo, SC injection, Lot number: (PBO-F10) 98-0404SE.

Criteria for Evaluation:
Pharmacodynamics: Comparison of post-Sustacal meal plasma glucose concentration profiles, plasmaglucagon concentration profiles, plasma insulin secretion, and gastric emptying as reflected by the appearance of orally administered acetaminophen in the serum. Efficacy: Comparison of satiety scores over time. Satiety evaluations included the following categories:well→sick, satisfied→hungry, and stomach full→empty.

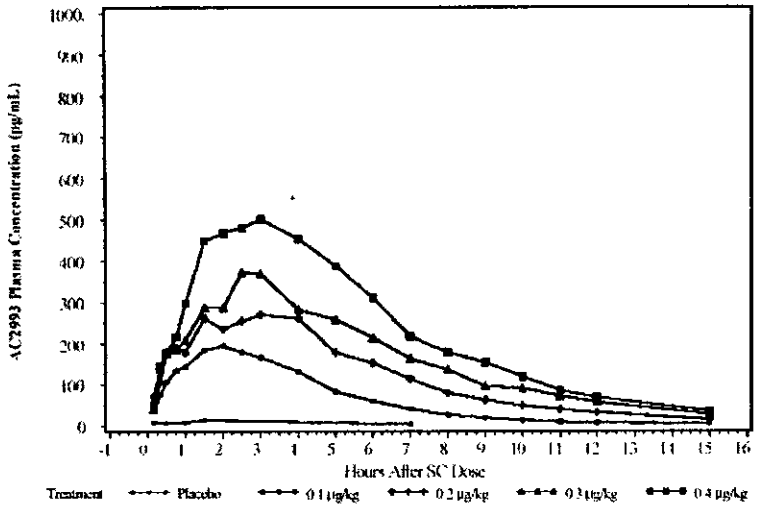
Pharmacokinetics: Comparison of plasma AC2993 concentrations over time. Comparison of area under the concentration time-curve from time 0 to 15 hours (AUC(0-15hr)), maximum concentration (Cmax), time to maximum concentration (Tmax), and time from Tmax to when plasma concentration had decreased to half of Cmax (t1/2Cmax). Safety: Adverse events, clinical laboratory measures, vital signs, electrocardiograms (ECGs), and physical examinations were assessed.

Statistical Methods:
Pharmacodynamics: Plasma glucose, plasma insulin, plasma glucagon, and serum acetaminophen concentrations over time by dose group were presented using descriptive statistics. Efficacy: Satiety scores, determined from a visual analog scale (VAS), were presented over time by dose group and category using descriptive statistics.
Pharmacokinetics: Pharmacokinetic parameters for plasma AC2993 concentrations were obtained using WinNonlin version 3.1 and were summarized using descriptive statistics. Safety: Adverse events, clinical laboratory measures, and vital signs were presented by descriptive statistics.

SUMMARY – CONCLUSIONS:
PHARMACODYNAMIC RESULTS:
Plasma Glucose Concentrations: A reduction in postprandial plasma glucose concentrations was observed for all AC2993 doses, as compared to placebo. Maximum postprandial plasma glucose concentrations were 300.0 mg/dL, 278.4 mg/dL, 286.6 mg/dL, and 254.4 mg/dL, for the 0.1 μg/kg, 0.2 μg/kg, 0.3 μg/kg, and 0.4 μg/kg doses, respectively; the maximum postprandial plasma glucose concentration for placebo was 373.4 mg/dL. Plasma glucose concentrations for all AC2993 doses peaked in response to a Sustacal meal within 30 to 45 minutes and returned to below baseline within 90 to 120 minutes. In contrast, plasma glucose concentrations for placebo continued to rise through 120 minutes, and did not return to baseline until 360 minutes post-Sustacal.
Plasma Glucagon Concentrations: A reduction in postprandial plasma glucagon concentrations was observed for all AC2993 doses, as compared to placebo. Plasma Insulin Concentrations: No differences were noted in plasma insulin concentrations for the AC2993 doses, as compared to placebo. Serum Acetaminophen Concentrations: Gastric emptying was delayed as evidenced by the slowerappearance of acetaminophen in serum for the AC2993 doses, as compared to placebo. The delay in gastric emptying was most pronounced at the 0.4 □g/kg dose.

EFFICACY RESULTS: There did not appear to be any notable differences in satiety scores for the AC2993 0.1 μg/kg, 0.2 μg/kg, and 0.3 μg/kg doses, as compared to placebo. Subjects appeared more satisfied and full at the 0.4 μg/kg dose, as demonstrated by the larger decrease from baseline in mean VAS scores at all time points, as compared to placebo. In addition, an increase in VAS scores for nausea was observed for the 0.4 □g/kg dose during the initial 3 hours after dosing, as compared to placebo.

PHARMACOKINETIC RESULTS: Mean peak plasma AC2993 concentrations increased in a dose proportional manner and were detectable up to 15 hours for doses 0.2 □g/kg and above. Cmax and AUC(0-15 hr) increased in proportion to dose, while Tmax and t1/2Cmax were dose independent.



Cross-Reference: Supporting Data Listings 2.7.9, Appendix 3.2.5.1

Pharmacokinetic Parameters	AC2993 0.1 µg/kg (N=8)	AC2993 0.2 µg/kg (N=7)	AC2993 0.3 µg/kg (N=7)	AC2993 0.4 µg/kg (N=5)
C_{max}				
Mean (pg/mL)	213.72	302.99	390.57	572.83
SD (pg/mL)	66.75	109.75	105.04	157.92
CV (%)	31.23	36.22	26.90	27.57
$AUC_{0-15\,hr}$				
Mean (pg•hour/mL)	926.04	1737.09	2405.58	3419.88
SD (pg•hour/mL)	159.66	408.53	433.03	852.54
CV (%)	17.24	23.52	18.00	24.93
T_{max}				
Mean (hours)	2.21	2.83	2.94	2.86
SD (hours)	0.71	1.87	0.74	0.98
CV (%)	32.15	66.12	25.06	34.29
$t_{1/2}C_{max}$				
Mean (hours)	2.58	4.02	3.96	4.19
SD (hours)	0.73	1.07	1.09	1.41
CV (%)	28.36	26.64	27.52	33.67

Cross-Reference: Supporting Data Listing 2.8, Appendices 3.2.5.1, 3.2.5.2

Plasma Pharmacokinetics of AC2993: Mean (SD)				
Pharmacokinetic Parameters	AC2993 0.1 µg/kg (N=8)	AC2993 0.2 µg/kg (N=7)	AC2993 0.3 µg/kg (N=7)	AC2993 0.4 µg/kg (N=5)
C_{max} (pg/mL)	213.7 (66.8)	303.0 (109.8)	390.6 (105.0)	572.8 (157.9)
$AUC_{0-15\,hr}$ (pg•hr/mL)	926.0 (159.7)	1737.1 (408.5)	2405.6 (433.0)	3419.9 (852.5)
T_{max} (hr)	2.21 (0.7)	2.83 (1.9)	2.94 (0.7)	2.86 (1.0)
$t_{1/2}C_{max}$ (hr)	2.58 (0.7)	4.02 (1.1)	3.96 (1.1)	4.19 (1.4)

Following the subcutaneous administration of single doses of AC2993 0.1 µg/kg, 0.2 µg/kg, 0.3 µg/kg, and 0.4 µg/kg, plasma AC2993 concentrations increased in a dose-proportional manner, with drug still

detectable at 15 hours at doses of 0.2 μg/kg and above. Cmax and AUC(0-15 hr) increased in proportion to dose, while Tmax (2.21 to 2.94 hours) and t1/2Cmax (2.58 to 4.19 hours) were dose independent.

SAFETY RESULTS:

Adverse Events: Subcutaneous administration of single doses of AC2993 at 0.1 μg/kg and 0.2 μg/kg appeared to be well-tolerated. A higher incidence of adverse events was observed at the 0.3 μg/kg (71.4%) and 0.4 μg/kg (80.0%) doses, as compared to the placebo (42.9%), 0.1 μg/kg (37.5%), and 0.2 μg/kg (28.6%) doses. The most common adverse events associated with AC2993 treatment were headache, nausea, tachycardia, postural hypotension, vomiting, and dizziness. AC2993 at doses of 0.3 μg/kg and 0.4 μg/kg elicited a dose-dependent increase in nausea. Vomiting andpostural hypotension occurred only at the 0.4 □g/kg dose. No apparent dose trends were observed for headache, dizziness, or tachycardia. The majority of adverse events (82.9%) were assessed by the investigator as mild in intensity. Five of the six adverse events assessed as moderate in intensity were associated with the 0.4 μg/kg dose (1-postural hypotension, 1-nausea, 2-vomiting, and 1-tachycardia). In addition, the majority of treatment-related adverse events occurred at doses above 0.2 μg/kg.

CONCLUSION:
AC2993 administered SC to oral agent-treated subjects with type 2 diabetes mellitus was: well-tolerated up to doses of 0.2 μg/kg. At doses above 0.2 μg/kg, an increase was observed in the incidence and intensity of treatment-emergent adverse events, most notably nausea, vomiting, and postural hypotension.

2993-103

Title: A Single-Blind, Placebo-Controlled Crossover Study to Evaluate the Safety, Tolerability, and Effects of Multiple Doses of AC2993 Given by the Subcutaneous Route to Subjects Having Type 2 Diabetes Mellitus

Investigators and Study Centers: [redacted]

Objectives:
Primary Objectives. To examine the safety and tolerability of multiple doses of AC2993 given by the subcutaneous route over 5 days in subjects with type 2 diabetes mellitus. To examine the effect of multiple doses of AC2993 on plasma glucose given by the subcutaneous route over 5 days in subjects with type 2 diabetes mellitus.

Secondary Objectives: To investigate the pharmacokinetics of multiple doses of AC2993 given by the subcutaneous route over 5 days in subjects with type 2 diabetes mellitus. To investigate the effect on plasma insulin, glucagon, and triglycerides of multiple doses of AC2993 given over 5 days. To investigate the effect on fasting lipid profiles of multiple doses of AC2993 given over 5 days. To investigate the effect on satiety of multiple doses of AC2993 given over 5 days. To investigate the effect on gastric emptying of multiple doses of AC2993 given over 5 days. To investigate the effect on 24 hour urine creatinine and free cortisol of AC2993 given over 5 days in a selected subgroup at one study site.

Methodology: Subjects enrolled in this single-blind, placebo-controlled, two-period crossover study were tobe divided among four groups according to baseline characteristics of hemoglobin A_{1c} (HbA_{1c}) concentration and method of diabetes treatment, as follows:
Group 1: Treatment of diabetes with diet management alone; $HbA_{1c} \leq 12.0\%$
Group 2: Treatment of diabetes with oral antidiabetic agents; $HbA_{1c} < 8.0\%$
Group 3: Treatment of diabetes with oral antidiabetic agents; $HbA_{1c} \geq 8.0\%$ to $\leq 12.0\%$
Group 4: Treatment of diabetes with insulin, with or without oral antidiabetic agents; $HbA_{1c} \leq 12.0\%$
Subjects were to be randomized to one of two sequences, A/B or B/A, where A was to be placebo and B was to be 0.1 µg/kg AC2993. Subjects were to receive study medication two times a day for 5 consecutive days while housed in an inpatient unit. After a 2-day to 3-day washout period, subjects were to receive the alternate study medication according to the same schedule. During each of the two 5-day treatment periods, timed blood draws were to follow a standard breakfast or lunch to determine the effect of AC2993 on concentrations of plasma glucose, plasma insulin, plasma glucagon, serum C-peptide, serum triglyceride, and plasma acetaminophen. Satiety (well-being, hunger, and fullness) was to be assessed using a questionnaire.

Key Demographics: All subjects had type 2 diabetes mellitus. The study population was 71% male; 58%Hispanic, 33% Caucasian, and 8% Black. Subjects' mean (±SD) age was 55.8±10.2 years (range, 29.2 to 68.7 years) and mean body mass index (BMI) was 28.8±3.9 kg/m_2. Mean height and weight were 169.3±9.6 cm and 82.9±16.2 kg, respectively. In general, subjects' demographic characteristics were balanced across the four groups.

Subject Disposition: Subjects were divided among four groups according to baseline characteristics of HbA_{1c} and method of diabetes treatment, as follows: Group 1, 4 subjects; Group 2, 6 subjects; Group 3, 8 subjects; and Group 4, 6 subjects. Subjects were randomized to either treatment sequence A/B (N = 12) or B/A (N = 12), where A was placebo and B was 0.1 ⌈g/kg AC2993. All subjects completed both treatment periods.

Diagnosis and Main Criteria for Inclusion: Eligible subjects were to be individuals with type 2 diabetes mellitus treated with either diet management (Group 1), oral antidiabetic agents (Group 2 and Group 3), or

insulin with or without oral antidiabetic angents (Group 4) for 6 months prior to screening; male or female (postmenopausal or surgically sterile); age 18 to 65 years; HbA_{1c} δ12.0%; BMI 25 kg/m2 to 35 kg/m2; and otherwise healthy.

Test Product: AC2993
Dose: 0.1 ⌈g/kg, two times a day (before breakfast and dinner)
Mode of Administration: Subcutaneous injection
Batch No.: AC2993-F1 [redacted] · Lot No. 98-0401SP

Duration of Treatment: The study duration was to be 30 - 33 days. Fourteen days after screening, subjects were to be admitted to an inpatient unit during two 5-day treatment periods separated by a 2-day to 3-day washout. Subjects were to return for follow up within 4 to 6 days following discharge. Subcutaneous injections were administered two times a day for 5 days during each of the two treatment periods.

Reference Therapy: Placebo
Dose: Same dose volume as calculated for AC2993
Mode of Administration: Subcutaneous injection
Batch No: PBO-F10; Lot No. 98-0404SE

Criteria for Evaluation:
Pharmacodynamics: The primary pharmacodynamic measures were 5-hr plasma glucose concentration profiles during both treatment periods. On Day 1 and Day 5, the profile followed a standard Sustacal® liquid breakfast consumed 15 minutes after dosing. On Day 3, the profile followed a standard solid lunch and began 5 hr after dosing. Blood samples were to be drawn at specified time points on each day. Secondary pharmacodynamic measures included concentration profiles of plasma insulin, plasma glucagon, serum triglyceride, and plasma acetaminophen; appearance of acetaminophen in plasma was a measure of gastric emptying rate (acetaminophen was orally ingested with a meal). Additional evaluations included concentrations of serum C-peptide (in subjects on insulin therapy) and serum lipids. Blood samples were to be drawn at specified times on Day 1, Day 3, and Day 5 of each treatment period (no acetaminophen was to be measured on Day 3).

Pharmacodynamic parameters ($AUC_{(0\text{-}t)}$, C_{max}, and T_{max}) were to be calculated from the respective plasma concentration profiles as appropriate. Satiety (well-being, hunger, and fullness) was to be assessed using a visual analog scale (VAS) questionnaire.
Pharmacokinetics: Blood sampling for plasma AC2993 measurement was to occur during a 10-hr time course on Day 1 and Day 5 of each treatment period. Time points were to include –15 min, 20 min, 30 min, 45 min, 60 min, 90 min, 120 min, and 150 min and 3 hr, 4 hr, 5 hr, 6 hr, 7 hr, 8 hr, 9 hr, and 10 hr.

Statistical Methods:
Pharmacodynamics/Pharmacokinetics: Enrolled subjects were to be individuals with type 2 diabetes with specific baseline characteristics defined by HbA_{1c} and method of diabetes treatment. Descriptive statistics were to be presented by day and by treatment for all pharmacodynamic and pharmacokinetic parameters, including $AUC_{(0\text{-}t)}$, C_{max}, and T_{max} for plasma glucose, plasma insulin, plasma glucagon, serum triglyceride, and plasma acetaminophen; and $AUC_{(0\text{-}10hr)}$, C_{max}, T_{max}, and $t_{1/2}$ for plasma AC2993. Each parameter was to be calculated from the respective plasma concentration profiles on Day 1, Day 3, and Day 5 of each treatment period as appropriate. $AUC_{(0\text{-}300min)}$, C_{max}, and T_{max} were to be calculated from baseline-subtracted incremental concentration curves for plasma glucose measurements on Day 1 and Day 5. $AUC_{(0\text{-}t)}$, C_{max}, and T_{max} were to be calculated for plasma glucose, plasma insulin, plasma glucagon, serum triglyceride, and plasma AC2993 measurements on Day 3 based on actual plasma or serum concentration values. Pharmacodynamic and pharmacokinetic parameters, as well as serum lipids, were to be analyzed using analysis of variance (ANOVA) and the Wilcoxon rank sum test. Time-weighted average change in satiety VAS scores was to be calculated and analyzed using ANOVA and the Wilcoxon rank sum test. P values <0.05 were to be construed as statistically significant.

SUMMARY - CONCLUSIONS:

PHARMACODYNAMIC RESULTS: Twenty subjects were evaluable for the pharmacodynamic analyses. Mean postprandial plasma glucose concentrations were substantially reduced for 3 to 4 hr after a standard Sustacal liquid breakfast following treatment with 0.1 ⌠g/kg AC2993 compared with placebo. Similarly, mean postprandial concentrations were substantially reduced for plasma insulin, plasma glucagon, and serum triglyceride. Serum acetaminophen concentrations were similarly reduced, indicating a reduction in the rate of gastric emptying. In contrast, no substantial difference was noted in mean postmeal plasma glucose concentrations during 5-hr profiles that began with a standard solid lunch at 5 hr following treatment with 0.1 µg/kg AC2993 compared with placebo. Mean postmeal concentrations were higher for plasma insulin and lower for plasma glucagon and serum triglyceride following treatment with 0.1 µg/kg AC2993 compared with placebo. This general pattern was demonstrated in each of the four groups of subjects, indicating an effect in subjects with a range of severity of type 2 diabetes mellitus. The statistical significance of the reduction in each pharmacodynamic parameter following treatment with 0.1 µg/kg AC2993 compared with placebo is displayed in the following table:

Table 10: Plasma Insulin Pharmacodynamic Parameters- Parametric Statistical Analysis[†]
Evaluable Subjects in Study 2993-103 (N = 20)

Pharmacodynamic Parameter	Placebo	0.1 µg/kg AC2993	Difference[‡] or Ratio	P Value
Day 1				
$AUC_{(0\text{-}300min)}$ (µU•min/mL)				
Geometric LS Mean	9548	5900	61.8%	0.0002*
C_{max} (µU/mL)				
Geometric LS Mean	63.4	33.0	52%	<0.0001*
T_{max} (min)				
LS Mean	126	139	13	0.6409
Day 3				
$AUC_{(0\text{-}300min)}$ (µU•min/mL)				
Geometric LS Mean	6347	8935	141%	0.0019*
C_{max} (µU/mL)				
Geometric LS Mean	28.1	37.1	132%	0.0070*
T_{max} (min)				
LS Mean	377	360	-18	0.3348
Day 5				
$AUC_{(0\text{-}300min)}$ (µU•min/mL)				
Geometric LS Mean	9265	6026	65%	0.0011*
C_{max} (µU/mL)				
Geometric LS Mean	62.9	38.3	60.9%	0.0009*
T_{max} (min)				
LS Mean	125	168	43	0.1062

[†]Analysis was based on data from Group 1, 2, and 3 subjects only.
[‡]Difference = B – A for the untransformed LS means. For the geometric LS means, the ratio = Exp [ln (B) – ln (A)] × 100
*p ≤0.05, statistically significant compared with placebo
Note: LS means were based on an ANOVA model that included terms for sequence, period, subject-within-sequence, and treatment. Geometric LS means are the antilog of LS mean of the natural logarithmic transformed endpoints
Cross-reference: Supporting Data Summary 2.6.3.1, 2.6.3.3, and 2.6.3.5, Appendix 3.7

No significant change was noted in average total cholesterol concentrations on Day 5, or in the change From Day 1 to Day 5; however, values were slightly lower in subjects treated with 0.1 ⌠g/kg AC2993 compared with placebo. The average LDL cholesterol concentration was reduced significantly from Day 1 to Day 5 in subjects treated with 0.1 ⌠g/kg AC2993 compared with placebo ($p = 0.0115$). In subjects on insulin therapy, mean postbreakfast serum C-peptide concentrations increased substantially from baseline at 2 hr following treatment with either placebo or 0.1 ⌠g/kg AC2993. However, the mean increase was smaller in subjects treated with 0.1 ⌠g/kg AC2993 (63% to 109%) compared with placebo (209% to 250%). Mean postlunch serum C-peptide concentrations increased similarly following either treatment (54%). No substantial differences in well-being or hunger were noted for subjects treated with 0.1 ⌠g/kg AC2993 or placebo as assessed using VAS scores. In general, subjects felt that their stomach was not as empty following treatment with AC2993 as subjects felt following treatment with placebo.

Figure 2: Mean (±SE) Plasma Glucose Concentration-Time Profile on Days 1, 3, and 5 Evaluable Subjects in Study 2993-103 (N = 20)

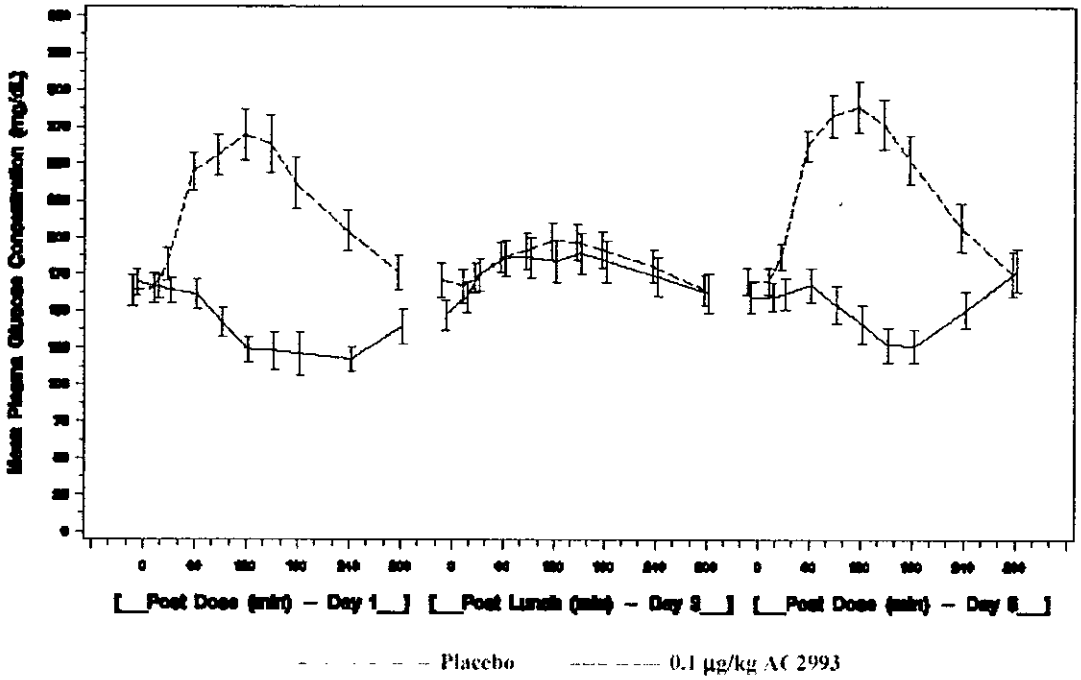


Figure 4: Mean (±SE) Plasma Glucagon Concentration-Time Profile on Days 1, 3, and 5
Evaluable Subjects in Study 2993-103 (N = 20)

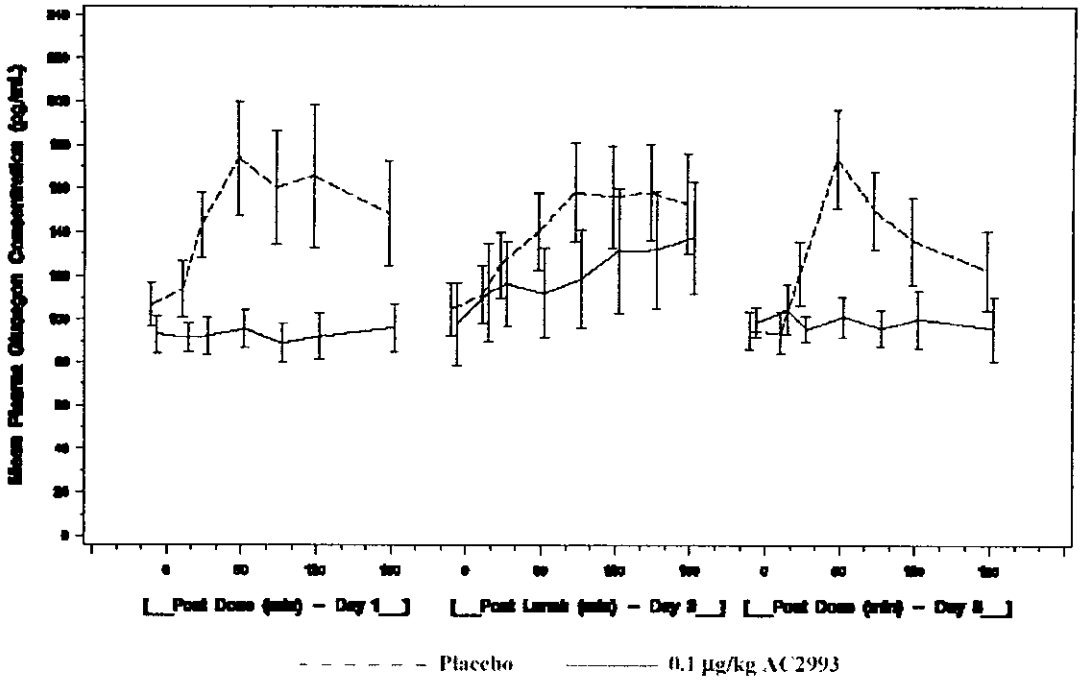


Figure 3: Mean (±SE) Plasma Insulin Concentration-Time Profile on Days 1, 3, and 5
Evaluable Subjects in Study 2993-103 (N = 16)*

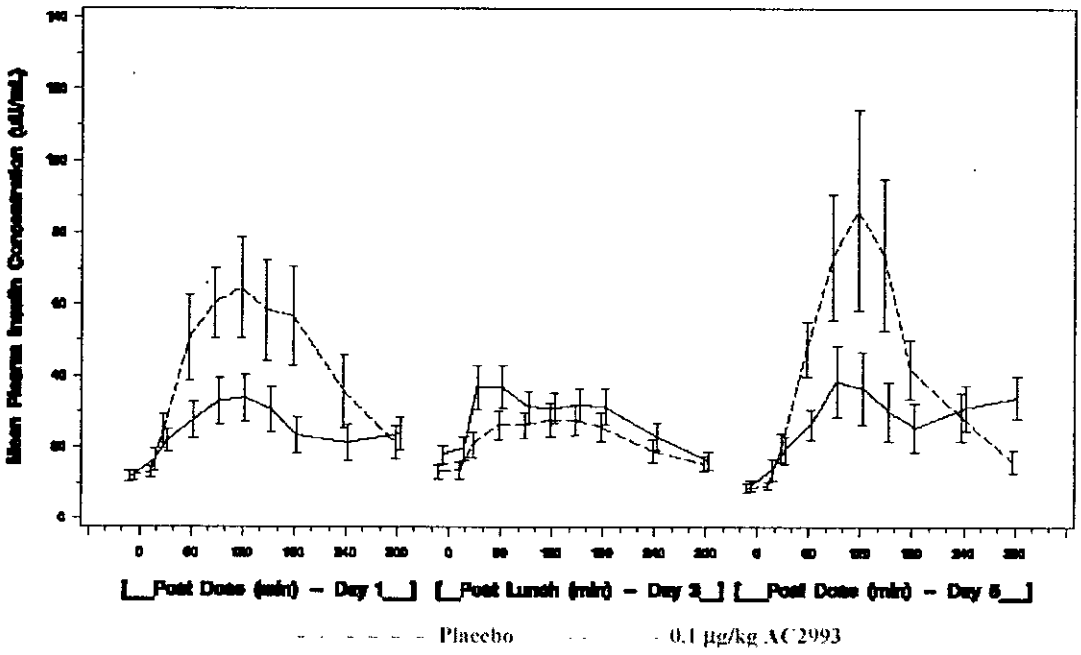
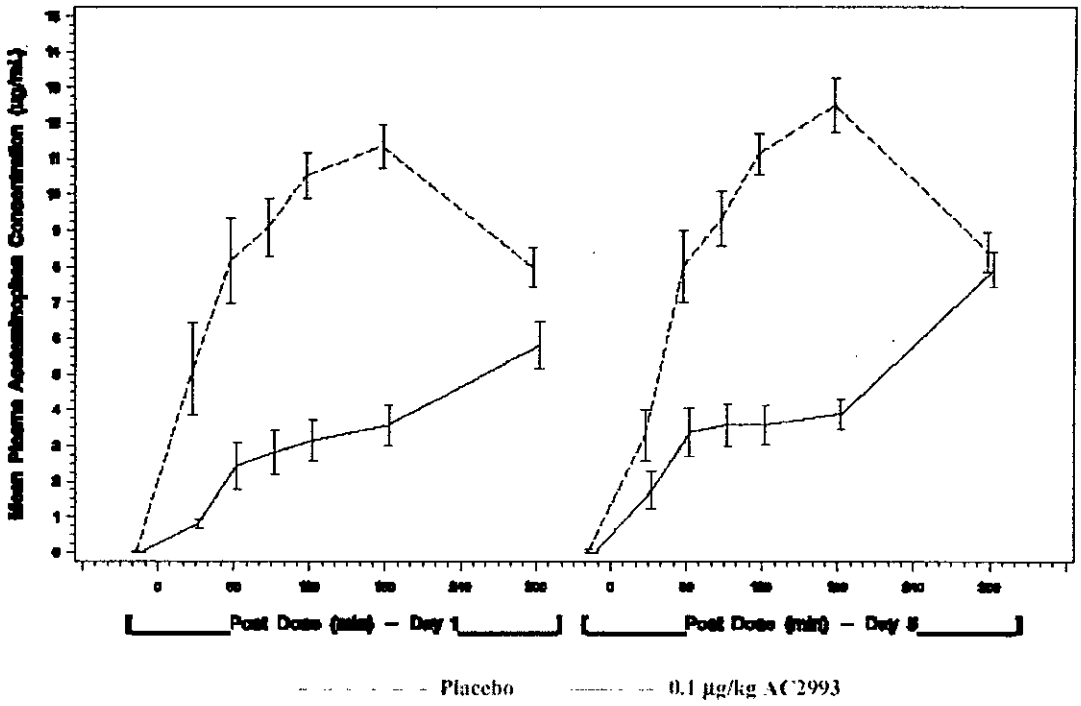


Figure 6: Mean (±SE) Plasma Acetaminophen Concentration-Time Profile on Days 1 and 5
Evaluable Subjects in Study 2993-103 (N = 20)



PHARMACOKINETIC RESULTS: Twenty-two subjects were evaluable for the AC2993 pharmacokinetic analysis. On Day 1 and Day 5, respectively, mean C_{max} was 233.0 pg/mL and 259.6 pg/mL; mean T_{max} was 2.4 hr and 2.2 hr; mean $AUC_{(0\text{-}10hr)}$ was 1057.8 pg.hr/mL and 1169.4 pg.hr/mL; and mean $t_{1/2}$ was 2.4 hr and 2.1 hr.

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Figure 7: Mean Plasma AC2993 Concentration-Time Profile on Day 1
Evaluable Subjects in Study 2993-103 (N = 22)*

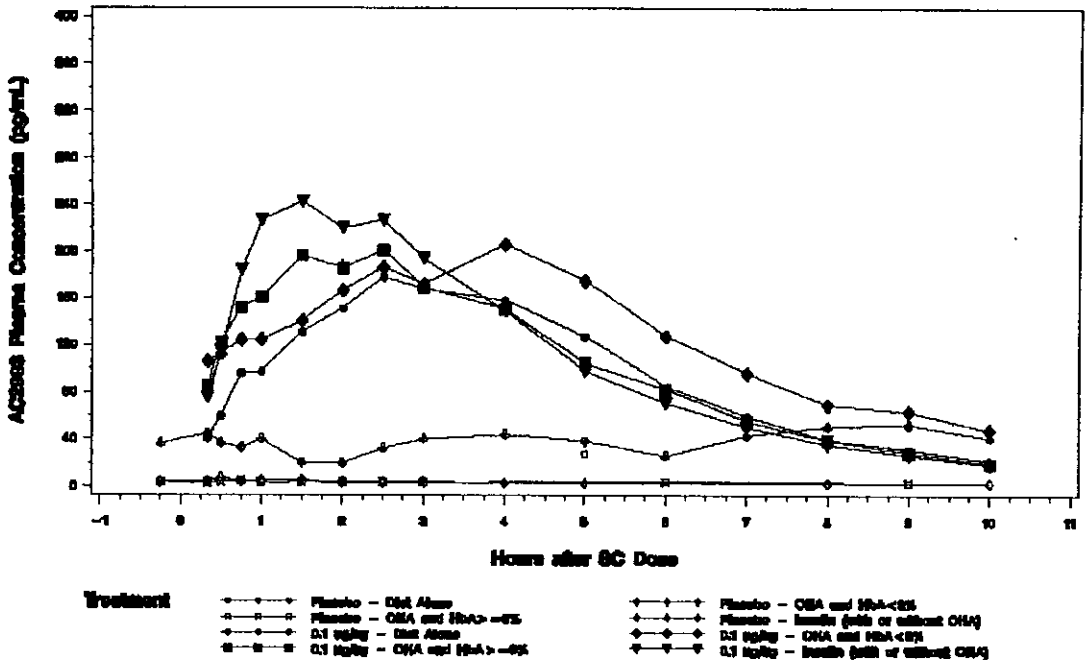


Figure 8: Mean Plasma AC2993 Concentration-Time Profile on Day 5
Evaluable Subjects in Study 2993-103 (N = 22)*

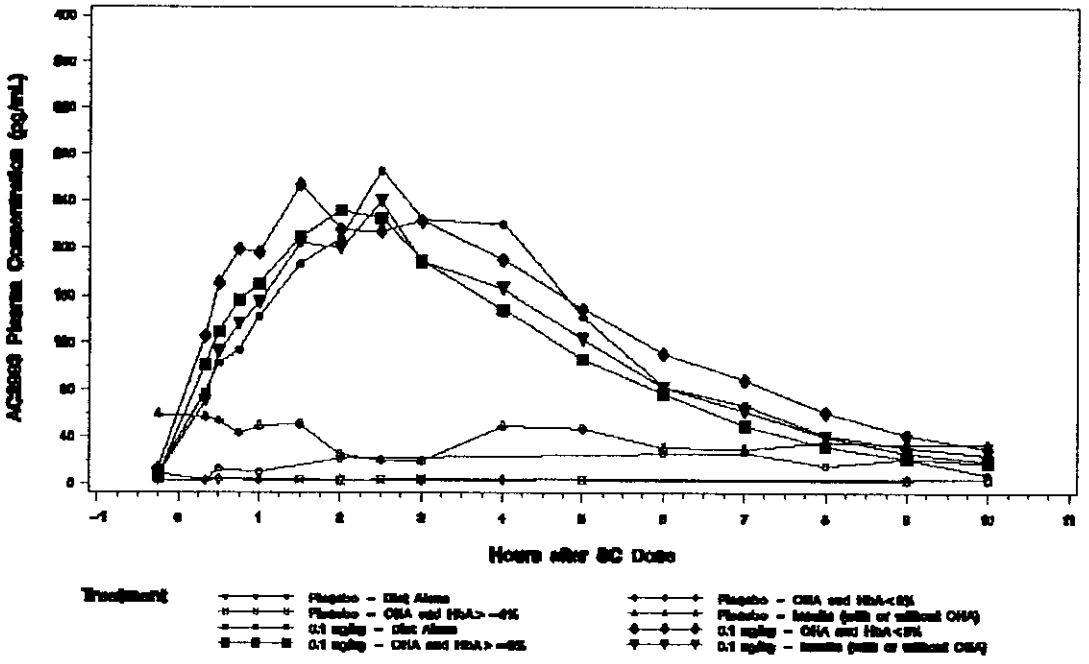


Table 16: Plasma AC2993 Pharmacokinetic Evaluation
Evaluable Subjects in Study 2993-103 (N = 22)*

Pharmacokinetic Parameter	Day 1	Day 5
$AUC_{(0\text{-}10hr)}$ (pg•hr/mL)		
Mean ± SD	1057.8±182.4	1169.4±197.0
C_{max} (pg/mL)		
Mean ± SD	233.0±57.1	259.6±44.7
T_{max} (hr)		
Mean ± SD	2.4±1.1	2.2±0.6
$t_{1/2}$ (hr)		
Mean ± SD	2.4±0.9	2.1±0.5

*Data were invalid or missing for subjects 0203 and 0204.
Cross-reference Supporting Data Summary 2.4.2.3 and 2.4.2.6, Appendix 3.4.2

On Day 1, mean plasma AC2993 concentrations increased steadily from aseline and reached a Cmax of 233 pg/mL at a Tmax of 2.4 hr. Similar results ere obtained on Day 5 (Cmax, 260 pg/mL; Tmax, 2.2 hr). At 10 hr, plasma C2993 concentrations had declined to 24.6 pg/mL and 21.3 pg/mL on Day 1 and Day 5, respectively. Additional pharmacokinetic parameters calculated from the two 10-hr AC2993 concentration profiles on Day 1/Day 5 were as follows: AUC(0-10hr), 1057.8/1169.4 pg.hr/mL; and t1/2, 2.4/2.1 hr.

CONCLUSION: AC2993 (0.1 µg/kg, given two times a day) is well-tolerated and has significant clinical activity in individuals with a range of severity of type 2 diabetes mellitus.

2993-104:

Title: A Single-Blind, Placebo-Controlled Study to Examine the Metabolic Effects of a Range of Doses of AC2993 Given by the Subcutaneous Route to Subjects with Type 2 Diabetes Mellitus

Investigators and Study Centers: [redacted]

Objectives: Primary Objectives: To examine the effect of a range of doses of AC2993 given to subjects with type 2 diabetes mellitus on plasma glucose and to examine the tolerability of a range of doses of AC2993 given by the subcutaneous (SC) route to subjects with type 2 diabetes mellitus.

Secondary Objectives: To investigate the effect of a range of doses of AC2993 given by the SC route on plasma insulin and glucagon. To investigate the effect of a range of doses of AC2993 given by the SC route on satiety. To investigate the effect of a range of doses of AC2993 given by the SC route on gastric emptying as measured by plasma acetaminophen following ingestion. To collect samples to investigate the pharmacokinetics of a range of doses of AC2993 given by the SC route to subjects with type 2 diabetes mellitus.

Methodology: Randomized, placebo-controlled, single-blind, four-period crossover study in subjects with type 2 diabetes mellitus, designed to assess the tolerability and effects of AC2993. In Part 1, six subjects were confined to an inpatient clinical research unit for 3 to 4 days and assigned to one of four treatment sequences, where they could receive each of the following doses: placebo or AC2993 at 0.1 µg/kg or 0.01µg/kg or possibly 0.001 µg/kg (the 0.001 µg/kg dose was to be given only if a glucose effect was observed in the 0.01 µg/kg dose). The doses were administered SC following an overnight fast. A standardized liquid meal was given15 minutes after injection of study medication. In Part 2, eight subjects were also confined to an inpatient clinical research unit for 4 days. These were different subjects from those who participated in Part 1. The doses of study medication (AC2993 0.02 µg/kg, 0.05 µg/kg, and 0.1 µg/kg) for Part 2 were determined after the effect on glucose in Part 1 had been observed. After an overnight fast, the doses were administered; 15 minutes later, a standardized liquid meal and liquid acetaminophen were given. Secondary pharmacodynamic measures (plasma insulin, plasma glucagon, and plasma acetaminophen), satiety, and pharmacokinetics were performed in Part 2 only.

Number of Subjects: A total of 14 subjects with type 2 diabetes mellitus were enrolled in the study: six in Part 1, eight in Part 2.

Key Demographics: The majority of subjects in Part 1 were Caucasian (66.7%) with a mean age of 56.3 years. The mean weight was 86.3 kg, and the mean height was 163.5 cm. The mean BMI of the subject population in Part 1 was 32.5 kg/m^2. Two (33.3%) subjects were receiving oral hypoglycemic agents (OHA) therapy prior to screening; all OHA therapy was discontinued prior to Day 0. Subjects in Part 2 were predominately Caucasian (87.5%) with a mean age of 52.3 years. Six (75.0%) subjects were receiving OHA therapy prior to screening; all OHA therapy was discontinued prior to Day 0.

Subject Disposition: All 14 (100.0%) subjects completed the study.

Diagnosis and Main Criteria for Inclusion: Subjects with type 2 diabetes mellitus, controlled with diet and/or with oral hypoglycemic agents (OHAs), and with glycosylated hemoglobin (HbA_{1c}) ≥7.0%; ≤12.0% atthe Screening Visit were enrolled in this study.

Test Product, Dose and Mode of Administration, Batch No.: AC2993; 0.1 mg/mL, 0.01 µg/kg, 0.02 µg/kg, 0.05 µg/kg, and 0.1 µg/kg per subject; SC injection; Lot number: (AC-2993-F3) 99-0801TP.

Duration of Treatment: In Part 1, subjects were exposed to single doses of placebo and AC2993 at 0.1 µg/kg, 0.01 µg/kg, and possibly 0.001 µg/kg over a 3-day (or 4-day, if the lowest concentration was to be administered) period. In Part 2, subjects were exposed to single doses of placebo and AC2993 at 0.02, 0.05, and 0.1 µg/kg over a 4-day period.

Reference Therapy, Dose and Mode of Administration, Batch No: Placebo; SC injection; Lot number: (PBO-F10) 99-0802TE.

Criteria for Evaluation:
Pharmacodynamics: The baseline (i.e., fasting value)-unadjusted and baseline-adjusted pharmacodynamic parameters, including area under the concentration-time curve from 0-300 minutes $AUC_{(0\text{-}300\ min)}$, peak concentration ($C_{max}$), and time to peak concentration (T_{max}) for plasma glucose and home glucose meter blood glucose; $AUC_{(0\text{-}120\ min)}$, C_{max}, and T_{max} for plasma insulin, and plasma glucagon were to be calculated from the plasma concentration profile within each treatment group. Plasma acetaminophen measures were calculated using unadjusted data only.

Pharmacokinetics: Comparison of plasma AC2993 concentrations over time. Plasma AC2993 pharmacokinetic parameters to be evaluated were as follows: area under the concentration-time curve from 0-300 minutes ($AUC_{(0\text{-}300\ min)}$), area under the concentration-time curve from 0-infinity ($AUC_{(0\text{-}inf)}$), peak concentration (C_{max}), time to peak concentration (T_{max}), and half life ($t_{½}$).

Efficacy: Comparison of satiety measurements over time using a Visual Analog Scale (VAS). Satiety measurements included the following categories: well → sick or nauseated, satisfied → hungry, and full →empty.

Statistical Methods:
Pharmacodynamics: Descriptive statistics were to be presented for all the pharmacodynamic parameters ($AUC_{(0\text{-}300\ min)}$ or $AUC_{(0\text{-}120\ min)}$, C_{max}, and T_{max}) within each treatment dose. Individual subject concentration profiles and mean concentration profiles were to be plotted for each treatment dose. Descriptive statistics were to be generated for both parts of the study, while statistical analysis was only to be conducted for Part 2of the study. Baseline-unadjusted and baseline-adjusted pharmacodynamic parameters were to be analyzed using ANOVA. Pairwise comparisons were done at the 0.05 significance level.

Pharmacokinetics: Descriptive statistics were to be presented for all the plasma AC2993 pharmacokinetic parameters ($AUC_{(0\text{-}300\ min)}$, $AUC_{(0\text{-}inf)}$, C_{max}, T_{max} and $t_{1/2}$) within each treatment dose. $AUC_{(0\text{-}300\ min)}$, $AUC_{(0\text{-}inf)}$, and C_{max} were to be log transformed and analyzed using ANOVA. T_{max}, and $t_{1/2}$ were to be analyzed without log transformation. Individual plasma AC2993 concentration profiles and mean plasma AC2993 concentration profiles were to be plotted for each treatment dose. Descriptive statistics were to be generated for both parts of the study, while pairwise comparisons between doses and pharmacokinetic analyses were only to be conducted for Part 2 of the study.

Efficacy: Satiety data by category were to be plotted across time points for each treatment dose. The time weighted average baseline-adjusted satiety scores were to be analyzed in the same way as the pharmacokinetic parameters, but without the log transformation, to compare the different treatment doses. Safety: Adverse events, clinical laboratory values, concomitant medication use, and vital signs were presented using descriptive statistics.

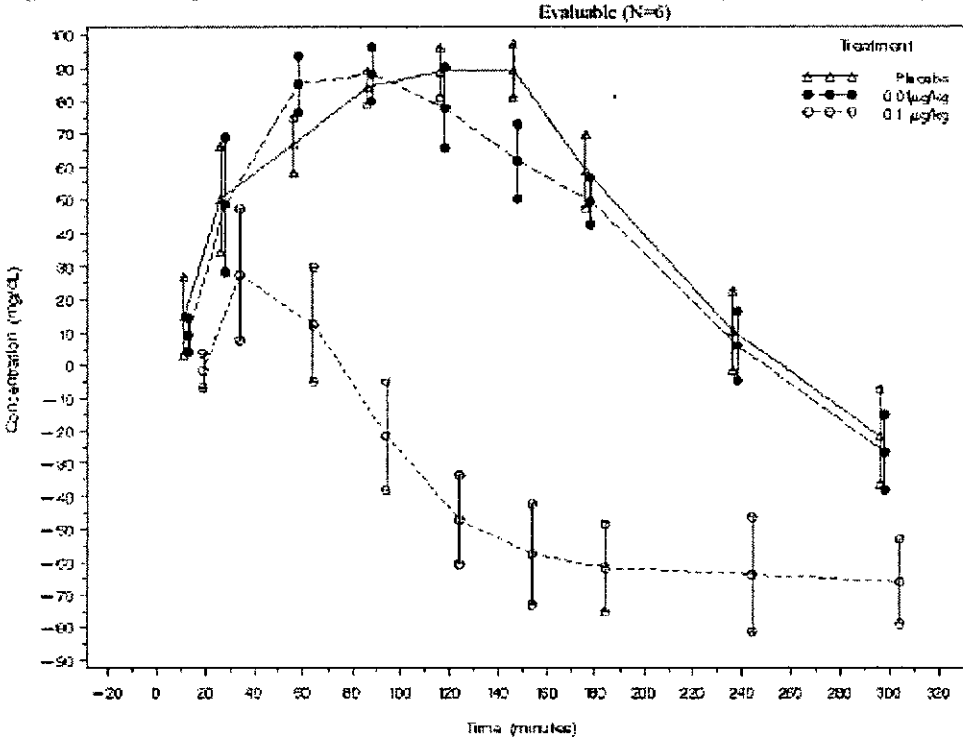
SUMMARY – CONCLUSIONS:
PHARMACODYNAMIC RESULTS:
Plasma Glucose Concentrations: In Part 1, AC2993 treatment at 0.1 µg/kg was associated with a reduction in mean glucose concentrations in response to a Sustacal meal compared to placebo and 0.01 µg/kg. The 0.01 µg/kg dose did not result in reduced mean glucose concentrations compared with placebo so the dose of 0.001 µg/kg dose was not administrated. Postprandial plasma glucose concentrations decreased in a dose dependent manner in response to AC2993 treatment in Part 2. The largest reduction was observed at the 0.1 µg/kg dose. Pairwise comparisons of baseline-adjusted $AUC_{(0\text{-}300\ min)}$ of each active treatment group vs. placebo were statistically significant ($p < 0.05$). Statistical significance was demonstrated for baseline adjusted C_{max} of the 0.05 µg/kg and 0.1 [g/kg treatment groups, compared to placebo ($p < 0.05$). Pairwise comparisons of T_{max} for all three AC2993 treatment groups vs. placebo were not statistically significant.

Baseline-Adjusted Plasma Glucose Pharmacodynamic Parameters by Treatment: Mean (SD)

Parameter	Placebo (N=8)	AC2993 0.02 µg/kg (N=8)	AC2993 0.05 µg/kg (N=8)	AC2993 0.1 µg/kg (N=8)
$AUC_{(0-300\ min)}$ (mg•min /dL)	12030 (11634)	7677* (8456)	-660* (11445)	-7974* (11152)
C_{max} (mg/dL)	110 (44)	96 (41)	59* (43)	39* (29)
T_{max} (min)	94 (37)	94 (43)	83 (44)	105 (86)

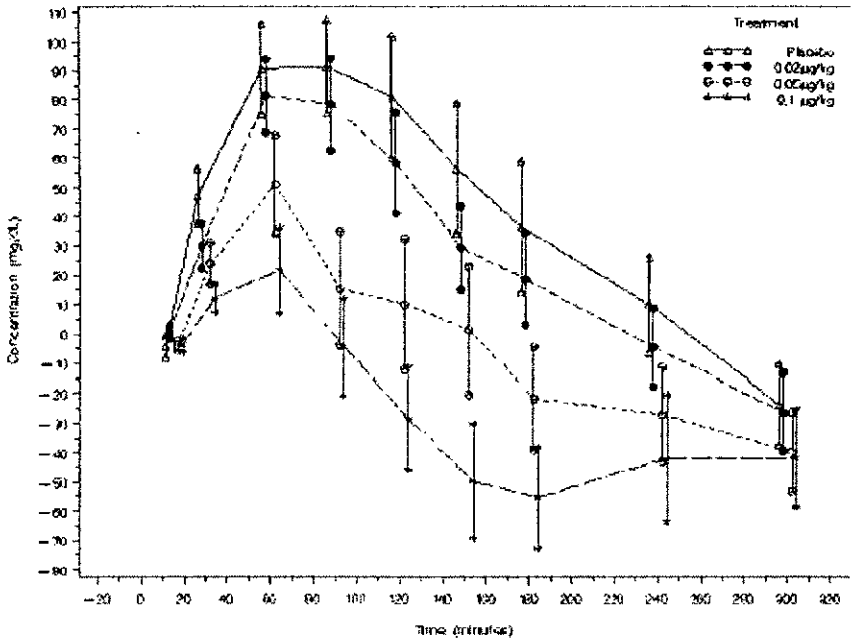
*Pairwise comparison vs placebo was statistically significant ($p < 0.05$)

Figure 1: Baseline-Adjusted Mean (+SE) Plasma Glucose Concentration – Time Curve by Treatment -- Part 1*Population: Evaluable (N=6)



*Baseline-adjusted concentration values were calculated from original postdose value minus average of predose values.
Note Study medication was administered at t=0 minutes; Sustacal meal was administered at t=15 minutes.
Cross references Supporting Data Summaries 2.1.4-1, 2.1.2-1, Appendix 3.7.3-1

Figure 2: Baseline-Adjusted Mean (±SE) Plasma Glucose Concentration – Time Curve by Treatment – Part 2* Population: Evaluable (N=8)



*Baseline-adjusted concentrations values were calculated from the original postdose value minus the average of the predose values.

Note: Study medication was administered at t=0 minutes; Sustacal meal was administered at t=15 minutes.

Cross references: Supporting Data Summaries 2.1.4-2, 2.1.6-2, Appendix 3.7.4-2.

Table 6: Baseline-Adjusted Plasma Glucose Pharmacodynamic Parameters by Treatment*: Descriptive Statistics - Part 2 Population: Evaluable (N=8)

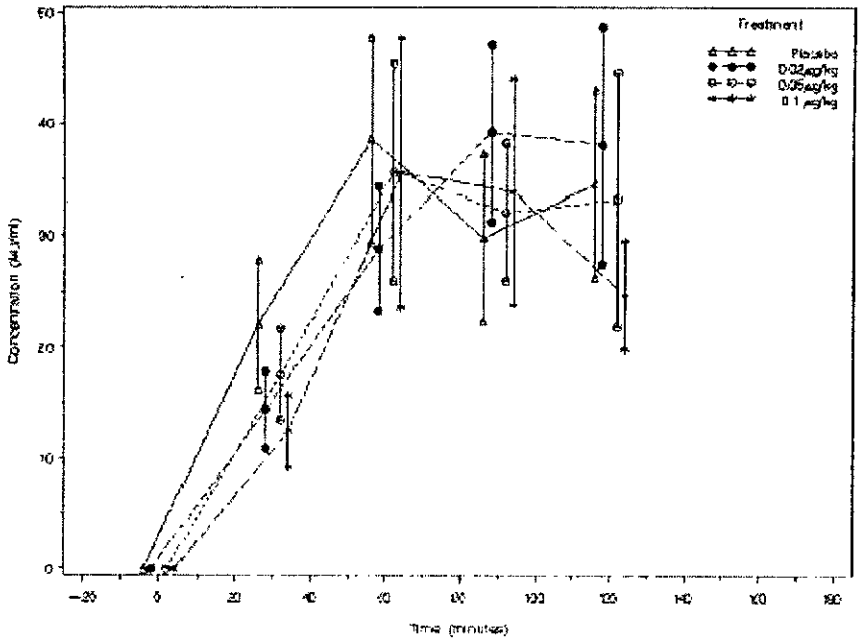
Pharmacodynamic Parameter	Placebo (N=8)	AC2993 0.02 µg/kg (N=8)	AC2993 0.05 µg/kg (N=8)	AC2993 0.1 µg/kg (N=8)
$AUC_{(0-300\ min)}$ (mgxmin/dL)				
Mean	12029.6	7677.3*	-659.6*	-7973.8†
SD	11634.43	8455.98	11444.61	11152.41
Min				
Max				
C_{max} (mg/dL)				
Mean	109.9	96.4	59.3*	39.1†
SD	44.15	40.70	42.52	29.42
T_{max} (min)				
Mean	94.0	94.3	82.6	105.0
SD	36.91	43.00	44.19	86.35
Min				
Max				

*Baseline-adjusted values were calculated as the original value minus the average of the predose values

†Pairwise comparison vs. placebo was statistically significant ($p < 0.05$).

Cross references: Supporting Data Summaries 2.1.2-2 and 2.1.3-2, Appendix 3.7.4-2.

Figure 3: Baseline-Adjusted Mean (±SE) Plasma Insulin Concentration – Time Curve by Treatment – Part 2♦ Population: Evaluable (N=8)



♦Baseline-adjusted concentrations values were calculated from the original postdose value minus the average of the predose values.

Note: Study medication was administered at t=0 minutes; Sustacal meal was administered at t=15 minutes.

Cross references: Supporting Data Summaries 2.3.1-2, 2.3.6-2, Appendix 3.7.11-2.

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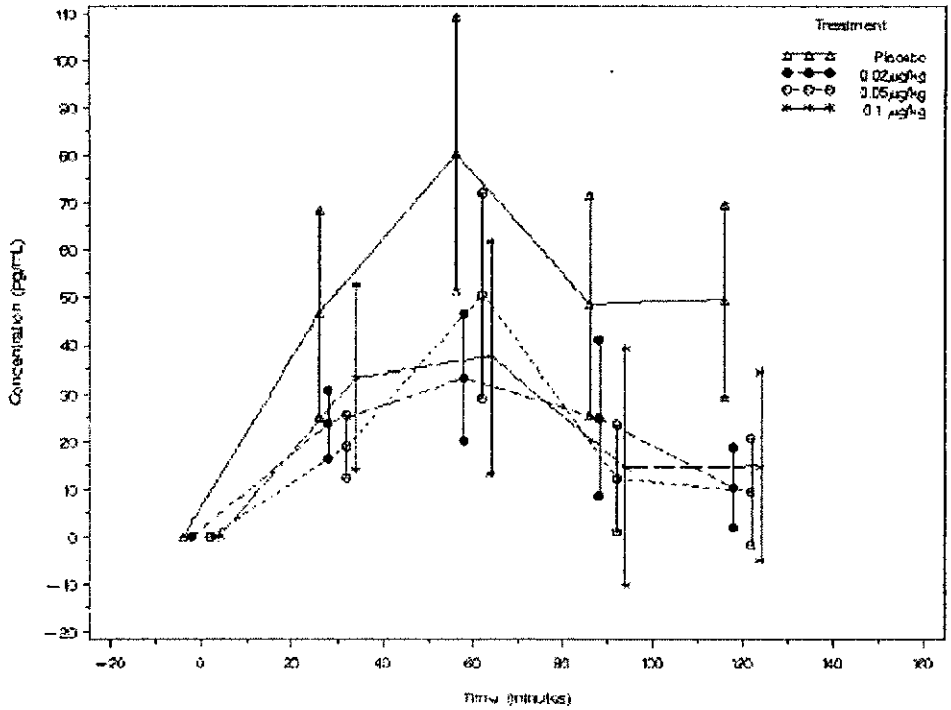
Figure 4: Baseline-Adjusted Mean (±SE) Plasma Glucagon Concentration: Time Curve by Treatment – —Part 2*
Population: Evaluable (N=8)

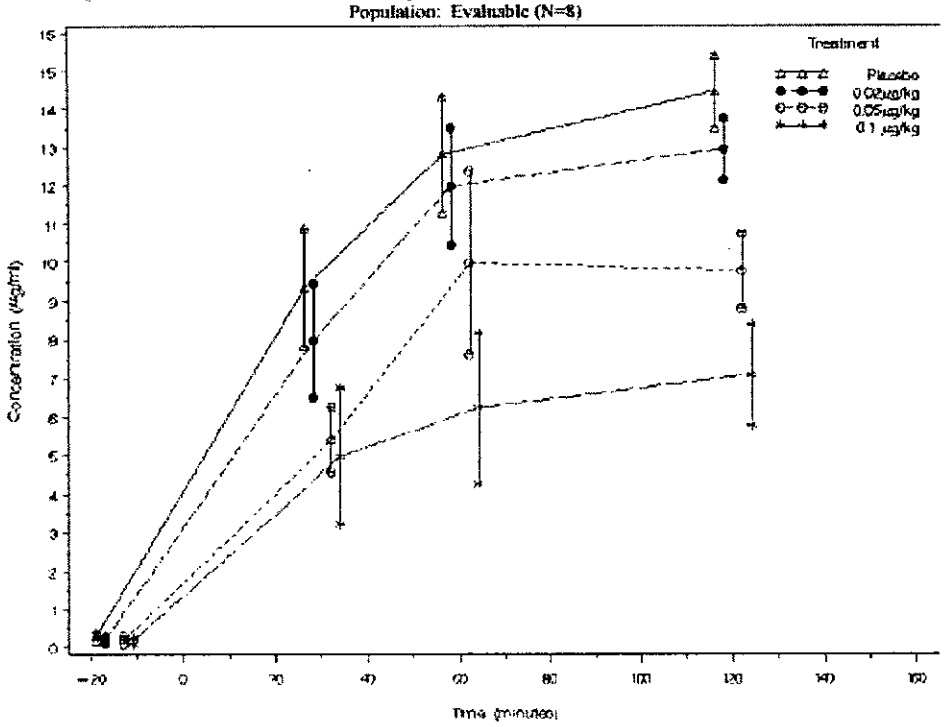


*Baseline-adjusted concentration values were calculated from the original postdose value minus the average of the predose values

Note: Study medication was administered at t=0 minutes; Sustacal meal was administered at t=15 minutes.

Cross references: Supporting Data Summaries 2.4.6-2, 2.4.5-2, Appendix 3.7.15-2

Figure 5: Mean (±SE) Plasma Acetaminophen Concentration – Time Curves by Treatment – Part 2
Population: Evaluable (N=8)



Note: Study medication was administered at t=0 minutes; Sustacal meal was administered at t=15 minutes.
Cross references: Supporting Data Summaries 2.6.4-2, 2.6.1-2, Appendix 3.7.8-2

Plasma Insulin Concentrations: Plasma insulin concentrations for the AC2993 doses were similar to placebo, despite lower plasma glucose concentrations. The pairwise comparisons between each of the three active treatment groups and placebo were not statistically significant (p ε0.05) for baseline-adjusted AUC $_{(0\text{-}120\ min)}$, C_{max}, or T_{max}.

Plasma Glucagon Concentrations: At all postdose measurement times, the AC2993 treatment groups had lower mean plasma glucagon concentrations compared to placebo. Baseline-adjusted $AUC_{(0\text{-}120\ min)}$ and C_{max} of the 0.02 ⌠g/kg and 0.05 ⌠g/kg treatment groups vs. placebo were statistically significant (p δ0.0405), while the 0.1 ⌠g/kg treatment vs. placebo approached significance for baseline-adjusted $AUC_{(0\text{-}120\ min)}$ (p = 0.0524) and C_{max} (p = 0.0560). None of the pairwise comparisons for baseline-adjusted T_{max} were statistically significant (pε0.05).

Plasma Acetaminophen Concentrations: Increasing doses of AC2993 resulted in decreased plasma acetaminophen concentrations, suggesting that AC2993 treatment modulates gastric emptying in a dosedependent manner. Both $AUC_{(0\text{-}120\ min)}$ and C_{max} decreased in response to increasing AC2993 treatment. Pairwise comparisons were statistically significant for $AUC_{(0\text{-}120\ min)}$ and C_{max} for all but the placebo 0.02 ⌠g/kg comparison.

EFFICACY RESULTS: Both the 0.02 ⌠g/kg and 0.1 ⌠g/kg treatment groups showed increases in feelings of wellness, fullness, and satisfaction, compared to placebo. The 0.05 ⌠g/kg treatment group had increases in wellness and fullness but not in satisfaction, compared to placebo. There were no statistically significant differences when the AC2993 treatment groups were compared to placebo.

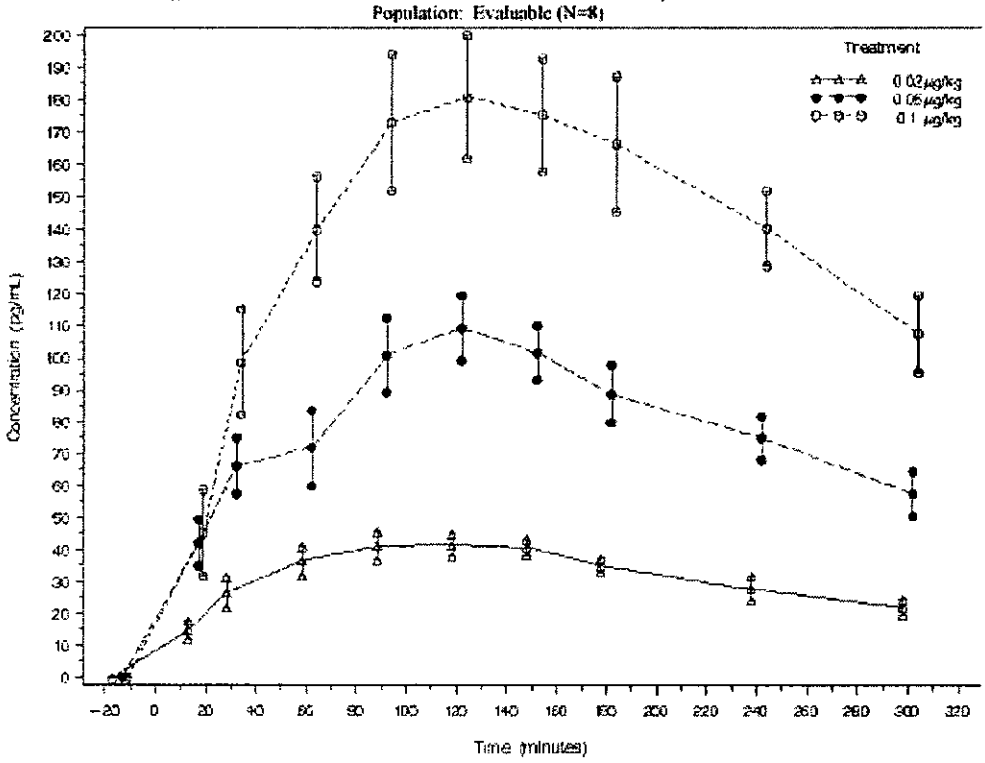
PHARMACOKINETIC RESULTS: For AC2993 measured in plasma, $AUC_{(0\text{-}300\ min)}$, $AUC_{(0\text{-}inf)}$, and C_{max}

increased in a dose-proportional manner while $t_{1/2}$ and T_{max} were dose independent.

Plasma Pharmacokinetics of AC2993: Mean (SD)

Parameters	AC2993 0.02 µg/kg (N=8)	AC2993 0.05 µg/kg (N=8)	AC2993 0.1 µg/kg (N=8)
$AUC_{(0-300\ min)}$ (pg•min /mL)	9488 (1571)	23791 (6018)	42484 (11157)
$AUC_{(0-inf)}$ (pg•min/mL)	15181 (3415)	45600 (17359)	78352 (23477)
C_{max} (pg/mL)	46 (10)	112 (27)	192 (48)
$t_{\frac{1}{2}}$ (min)	189 (109)	238 (134)	224 (94)
T_{max} (min)	124 (57)	125 (32)	131 (36)

Figure 9: Mean (±SE) AC2993 Concentration – Time Curves by Treatment – Part 2
Population: Evaluable (N=8)



Note: Study medication was administered at t=0 minutes; Sustacal meal was administered at t=15 minutes.
Cross references: Supporting Data Summaries 2.5.1-2 and 2.5.4-2, Appendix 3.7.8-2.

Table 13: Plasma AC2993 Pharmacokinetic Parameters by Treatment: Descriptive Statistics – Part 2
Population: Evaluable (N=8)

Pharmacokinetic Parameter	AC2993 0.02 µg/kg (N=8)	AC2993 0.05 µg/kg (N=8)	AC2993 0.1 µg/kg (N=8)
$AUC_{(0\text{-}240\ min)}$ (pg•min/mL)			
N	8	8	8
Mean	9487.6	23791.0	42483.6
SD	1570.87	6018.34	11157.45
Min	7029.1	16976.9	32155.8
Max	11375.3	37337.3	66385.4
$AUC_{(0\text{-}inf)}$ (pg•min/mL)			
N	7	8	8
Mean	15180.8	45600.2	78351.9
SD	3414.94	17359.17	23476.98
Min	11059.8	22716.3	50534.6
Max	20092.8	67877.6	110703.4
C_{max} (pg/mL)			
N	8	8	8
Mean	45.6	111.7	191.9
SD	9.99	27.05	47.70
Min			
Max			
$t_{1/2}$ (min)			
N	7	8	8
Mean	188.8	237.6	223.7
SD	108.92	133.69	93.69
Min	83.6	83.0	122.8
Max	375.7	430.6	379.7
T_{max} (min)			
N	8	8	8
Mean	123.9	124.9	131.1
SD	56.77	31.80	35.80
Min	61.0	90.0	89.0
Max	241.0	188.0	180.0

Cross references: Supporting Data Summary 2.5.2-2, Appendix 3.7.18-2.

CONCLUSION:

SC administration of AC2993 given to subjects with type 2 diabetes mellitus at doses of 0.02 µg/kg to 0.1 µg/kg were pharmacologically active, as was evidenced by postprandial reductions in plasma glucose, plasma glucagon, and the delay of the appearance of plasma acetaminophen. Postprandial plasma glucose concentrations were not reduced following administration of the 0.01 µg/kg dose, thus defining the minimal effective dose as 0.02 µg/kg. SC administration of AC2993 in doses up to 0.1 µg/kg was well tolerated in subjects with type 2 diabetes mellitus.

2993-105

Title: A Balanced Study to Examine the Effect on Frequency of Subcutaneous Administration of a Constant Total Daily Dose of AC2993 (0.2 µg/kg) on Plasma Glucose in Subjects with Type 2 Diabetes Mellitus

Investigators and Study Centers: [redacted]

Study initiation: 7 March 2000
Study completion: 13 April 2000

Phase of Development: 2

Objectives: Primary Objectives: To examine the pharmacodynamic effects on plasma glucose of a constant total daily dose of a continuous subcutaneous (SC) infusion of AC2993 versus once, twice, and four times dailybolus dosing given by the subcutaneous route in subjects with type 2 diabetes mellitus. To examine the safety and tolerability of a constant total daily dose of a continuous SC infusion of AC2993 versus once, twice and four times daily bolus dosing given by the SC route in subjects with type 2 diabetes mellitus. Secondary Objectives: To collect samples to investigate the pharmacokinetics of a constant total daily dose of a continuous SC infusion of AC2993 versus once, twice and four times daily bolus dosing given by the SC route in subjects with type 2 diabetes mellitus. To examine the effect of a constant total daily dose of a continuous SC infusion of AC2993 (0.20 µg/kg) administered via the dosing regimens listed below on 48-hour glucose profiles assessed using a [redacted] Continuous Glucose Monitoring System.

Methodology: This was a double-blind, single-center, four-period crossover study comparing 4 dose frequencies of a constant daily dose of AC2993 0.20 µg/kg, administered subcutaneously as a bolus injection or a continuous infusion; each regimen was administered for 2 consecutive days: (A) 0.20 µg/kg once a day (QD) in the morning at 0700 hr or in the evening at 0100 hr; (B) 0.10 µg/kg given twice a day (BID); (C) 0.05 µg/kg given four times a day (QID); and (D) 0.20 µg/kg/day given as continuous subcutaneous infusion. Each dosing regimen was separated by a 12-hr washout period. Blood samples were to be collected at the same time points during each of the four 2-day treatment periods to evaluate the effects of AC2993 on plasma glucose in each dosing regimen.**Number of Subjects:** Twelve subjects were enrolled in this study.

Key Demographics: The majority of subjects were Hispanic (83.3%) and the mean age was 55.8 years. The mean body weight was 73.8 kg. Subjects randomized to Treatment Sequence 3 had the highest mean body weight (83.0 kg) and subjects randomized to Treatment Sequence 4 had the lowest (60.9 kg). Treatment sequences were generally well balanced with regard to subject height and BMI.

Subject Disposition: Eleven subjects (91.7%) completed all study procedures and treatment periods (screening, Day 0, treatment periods 1-4, and study discharge on Day 15). One subject withdrew prematurely due to a serious adverse event (hyponatremia); this serious adverse event was considered to be unrelated to study medication.

Diagnosis and Main Criteria for Inclusion: Eligible subjects were males or females (postmenopausal or surgically sterile) with type 2 diabetes mellitus; age 18 to 65 years; treated with diet alone or combined with asulf onylurea, metformin, or the two agents combined for a minimum of 6 months at screening. In addition, subjects were to have an HbA_{1c} concentration ≥ 7.0% but ≤ 12.0%.

Dose: 0.20 µg/kg AC2993 QD, 0.10 µg/kg AC2993 BID, 0.05 µg/kg AC2993 QID, and 0.20 µg/kg/day AC2993 given as continuous SC infusion

Mode of Administration: Bolus SC injection and continuous SC infusion
Lot No.: AC2993 (0.1 mg/mL) 99-0801TP

Duration of Treatment: The study was 19-21 days in duration. Subjects were admitted to an inpatient unit for 15 days and were to return in 4 to 6 days for a follow-up termination visit. Treatment was administered in 2-day periods. A 2-day placebo lead-in period was followed by four 2-day treatment periods that included a 12-hour washout between treatments.

Reference Therapy: Placebo

Dose: Same dose volume as calculated for AC2993 (0.20 µg/kg for bolus injection; 0.20 µg/kg/day for continuous infusion)

Mode of Administration: Bolus SC injection and continuous SC infusion
Lot No.: 99-0802TE

Criteria for Evaluation:
The primary evaluations were based on plasma glucose profiles on the second day of each treatment period. In addition, 48–hour continuous glucose monitoring data were collected using a continuous glucose monitorings ystem. The primary pharmacodynamic parameters were the area under the concentration-time curve (AUC), time-weighted average concentration (C_{ave}), and the maximum concentration observed (C_{max}) for plasma glucose. Secondary evaluations included pharmacokinetic parameters for plasma AC2993, including AUC, C_{ave}, C_{max}, and time to maximum observed concentration (T_{max}). Safety: Safety measures included monitoring of adverse events, vital signs (blood pressure and pulse), electrocardiograms, clinical laboratory measures (hematology, serum chemistry, and urinalysis), and physical examination.

Statistical Methods:
Efficacy: The pharmacodynamic parameters for plasma glucose were to be calculated and analyzed using general linear mixed models and the 95% confidence intervals were to be calculated for the differences among treatment regimens. The AUC and C_{max} for uncorrected plasma glucose and AC2993 were to be calculated, log-transformed, and analyzed in a similar manner as incremental (baseline-adjusted) plasma glucose. The 95% confidence intervals were to be calculated for the ratios among the treatment regimens. T_{max} was to be analyzed similarly without the log-transformation. An alternate secondary analysis was used to facilitate comparisons of placebo lead-in data with the four active dosing regimens and to enable comparison of morning versus evening dosing for the 0.20 µg/kg QD regimen

Safety: Safety data were to be summarized by treatment with event frequency and subject incidence in each body system overall, as well as in each WHOART 1997 term. Descriptive statistics were to be presented for vital signs and laboratory values.

SUMMARY - CONCLUSIONS:
PHARMACODYNAMIC RESULTS:
Mean postprandial plasma glucose concentrations generally decreased in response to AC2993 treatment. The reduction was greater with 0.10 µg/kg BID than with 0.05 µg/kg QID; the greatest reduction appeared to be associated with the breakfast dose. AC2993 administered as a continuous infusion at 0.20 µg/kg/day had little effect on mean plasma glucose concentrations. Over the total (2-day) treatment period, significant reductions in plasma glucose AUC and C_{ave} were noted with bolus SC injections and continuous infusion of AC2993 compared with placebo ($p<0.05$). Better glycemic control was achieved with bolus SC AC2993 injections than with a continuous infusion of 0.20 µg/kg/day.

Plasma Glucose Pharmacodynamic Parameters Over the Total Period: Comparisons With Placebo
Dosing Regimen A (AM) A (PM) B C D
During the prandial period, significant reductions were noted in plasma glucose AUC and C_{ave} in the 0.20 µg/kg QD (AM), 0.10 µg/kg BID, and 0.05 µg/kg QID dosing regimens compared with placebo. During the fasting period, significant reductions were noted in plasma glucose AUC and C_{ave} in the 0.20 µg/kg QD (PM), 0.05 µg/kg QID, and 0.20 µg/kg/day continuous infusion regimens compared with placebo. The greatest reduction was noted with the 0.20 µg/kg QD (PM) regimen ($p\leq0.001$). Significant reductions in absolute and incremental postprandial mean plasma glucose concentrations were noted with

bolus SC AC2993 injections compared with placebo.

Figure 1: Mean Plasma Glucose Concentration-Time Curves for Placebo Lead-in, and 0.10 µg/kg BID, 0.05 µg/kg QID, and 0.20 µg/kg/day Regimens on Days 2, 5, 8, 11, and 14
Population: Evaluable Subjects in Study 2993-105 (N=12)

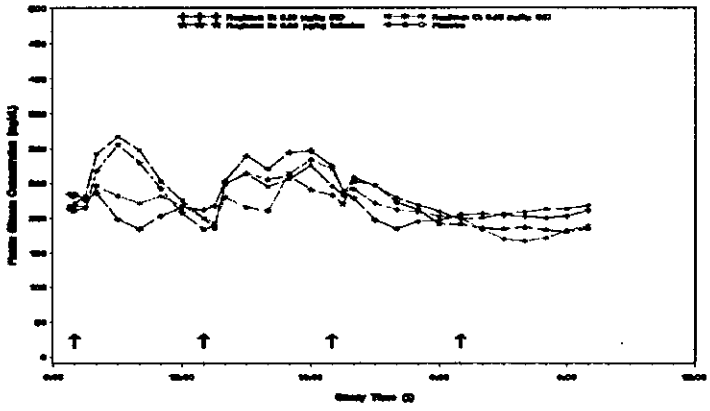


Figure 2: Mean Plasma Glucose Concentration-Time Curves by Dosing Regimen for Placebo Lead-in and the 0.20 µg/kg QD (AM) Regimen
Population: Evaluable Subjects in Study 2993-105

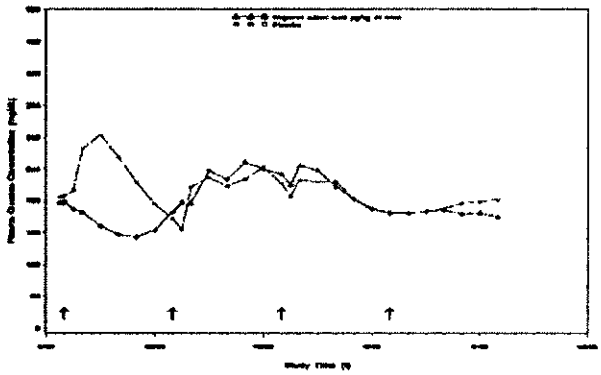


Figure 3: Mean Plasma Glucose Concentration-Time Curves for Placebo Lead-in and the 0.20 µg/kg QD (PM) Regimen
Population: Evaluable Subjects in Study 2993-105 (N=6)

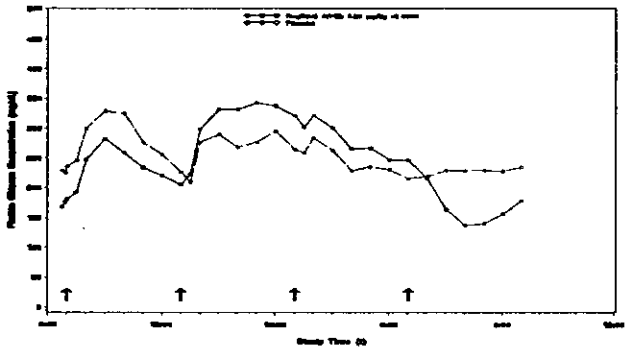


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Table 9: Plasma Glucose Pharmacodynamic Parameters Over the Total Period: Comparisons With Placebo
Population: Evaluable Subjects in Study 2993-105 (N=12)

Dosing Regimen	A (AM)	A (PM)	B	C	D	
Dosage	0.20 µg/kg QD (N=5)	0.20 µg/kg QD (N=6)	0.10 µg/kg BID (N=12)	0.05 µg/kg QID (N=12)	0.20 µg/kg Infusion (N=12)	Placebo (N=12)
AUC (mg•h/dL)						
LS Geometric Mean	4973.44	5421.12	5157.75	4952.71	5202.15	5555.30
AC2993/Placebo Ratio	0.90	0.98	0.93	0.89	0.94	
p-value	0.017*	0.550	0.024*	<0.001*	0.044*	
C_{ave} (mg/dL)						
LS Geometric Mean	284.7	340.8	312.6	290.7	313.6	327.6
AC2993/Placebo Ratio	0.87	1.04	0.95	0.89	0.96	
p-value	0.031*	0.493	0.303	0.011*	0.334	
C_{ave} (mg/dL)†						
LS Geometric Mean	206.96	225.51	214.98	206.08	216.46	231.15
AC2993/Placebo Ratio	0.90	0.98	0.93	0.89	0.94	
p-value	0.017*	0.545	0.027*	<0.001*	0.044*	

*p< 0.05, statistically significant compared with placebo
†C_{ave} = AUC ÷ Sampling period duration (hr)
Note: The following data points were excluded from analysis: Subject 0102, Day 2, 6.5 hr; Subject 0104, Day 11, 15.0 hr; Subject 0107, Day 11, 15.0 hr; Subject 0111, Day 5, 7.0 hr
Cross-reference: SDS 2.1.4 and Appendix 3.6.3

For the post-breakfast period, significant reductions in plasma glucose AUC, Cave, and Cmax (LS geometric means) were noted for the 0.20 µg/kg QD (AM), 0.10 µg/kg BID, and 0.05 µg/kg QID regimens compared with placebo. For the post-lunch period, significant reductions in plasma glucose AUC, Cave, and Cmax (LS geometric means) were noted for the 0.05 µg/kg QID regimen, and mean plasma glucose increased significantly for the 0.20 µg/kg QD (PM) regimen compared with placebo. For the post-dinner period, significant reductions in plasma glucose AUC, Cave, and Cmax (LS geometric means) were noted for the 0.10 µg/kg BID and 0.05 µg/kg QID regimens.

PHARMACOKINETIC RESULTS:
Mean plasma AC2993 concentrations increased steadily following SC bolus administration of AC2993, reaching peak concentrations at 2 to 3 hours after dosing. C_{max} increased in a dose-related manner. AC2993 AUC was lower with a continuous infusion than a bolus SC injection.

Figure 4: Mean Plasma AC2993 Concentration-Time Curve by Dosing Regimen
Population: Evaluable Subjects in Study 2993-105 (N=12)

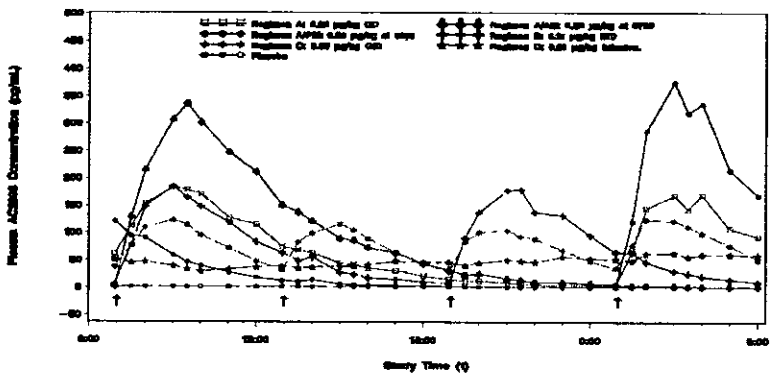


Table 12: Plasma AC2993 24-Hour Pharmacokinetic Parameters:
Descriptive Statistics by Dosing Regimen
Population: Evaluable Subjects in Study 2993-105 (N=12)

Pharmacokinetic Parameters	A (AM) 0.20 µg/kg QD (N=5)*	A (PM) 0.20 µg/kg QD (N=5)*	B 0.10 µg/kg BID (N=12)	C 0.05 µg/kg QID (N=12)	D 0.20 µg/kg Infusion (N=12)
			AUC (pg•h/mL)		
Mean	1912.46	1642.45	1764.42	1859.82	1073.10
SD	392.55	254.24	333.66	536.18	376.18
			C_{max} (pg/mL)		
Mean	348.02	385.08	218.33	144.20	77.37
SD	67.81	45.19	40.20	28.59	28.52
			C_{ave} (pg/mL)		
Mean	82.85	71.15	76.44	80.73	46.49
SD	17.01	11.01	14.46	23.19	16.30
			T_{max} (hr)		
Mean	3.18	20.10	6.21	12.08	9.76
SD	1.57	0.74	5.81	6.92	9.35

*N = 5 due to withdrawal of Subject 0111 (AM) and insufficient values to compute meaningful parameters for Subject 0103 (PM)
†Cave = AUC ÷ Sampling period duration (hr)
‡T_{max} was not calculated relative to first dose
Cross-reference: SDS 2.2.2 and Appendix 3.7.2

CONCLUSION:
Over the total period, significant reductions were noted in plasma glucose AUC following bolus SC injection of AC2993 compared with placebo. Better glycemic control was achieved with bolus SC AC2993 injections than with a continuous SC infusion of 0.20 µg/kg/day. Absolute and incremental postprandial mean plasma glucose concentrations were reduced significantly following bolus SC AC2993 injections. During the fasting period, mean plasma glucose concentrations were reduced significantly following bolus SC AC2993 injections and continuous SC infusion of AC2993; the greatest reduction was achieved with the 0.20 µg/kg QD (PM) treatment. Mean plasma AC2993 concentrations increased steadily following bolus SC injections, reaching peak concentrations at 2 to 3 hours after dosing. C_{max} increased in a dose-related manner. AC2993 AUC was lower with a continuous infusion than a bolus SC injection. AC2993 was well tolerated at a total daily dose of 0.20 µg/kg given subcutaneously in bolus or continuous infusion regimens, in subjects with type 2 diabetes mellitus.

2993-106

Title of Study: The Effects of the Hormone GLP-1 and AC2993 on Glucose Metabolism in the Presence of Different Insulin Concentrations

Rationale for Abbreviated Clinical Study Report: This study was not done to support the overall development plan and was more exploratory in nature. In addition, although safety data were collected according to Amylin standard operating procedures and within the confines of Good Clinical Practices (GCPs), the insulin sensitivity data were not collected and managed under rigorous GCP constraints. Therefore, only safety data are presented in this abbreviated Clinical Study Report.

Investigators and Study Centers: Robert A. Rizza, MD, Mayo Clinic & Foundation, Division of Endocrinology & Metabolism, General Clinical Research Center, St. Mary's Hospital, 200 First St. SW, Rochester, MN 55905 USA

Publication (Reference): Vella A, Shah P, Reed AS, Adkins AS, Basu R, Rizza RA. Lack of effect of exendin-4 and glucagon-like peptide-1-(7,36)-amide on insulin action in non-diabetic humans. *Diabetologia* 2002 45:1410-1415.

Studied Period: 24 March 2000 to 17 March 2001. **Phase of Development:** 1

Objectives:
Primary Objectives: To determine if acute administration of AC2993 increases insulin-induced stimulation of glucose uptake and suppression of glucose production under euglycemic and hyperinsulinemic conditions in healthy subjects. To determine if acute administration of AC2993 compared to GLP-1 increases insulin-induced stimulation of glucose uptake and suppression of glucose production under euglycemic and hyperinsulinemic conditions in healthy subjects. To determine if higher insulin concentrations are required to suppress gluconeogenesis than are required to suppress glycogenolysis in healthy subjects.
Secondary Objective: To collect samples to investigate the pharmacokinetics of AC2993 under euglycemic and hyperinsulinemic conditions in non-diabetic healthy subjects.

Methodology: This single-blind study was designed to determine the acute effects of AC2993 compared to GLP-1 on insulin action as measured by euglycemic and hyperinsulinemic clamp methodology using the following three treatment groups: Control, GLP-1 infusion, and AC2993 infusion. Subjects were to be admitted to an inpatient unit the evening before infusions. During each treatment, blood samples were to be collected for tracers [3-3H-glucose (all treatment groups); and 14C-galactose (control group only)], hormones: insulin, growth hormone, cortisol, C-peptide, and glucagon (Control, GLP-1 and AC2993 groups), GLP-1 or AC2993 (GLP-1 or AC2993 treatment group, respectively), and glucose determinations. There was to be a 1-week washout period between each of the three 1-day treatments.

Number of Subjects: Eleven subjects were included in the intent-to-treat (ITT) population. Eight subjects completed the study and were included in the evaluable population.

Key Demographics: Half of the evaluable population was male and the mean age was 28.3 years. Seven subjects (87.5%) were Caucasian and one (12.5%) was Black. The mean weight and BMI at screening were 76.3 kg and 27.2 kg/m2, respectively.

Subject Disposition: Eight of the 11 subjects completed the study. Three subjects withdrew from the study. Two subjects withdrew from the study due to an adverse event while receiving AC2993 treatment. Subject 510 withdrew due to moderate nausea and Subject 511 withdrew due to severe nausea and retching (verbatim term: dry heaves). One other subject (509) withdrew due to the investigator's decision.

Diagnosis and Main Criteria for Inclusion: Eligible subjects were healthy males or females (surgically

sterile or postmenopausal), age 18 to 65, and otherwise healthy and ambulatory. All subjects were to have no personal or immediate family history of diabetes mellitus and were to have stable body weight for at least 1 month prior to the study.

Test Product, Dose and Mode of Administration, Batch No.: AC2993 (0.12 pmol/kg/min) administered as a continuous infusion. Lot number: 99-0801 TP. GLP-1 (1.2 pmol/kg/min) administered as a continuous infusion.

Duration of Treatment: One day of study medication followed by a 1-week washout period (total duration of 30 days).

Criteria for Evaluation:
Pharmacokinetics: Plasma concentrations of AC2993 were to be determined using an immunoassay. However, no blood samples were collected from any subject for these measurements.
Safety: Safety was to be assessed by analysis of physical exams, adverse events, vital signs, electrocardiograms (ECGs), and clinical laboratory measurements. No ECGs were preformed for any subject during the screening visit. Neither hematology nor urinalysis laboratory panels were performed for any subject at the study termination visit.

Statistical Methods: Safety: Adverse events were to be summarized by presenting subject incidence and event frequency in each system organ class and in each preferred term defined by the Medical Dictionary for Regulatory Activities (MedDRATM version 5.0), by treatment. Treatment-emergent adverse events (TEAEs) were defined as those occurring on or after the subject's first dosing, and were to be assigned by treatment and summarized. Adverse events that occurred before the first dosing were to be classified as pretreatment (nontreatment-emergent) and were only to be listed. TEAEs, including those occurring during the one week wash out period, were to be assigned to the treatment received prior to the occurrence (or worsening) of that adverse event. TEAEs were to be summarized by system organ class, preferred term, and treatment. The number of events and the percentage of subjects who experienced at least one adverse event were to be presented. These percentages were to be based on the number of subjects at risk in each treatment, with each subject contributing at most one count for any event. Descriptive statistics were to be summarized for clinical chemistry, hematology, and urinalysis values. Vital signs and ECG data were to be summarized. Data of interest related to physical examinations were to be listed.

SUMMARY - CONCLUSIONS:
SAFETY RESULTS:
Seven (63.6%) of the 11 subjects in the intent-to-treat population experienced 27 treatment-emergent adverse events during the study. Five of 10 subjects (50.0%) experienced 17 events while receiving AC2993, three (33.3%) of nine subjects experienced six events while receiving Control, and three (33.3%) of nine subjects experienced four events while receiving GLP-1. The most frequent adverse events experienced by subjects receiving AC2993 treatment were: nausea (5 subjects; 50.0%; 6 events with AC2993, 1 subject; 11.1%; 1 event with Control and GLP-1), vomiting (4 subjects; 40.0%; 4 events with AC2993, zero subjects with Control and GLP-1), retching (3 subjects; 30.0%; 3 events with AC2993, zero subjects with Control and GLP-1), and dizziness (1 subject; 10.0%; 1 event with AC2993, 2 subjects; 22.2%; 2 events with Control, and zero subjects with GLP-1). The most frequent adverse event experienced by subjects while receiving Control treatment was dizziness (2 subjects; 22.2%; 2 events). No subject experienced more than one event when receiving GLP-1 treatment. Sixteen of the 27 treatment-emergent adverse events were considered by the investigator as mild, nine moderate (nausea, vomiting, headache, pain in limb, peripheral swelling), and two severe (nausea and retching). Fourteen of the 15 events occurring during AC2993 administration were considered possibly, probably, or definitely related to treatment.

Serious Adverse Events: No serious adverse events were reported during this study.
Withdrawals Due to Adverse Events: Two subjects withdrew from the study due to an adverse event experienced during AC2993 treatment. Subject 510 withdrew due to moderate nausea and Subject 511 withdrew due to nausea and severe retching. The investigator was unblinbed to treatment allocation and

considered both events as definitely related to study medication. Both subjects recovered and no concomitant medications were taken for the events.

Clinical Laboratory Values: No clinically important abnormal values or findings were observed in clinical laboratory evaluations. No adverse events were associated with a laboratory abnormality.

CONCLUSION: No safety concerns were identified with a continuous infusion of AC2993 (0.12 pmol/kg/min; 0.7 µg/kg/day) in healthy volunteers.

2993-107a

Title of Study: A Phase 2, Randomized, Double-Blind, Placebo-Controlled, Multicenter Study to Examine the Effect on Glucose Control of AC2993 (0.08 µg/kg) Given Two Times a Day Versus Three Times a Day for28 Days in Subjects With Type 2 Diabetes Mellitus Treated With Sulfonylureas and/or Metformin.

Investigators and Study Centers: 24 investigators at 24 centers in the US (see Appendix 1.5)

Publication (Reference): Fineman M, Bicsak T, Shen L, Taylor K, Gaines E, Varns A, Kim D, and Baron A. Effect on Glycemic Control of Synthetic Exendin-4 (AC2993) Additive to Existing Metformin and/or Sulfonylurea in Patients With Type 2 Diabetes. Diabetes Care 2003 Aug; 26 (8): 2370-2377.

Studied Period: 04 November 2000 - 04 April 2001 **Phase of Development:** 2

Objectives: Primary Objectives: To examine the effect on glucose control, of subcutaneously (SC) injected AC2993 (0.08 µg/kg) administered two or three times a day for 28 days in subjects with type 2 diabetes mellitus treated with sulfonylureas and/or metformin, as measured by the following: serum fructosamine concentrations and plasma glucose profiles during a standardized meal tolerance test. To assess the safety and tolerability of SC injected AC2993 (0.08 µg/kg) administered two or three times a day for 28 days in subjects with type 2 diabetes mellitus treated with sulfonylureas and/or metformin.
Secondary Objectives: To examine the pharmacokinetics of AC2993 (0.08 µg/kg) during 28 days of SC dosing, two or three times a day, in subjects with type 2 diabetes mellitus treated with sulfonylureas and/or metformin. To examine the effect of SC injected AC2993 (0.08 µg/kg) administered two or three times a day for 28 days in subjects with type 2 diabetes mellitus treated with sulfonylureas and/or metformin, on the following: fasting plasma glucose concentrations, fasting and postprandial lipid concentrations, body weight, and hemoglobin A_{1c}(HbA_{1c}).

Methodology: This was a Phase 2, balanced, randomized, double-blind (study site personnel, subjects, and the sponsor were to be blinded to treatment allocation), placebo-controlled, parallel-group, and multicenter study with a 2-week, single-blind placebo lead-in period. The study was designed to assess glucose control and evaluate safety in subjects who were to receive one of three regimens of AC2993 (0.08 µg/kg) injected SC compared with placebo, given daily over 28 days. The study groups were: BID (bd)(breakfast and dinner) injections of AC2993 (0.08 µg/kg); BID (bs) (breakfast and bedtime) injections of AC2993 (0.08 µg/kg); TID (breakfast, dinner, bedtime) injections of AC2993 (0.08 µg/kg); or TID (breakfast, dinner, bedtime) injections of placebo. Subjects randomized to the BID regimens received a third injection of placebo in order to preserve the blind.

Number of Subjects: One hundred and nine subjects were randomized and included in the intent-to-treat population. A greater number of male (64%) than female (36%) subjects were enrolled in this study. The majority (55%) of subjects were Caucasian and the mean age of the population was 51.8 years. The mean body weight was 97.4 kg. Treatment groups were generally well balanced with regard to subject gender, age, race, body weight, height, and BMI.

Key Demographics: The intent-to-treat population was 64% male; 55% Caucasian; mean age of 51.8 years.

Subject Disposition: Ninety-seven subjects (89%) completed the study and 12 (11%) subjects withdrew. Seven subjects withdrew from the study due to an adverse event.

Diagnosis and Main Criteria for Inclusion: Males or females (surgically sterile or postmenopausal), with type 2 diabetes mellitus, aged 18 to 65 years, treated with diet and a specified antidiabetic agent, consisting of sulfonylurea or metformin, either alone or in combination. Subjects were to have a baseline HbA_{1c} value between 8.0% and 11.0%, inclusive, at the Screening Visit, and a Body Mass Index (BMI) of 27 kg/m_2 to 40 kg/m_2, inclusive.

Test Product, Dose and Mode of Administration, Batch No.: Subcutaneous injection of AC2993 (0.08 µg/kg) administered two or three times a day. Lot No: 00-0605TP.

Duration of Treatment: 2-week single-blind placebo lead-in period followed by a 28-day active treatment period and a 1-week follow-up period.
Reference Therapy, Dose and Mode of Administration, Batch No: Subcutaneous injection of placebo (same volume as calculated for AC2993). Lot No: 00-0604TE.

Criteria for Evaluation:
Efficacy: The primary efficacy endpoints were the change in serum fructosamine concentrations from Day 1 to Day 28 and the change in time-weighted average postprandial plasma glucose concentrations from Day -1 to Day 1 and Day 28. Secondary efficacy endpoints included the change in time-weighted average postprandial plasma glucose concentrations from Day -1 to Day 14, the change in time-weighted average incremental postprandial plasma glucose concentrations from Day -1 to Day 14 and Day 28, the change in fasting plasma glucose concentrations from Day -1 to Day 14 and Day 28, change in fasting lipid concentrations from Day -1 to Day 28 (serum lipids included LDL cholesterol, HDL cholesterol, LDL/HDL cholesterol ratio, triglyceride, and Apo B), change in HbA_{1c} from Day 1 to Day 28, number and proportion of subjects who achieved at least 0.5% reduction in HbA_{1c} at Day 28, and the change in body weight from Day 1 to Day 28.
Safety: Safety measures included monitoring of adverse events, vital signs (blood pressure and pulse), electrocardiograms (ECGs), clinical laboratory measures (hematology, serum chemistry, and urinalysis), physical examination, and anti-AC2993 antibodies.
Statistical Methods:
Efficacy: Primary efficacy endpoint presentations were to emphasize the change from baseline for fructosamine concentrations (Day 1 to Day 28) and postprandial plasma glucose (Day -1 to Day 1, and Day -1 to Day 28). Changes were to be computed as follow-up day minus baseline day. A one-way ANOVA, was to be used to test the null hypotheses of no difference among treatment groups versus the alternative hypothesis of a difference among treatment groups. Pairwise comparisons of interest included comparing each of the three AC2993 treatment groups to the placebo group. Both the unadjusted p-values and the Dunnett adjusted p-values are calculated and presented.
Safety: Safety data were to be summarized by adverse event data that were to be tabulated by treatment, system organ class, preferred term, severity, and drug relationship, utilizing the Medical Dictionary for Regulatory Activities (MedDRA™). Descriptive statistics were to be presented for vital signs and clinical laboratory values.

SUMMARY – CONCLUSIONS:
EFFICACY RESULTS: Reductions in mean serum fructosamine concentrations from Day 1 to Day 28 were significantly greater for subjects receiving AC2993 (range of means: -39.0 to -45.6 µmol/L) compared to placebo (-5.3 µmol/L). Reductions in mean postprandial plasma glucose concentrations from Day –1 to Day 28 were also significantly greater for subjects receiving AC2993 (range of means: –79.1 to –56.9 mg/dL) compared to placebo (-11.3 mg/dL) as well as from Day –1 to Day 1, and Day –1 to Day 14. HbA_{1c} was significantly reduced following treatment with AC2993 after 28 days. Mean HbA_{1c} values decreased from Day 1 to Day 28 by –1.08%, –0.70%, and –1.02%, in the AC2993 BID (bd), AC2993 BID (bs), and AC2993 TID groups, respectively, compared with a mean decrease of –0.25% in the placebo group.

Table 13: Fasting Insulin: Glucose Ratio: Change From Day −1 to Day 28
(Population: Intent-to-Treat Subjects in Study 2993-107 [N=109])

	Placebo N=28	AC2993 BID (bd) N=26	AC2993 BID (bs) N=27	AC2993 TID N=28
Fasting Insulin: Glucose Ratio				
Day −1 Mean (SD)	0.10 (0.131)	0.07 (0.057)	0.08 (0.058)	0 10 (0.066)
Day 28 Mean (SD)	0.09 (0.072)	0 12 (0 097)	0.11 (0 068)	0 14 (0.092)
Mean (SD) Change From Day −1 to Day 28	-0.02 (0.085)	0.04 (0.069)	0.03 (0.049)	0 04 (0.051)
p-value (unadjusted)	[redacted]	<0.001	0.007	0.002

AC2993 BID (bd)= twice daily at breakfast and dinner; AC2993 BID (bs)= twice daily at breakfast and bedtime; AC2993 TID= three times daily at breakfast, dinner, and bedtime.
Cross reference: Supporting Data Summary 2.18.6 and Appendix 3 9.17

A statistically significant greater number of subjects receiving AC2993 achieved reductions in HbA_{1c} ε0.5% at Day 28 compared to placebo subjects. Twenty-one (81%), 18 (67%), and 24 (86%) subjects in the AC2993 BID (bd), AC2993 BID (bs), and AC2993 TID treatment groups, respectively, achieved reductions in HbA_{1c} of ε0.5% at Day 28 compared with 8 (29%) placebo subjects. After 28 days of treatment, of the 65 AC2993 treated subjects with baseline HbA_{1c} values ≥7%, a total of 15% had reduced HbA_{1c} values <7% after 28 days of treatment compared to 1 out of 23 subjects (4%) receiving placebo. Of the 54 AC2993 treated subjects with baseline HbA_{1c} values ≥8%, 43% had reduced HbA_{1c} values <8% after 28 days of treatment compared to 1 out of 20 subjects (5%) receiving placebo. Reductions in mean incremental postprandial plasma glucose concentrations from Day −1 to Day 28 and to Day 14 were significantly greater from for all three AC2993 treatment groups compared to placebo. No significant differences were observed for mean changes in fasting plasma glucose concentrations, fasting lipid concentrations, and postprandial incremental triglyceride concentrations from Day −1 to Day 28. Following 28 days of study medication administration, the mean fasting insulin: glucose ratio was significantly increased for all three AC2993 treatment groups compared to placebo. There was no statistically significant effect of AC2993 on change in body weight from Day 1 to Day 28 (range of means: −0.8 to +0.1 kg) compared to placebo subjects (+0.9 kg).

Primary and Key Secondary Efficacy Parameters: Comparisons to Placebo

(Population: Intent-to-Treat)

	Placebo (N=28)	AC2993 BID (bd) (N=26)	AC2993 BID (bs) (N=27)	AC2993 TID (N=28)
Primary Efficacy Parameters				
Serum Fructosamine (µmol/L)				
Mean Change From Day 1 to Day 28	-5.3	-45.1	-39.0	-45.6
Unadjusted p-value		<0.001	0.004	<0.001
Postprandial Plasma Glucose (mg/dL)				
Mean Change From Day-1 to Day 28	-11.3	-79.1	-58.9	-60.4
Unadjusted p-value		<0.001	0.004	0.002
Mean Change From Day-1 to Day 1	-0.7	-88.7	-81.5	-67.2
Unadjusted p-value		<0.001	<0.001	<0.001
Key Secondary Efficacy Parameters				
HbA_{1c} (%)				
Mean Change From Day 1 to Day 28	-0.25	-1.08	-0.70	-1.02
Unadjusted p-value		<0.001	0.006	<0.001
Number and proportion of subjects with a HbA_{1c} of <7% at Day 28	1 (0.04)	3 (0.15)	2 (0.09)	5 (0.22)
Number and proportion of subjects with a HbA_{1c} of <8% at Day 28	1 (0.05)	9 (0.56)	5 (0.26)	9 (0.47)
Number and proportion of subjects with a change in HbA_{1c} of ≥0.5% Fisher's Exact Test p-value	8 (29%)	21 (81%)	18 (67%)	24 (86%)
		<0.001	0.010	<0.001
Body Weight (kg)				
Mean Change From Day 1 to Day 28	0.9	-0.8	0.1	0.0
Unadjusted p-value		0.005	0.136	0.071

AC2993 BID (bd)= twice daily at breakfast and dinner; AC2993 BID (bs)= twice daily at breakfast and bedtime; AC2993 TID= three times daily at breakfast, dinner, and bedtime

PHARMACOKINETIC RESULTS: Following SC administration of AC2993, mean plasma AC2993 concentrations increased steadily, reaching peak concentrations approximately 90-120 minutes after dosing and were detectable at 360 minutes. The mean plasma AC2993 profiles at Day 1 and Day 28 were similar for subjects who were negative for anti-AC2993 antibodies. Mean plasma AC2993 concentrations were higher at each time point at Day 28 compared to Day 1 for subjects who were positive for anti-AC2993 antibodies.

Figure 5: Mean Pooled Plasma AC2993 Concentration-Time Curves for Day 1 and Day 28 (Population: Intent-to-Treat Subjects in Study 2993-107 [N=81])

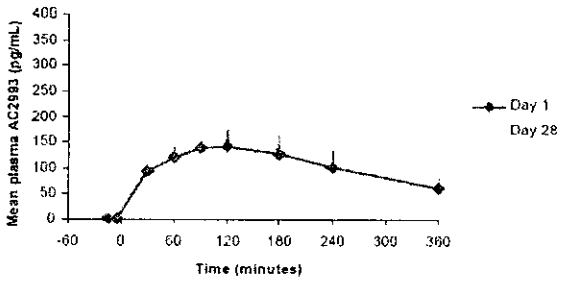


Figure 6: Mean Pooled Plasma AC2993 Concentration-Time Curves for Day 1 and Day 28 Excluding Subjects Who Were Positive for Anti-AC2993 Antibodies (Population: Intent-to-Treat Subjects in Study 2993-107 [N=63])

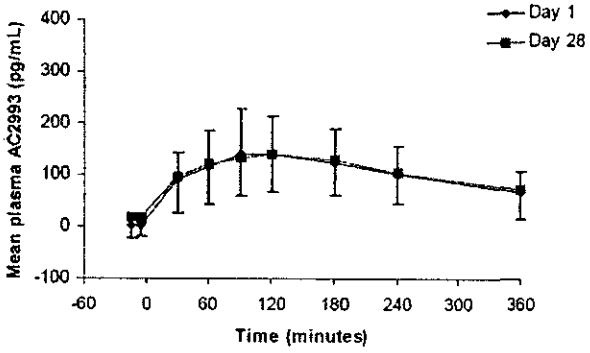
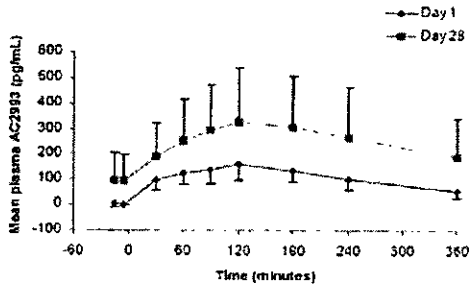


Figure 7: Mean Pooled Plasma AC2993 Concentration-Time Curves for Day 1 and Day 28 for Subjects With Positive Anti-AC2993 Antibodies at any Visit (Population: Intent-to-Treat Subjects in Study 2993-107 [N=18])



SAFETY RESULTS:

Adverse Events: A total of 68 (62%) of 109 subjects experienced at least one treatment-emergent adverse event during the study. A total of 40 subjects (36.7%) experienced an adverse event that was considered possibly, probably, or definitely related to treatment. The majority of adverse events in each treatment group were considered as mild to moderate in intensity (6 events were considered severe). The most frequent treatment-emergent adverse events were nausea, hypoglycemia, and vomiting

Twelve (46%) subjects in the AC2993 BID (bd), 8 (29%) in the AC2993 TID, and 5 (19%) in the AC2993 BID (bs) groups experienced nausea. Five (19%) subjects in the AC2993 BID (bd), 4 (15%) in the AC2993 BID (bs), and 3 (11%) in the AC2993 TID groups experienced hypoglycemia. Four (15%) subjects in the AC2993 BID (bd) and 2 (7%) in the AC2993 TID groups experienced vomiting. Nausea was most pronounced between days 1 to 4 of the study for all three treatment groups. All withdrawals due to nausea occurred within the first 12 days of the study. There were no reports of severe hypoglycemia; hypoglycemia was self-reported by 15% of the subjects treated with AC2993. Reported symptoms of hypoglycemia were mild and most often not confirmed by actual blood glucose measurements. Only those subjects taking a sulfonylurea either alone or in combination with metformin reported hypoglycemic events during the study.

Deaths: One subject died during the placebo lead-in period of the study, this subject had received no active study medication. The subject was hospitalized for injuries sustained in a motor vehicle accident and died 6 days later due to these injuries.

Serious Adverse Events: Three subjects receiving AC2993 treatment [2 subjects in the AC2993 TID and 1 subject in the AC2993 BID (bd) group] experienced a serious adverse event during the study. Two subjects experienced chest pain considered unrelated to study medication; both subjects recovered and completed the study. Of these subjects, one also experienced headache within 30 days of receiving the last dose of study medication, which required hospitalization. One subject randomized to AC2993 TID

withdrew from the study due to gastrointestinal disorder that was considered definitely related to study medication.
Withdrawals Due to Adverse Events: A total of 7 subjects withdrew from the study due to a treatment-emergent adverse event [4 (15%) subjects in the AC2993 BID (bd) and 3 (11%) subjects in the AC2993 TID treatment groups]. The events leading to withdrawal were: nausea (4 subjects), vomiting (1 subject), hypoglycemia (1 subject), gastrointestinal disorder (1 subject), influenza like illness (1 subject), and pruritus (1 subject). All events were considered probably, possibly, or definitely related to study medication. Clinical Laboratory Values: No unexpected changes were observed for this study population in clinical laboratory values; no trends of clinical importance were apparent. Serum Cortisol: AC2993 showed no effect on the hormone, cortisol after 28 days of administration. While there was a small, acute, transient increase in serum cortisol concentrations observed after dosing with AC2993 on Day 1, compared with placebo, there was no rise in postdose mean cortisol concentrations in any treatment group at Day 28. Vital Signs, Physical Examinations, and Electrocardiograms: No safety issues were associated with AC2993 upon review of vital signs, physical examination findings, or ECG recordings. Anti-AC2993 Antibodies: Fifteen subjects (20% of those with Week 28 data) receiving AC2993 and zero placebo subjects generated treatment-emergent positive antibody responses by Day 28. Five subjects had a low titer (1:5) antibody response at baseline (2 placebo/3 active) that did not increase in titer during the study.

CONCLUSION: AC2993 0.08 µg/kg administered subcutaneously two or three times a day for 28 days significantly improved glycemic control as assessed by a reduction in serum fructosamine, HbA_{1c}, and postprandial plasma glucose. The glycemic improvement was not associated with a change in body weight. Subcutaneous administration of AC2993 0.08 µg/kg two or three times a day for 28 days was well tolerated in subjects with type 2 diabetes mellitus treated with sulfonylurea or metformin, either alone or in combination.

2993-108

Title of Study: A Phase 2, Randomized, Triple-Blind, Placebo-Controlled, Multicenter, Forced Dose-Escalation Study to Examine Dose Tolerability in Subjects With Type 2 Diabetes Mellitus Given AC2993 Subcutaneously

Investigators and Study Centers: Multicenter; 34 investigators at 34 centers in the US. Of the 34 qualified investigators and centers, 31 investigators at 31 centers enrolled subjects. The sponsor closed down one (Site 054) of the 31 centers that enrolled subjects after a monitoring visit at which the sponsor's representative found the site lacked appropriate study staffing and management.

Publication (Reference): Fineman MS, Shen L, Smitzi J, Aisporna M, Bicsak T, Taylor K, Baron A. Unique Study Design: Evaluation of the Effect of Dose Titration on Dose-Limiting Nausea. *Clin Pharm Ther* 2002; 71:P19.

Studied Period: 17 January 2001 – 01 August 2001 **Phase of Development:** 2

Objectives: Primary Objectives: To examine the effect of progressive dose-escalation of subcutaneously administered AC2993 on the incidence of dose-limiting adverse events (nausea and vomiting) in subjects with type 2 diabetes mellitus. Secondary Objectives: To examine the effects of progressive dose-escalation of subcutaneously administered AC2993 in subjects with type 2 diabetes mellitus on the following: safety and tolerability, including adverse events and subject withdrawal; development of anti-AC2993 antibodies; body weight; and population pharmacokinetics.

Methodology: This was a two-arm, randomized, placebo-controlled, triple-blind, multicenter study designed to examine the incidence of nausea and vomiting in subjects who received either (1) progressively increasing doses of AC2993, starting from 0.02 μg/kg and increasing in 0.02 μg/kg increments, every 3 days for approximately 35 days (Day 1 to Day 35 ± 1; 11 total dose levels); or (2) placebo for approximately 35 days. At Visit 6 (Day 35 ± 1), both arms were to receive a first-time dose of 0.24 μg/kg AC2993 to be given each day for 3 days. Each dose of study medication was to be injected subcutaneously 3 times a day, 15 minutes before breakfast, dinner, and bedtime.

Number of Subjects: 123 intent-to-treat subjects (i.e., all subjects who received at least one dose of randomized study medication). Primary and secondary analyses were performed on the intent-to-treat population.

Key Demographics: All subjects had type 2 diabetes mellitus. Composition of the intent-to-treat population was as follows: 56.9% female; 70.7% Caucasian, 10.6% Black, 9.8% Hispanic, 5.7% Asian, 0.8% Native American, and 2.4% other. Subjects' mean age was 53.7 ± 7.1 years; mean BMI was 33.8 ± 5.2 kg/m2. Mean height and weight were 168.8 ± 9.3 cm and 96.6 ± 18.0 kg, respectively. The mean HbA_{1c} for the population was 7.7 ± 1.4%. Metformin and TZD use by the intent-to-treat population: 81 subjects (65.9%) received metformin (control, 38 subjects, 62.3%; dose-escalation, 43 subjects, 69.4%) and 19 subjects received a TZD (control, 9 subjects, 14.8%; dose-escalation, 10 subjects, 16.1%). Included in these numbers are subjects who received combination therapy; 3 subjects in the control group and 7 subjects in the dose-escalation group received metformin and a TZD in combination.

Subject Disposition: Subjects were divided between two treatment arms with 61 subjects in the control arm and 62 subjects in the dose-escalation arm.

Diagnosis and Main Criteria for Inclusion: Eligible subjects were to be individuals with type 2 diabetes mellitus treated with diet alone, metformin alone, thiazolidinediones (TZDs) alone, or a combination of diet, metformin and TZDs. Both males and females (surgically sterile or postmenopausal) were eligible as long as they were: 18 to 65 years, on a stable treatment regimen for at least 3 months prior to screening, had a baseline glycosylated hemoglobin A_{1c} (HbA_{1c}) measurement of 6.5% to 11.0%, inclusive, and a BMI of 27 kg/m2 to 40 kg/m2, inclusive.

Test Product; Dose; Mode of Administration; and Batch No.: AC2993 Injectable; Dose-Escalation Arm: 0.02 ⌈g/kg, three times a day (before breakfast, dinner, and bedtime), increasing 0.02 ⌈g/kg every three days to receive a maximum dose of 0.24 ⌈g/kg on Day 35 ± 1, Control Arm: 0.24 μg/kg at Day 35 ± 1 (after approx. 35 days of placebo); subcutaneous injection; Lot No. 00-0605TP.

Duration of Treatment: Approximately 37 days.

Reference Therapy; Dose; Mode of Administration; and Batch No.: Placebo; same dose volume as calculated for the AC2993 dose given to the dose-escalation arm on the corresponding day (until Day 35 ± 1, then 0.24 ⌈g/kg AC2993); subcutaneous injection; Lot No. 00-0604TE.

Criteria for Evaluation:
Clinical Outcomes: The primary study endpoint was the incidence of severe nausea, nausea leading to withdrawal, or vomiting occurring by the last treatment day (Day 37 ± 1). Change in body weight between baseline and Visit 6 was evaluated.
Safety: Safety measures included monitoring of adverse events, clinical laboratory measures (clinical chemistry, hematology, and urinalysis), vital signs (blood pressure and pulse), physical examinations and electrocardiograms (ECGs), and anti-AC2993 antibody development.

Statistical Methods:
Clinical Outcomes: The two treatment arms were compared using Fisher's Exact Test. The analysis included all intent-to-treat subjects in the denominators. Subjects who withdrew before Day 37 ± 1 due to reasons other than nausea and vomiting were included in the analysis, but were not to considered to have met the primary study endpoint. Kaplan-Meier estimates of the incidences of nausea, nausea leading to withdrawal, or vomiting over the entire course of the study were calculated. A similar analysis of the two treatment arms compared subject withdrawal rates due to nausea and vomiting. An interim analysis of the primary endpoint was conducted when approximately 50% of the subjects completed the study. The O'Brien & Fleming boundary was applied to the interim and final analyses to control the overall type I error. Accordingly, the nominal significance levels for the interim and final analyses were designated as 0.0031 and 0.0499, respectively.
Safety: Adverse events were summarized by presenting event frequency and subject incidence in each system organ class, as well as in each adverse event preferred term defined by the Medical Dictionary for Regulatory Activities (MedDRA™), by treatment. Data were summarized or listed for adverse events, clinical laboratory measures (clinical chemistry, hematology, and urinalysis), vital signs (blood pressure and pulse), physical examinations and electrocardiograms (ECGs), and anti-AC2993 antibody development. Descriptive statistics were presented for clinical chemistry, hematology, and urinalysis.

SUMMARY - CONCLUSIONS:
CLINICAL OUTCOMES RESULTS:
A statistically significant difference was noted in the proportion of subjects with severe nausea, nausea leading to withdrawal, or vomiting by the date of the last dose; 34 subjects (55.7%) in the control arm compared to 17 (27.4%) in the dose-escalation arm ($p = 0.0018$). The Kaplan-Meier estimates of the incidences of severe nausea, nausea leading to withdrawal, or vomiting over the entire course of the study measured at Day 43 (the day after the last dose day for the last subject within the treatment arm) was 0.68 for the control arm and 0.28 for the dose-escalation arm ($p < 0.0001$).

Subject drop-out (early withdrawal) rates due to nausea or vomiting were based on the raw proportion of subjects who withdrew due to nausea or vomiting by the last dosed date. Three subjects (4.9%) in the control arm and seven subjects (11.3%) in the dose-escalation arm withdrew due to nausea or vomiting prior to receiving the 0.24 μg/kg dose. Two of the seven subjects in the dose-escalation arm withdrew due to nausea or vomiting at doses ε0.2 μg/kg. At Day 43, subjects in the control arm who received a first-time dose of 0.24 μg/kg had a greater incidence of all nausea compared to the dose-escalation arm (62.3% compared to 46.8%). The Kaplan-Meier estimate of the incidence of nausea by the date of the last dose was 0.73 for the control arm and 0.48 for the dose-escalation arm ($p = 0.0047$). A statistically significant difference in body weight was noted between the control and dose-escalation arms using analysis of variance (ANOVA). The least square mean change in body weight between Visit 2 (baseline) and Visit 6

for the control arm was –0.38 kg (range, -6.4 to 2.3kg) and for the dose-escalation arm was -1.54 kg (range, -6.4 to 3.8 kg) (p = 0.0005).

SAFETY RESULTS:
Adverse Events: A total of 108 subjects experienced 508 treatment-emergent adverse events. Similar numbers of subjects in each arm experienced treatment-emergent adverse events with 57 subjects (93.4%) in the control arm experiencing 231 adverse events and 51 subjects (82.3%) in the dose-escalation arm experiencing 277 adverse events. The most common treatment-emergent adverse events were gastrointestinal disorders with 47 subjects (77.0%) in the control arm experiencing 132 events (116 events were nausea or vomiting) and 41 subjects (66.1%) in the dose-escalation arm experiencing 186 events (135 events were nausea or vomiting). Other common adverse events (occurred in more than 5% of subjects) were diarrhea, headache, decreased appetite, dizziness, and injection site bruising. Of the treatment emergent adverse events considered possibly, probably, or definitely related to treatment, nausea and vomiting were the most common. Other treatment-emergent adverse events that occurred in more than 5% of subjects and were rated as possibly, probably, or definitely related to study medication by the investigator were diarrhea, decreased appetite, headache, and injection site bruising.

Deaths: There were no deaths in this study.

Serious Adverse Events: There were no serious adverse events in this study.
Withdrawals Due to Adverse Events: Withdrawals due to an adverse event were fairly balanced between the study arms with six subjects in the control arm and seven subjects in the dose-escalation arm withdrawing due to an adverse event. Half the subjects in the control arm withdrew due to either nausea or vomiting and half withdrew due to another type of adverse event. All withdrawals in the dose-escalation due to an adverse event arm were due to either nausea or vomiting.

Clinical Laboratory Values: No unexpected changes in clinical lab values were observed for this study population.

No trends of clinical importance were apparent.
Vital Signs, Physical Examinations, and Electrocardiograms: No safety issues were associated with AC2993 upon review of vital signs, physical examination findings, or electrocardiogram recordings.
Anti-AC2993 Antibodies: Anti-AC2993 antibodies were assessed at Visit 2 (baseline) and Termination. A subject who was anti-AC2993 antibody negative at baseline, but positive at Termination was considered to have treatment-emergent antibody development. Anti-AC2993 antibody development was assessed for all subjects who had a sample available for testing at termination (N = 112). There were no cases of treatment-emergent anti-AC2293 antibody development in the control arm and 16 cases (26.7%) in the dose-escalation arm. One subject (1.92%) in each treatment arm (control and dose-escalation) had tested positive for anti-AC2993 antibodies at baseline (non-treatment emergent).

CONCLUSION: Dose escalation to a target dose of 0.24 μg/kg AC2993 appears to significantly reduce the incidence of severe nausea, nausea leading to withdrawal, or vomiting compared with a regimen that does not allow for doses to increase over time. AC2993 appears safe and well tolerated at anticipated dosing levels. The emergence of anti-AC2993 antibodies in the dose titration arm merits further evaluation in studies of longer duration.

2993-109

Title of Study: A Single-Blind, Placebo-Controlled, Dose-Rising Pilot Study to Examine the Pharmacodynamics and Pharmacokinetics of AC2993 Administered via Continuous Subcutaneous Infusion in Subjects with Type 2 Diabetes Mellitus

Investigators and Study Centers: [redacted]

Publication (Reference): Taylor K, Kim D, Bicsak T, Heintz S, Varns A, Aisporna M, Fineman M, Baron A. Continuous subcutaneous infusion of AC2993 (synthetic exendin-4) provides sustained day-long glycemic control in patients with type 2 diabetes. 2002; 62nd Annual Meeting and Scientific Sessions, American Diabetes Association. Taylor K, Kim D, Bicsak T, Heintz S, Varns A, Aisporna M, Fineman MS, Baron A. Continuous subcutaneous infusion of AC2993 (synthetic exendin-4) provides sustained day-long glycemic control to patients with type 2 diabetes. Diabetes 2002;51(suppl 2):A85 (abstract 344-OR).

Studied Period: 10 April 2001- 2 October 2001 **Phase of Development:** 2

Objectives: Primary Objective: To examine the effect of rising doses of AC2993 delivered via continuous subcutaneous infusion on plasma glucose concentrations in subjects with type 2 diabetes.
Secondary Objectives: To assess the effects of rising doses of AC2993 delivered via continuous subcutaneous infusion on the following: concentrations of plasma insulin, plasma glucagon, plasma proinsulin, plasma amylin, and serum cortisol; safety and tolerability of AC2993; and pharmacokinetics of AC2993. To collect samples to examine the metabolites of AC2993 under steady-state conditions.

Methodology: This was a randomized, placebo-controlled, single-blind, dose-rising study designed to compare 23-hour continuous subcutaneous infusions of four doses of AC2993 (0.2, 0.4, 0.6, and 0.8 µg/kg/day) with placebo, in subjects with type 2 diabetes mellitus. Subjects were to be housed in an inpatient unit for 12 days and randomly assigned to one of five treatment sequences. Subjects were to receive 10 infusions comprising five treatments (four AC2993 and one placebo) and five placebo washouts over 10 consecutive days. The five treatments, which were administered in a dose-rising manner, consisted of four AC2993 doses (0.2, 0.4, 0.6, and 0.8 µg/kg/day) and a placebo dose. Placebo washout infusions were given on non-treatment days. Blood and urine were to be collected daily at specified time points to measure the effects of AC2993 on plasma glucose, pharmacodynamic and pharmacokinetic variables, and AC2993 metabolites. Satiety was to be assessed using a visual analog questionnaire. Treatment sequences and the dosing schedule are presented in the following table.

Dosing Schedule

Tx	Treatment Day											
Seq.*	1	2	3	4	5	6	7	8	9	10	11	Study Term
1	pbo	pbo	pbo	0.2	pbo	0.4	pbo	0.6	pbo	0.8	—	—
2	pbo	0.2	pbo	pbo	pbo	0.4	pbo	0.6	pbo	0.8	—	—
3	pbo	0.2	pbo	0.4	pbo	pbo	pbo	0.6	pbo	0.8	—	—
4	pbo	0.2	pbo	0.4	pbo	0.6	pbo	pbo	pbo	0.8	—	—
5	pbo	0.2	pbo	0.4	pbo	0.6	pbo	0.8	pbo	pbo	—	—

* Each treatment was to be given as a continuous subcutaneous infusion for 23 hours, beginning at ~0700 and ending the following morning at ~0600.
pbo = placebo; all AC2993 doses are µg/kg/day; — = no infusions given

Number of Subjects: The study population consisted of: 12 randomized subjects (i.e., all subjects who were allocated a randomization number), 12 intent-to-treat subjects (i.e., all subjects who received any infusion of study medication on or after Day 2 of the study), and 11 evaluable subjects (i.e., all intent-to-treat subjects who completed at least two treatment periods with sufficient measurement data to permit reliable calculation of the pharmacodynamic parameters for plasma glucose concentration).

Key Demographics: The intent-to-treat population consisted of 12 subjects with type 2 diabetes mellitus. The study population was 75.0% male; 100.0% Hispanic. Subjects' mean age was 54 years and mean body

mass index (BMI) was 28.8 kg/m2. Mean height and weight were 162.0 cm and 75.7 kg, respectively. The mean duration of diabetes was 7.4 years. Mean glycosylated hemoglobin, specific A_{1c} fraction (HbA_{1c}) at baseline was 9.2%. Overall, 83.3% of the subjects were using an oral antidiabetic agent with 100% subjects in Treatment Sequences 1, 2, and 4; 66.7% subjects in Treatment Sequence 3; and 50.0% subjects in Treatment Sequence 5 using metformin.

Subject Disposition: Of the 12 subjects randomized to treatment, 10 (83.3%) completed the study and two (16.7%) withdrew prior to receiving all treatments. One of the two subjects who withdrew was included in the evaluable population.

Diagnosis and Main Criteria for Inclusion: Eligible subjects were to be males or infertile females (surgically sterile or postmenopausal) with type 2 diabetes mellitus, 18 to 65 years, treated either with diet alone, metformin alone, a thiazolidinedione alone (rosiglitazone or pioglitazone), or a combination of metformin and one of the thiazolidinediones. Subjects treated with oral antidiabetic agents may also have been on an assigned diet regimen. At the screening visit, subjects were to have a baseline HbA_{1c} value of 8.0% to 11.0%, inclusive, and a body mass index (BMI) of 27 kg/m2 to 40 kg/m2, inclusive.

Test Product, Dose and Mode of Administration, Batch No.: AC2993, 0.1 mg/mL. Doses of 0.2 ∝g/kg/day, 0.4 ∝g/kg/day, 0.6 ∝g/kg/day, and 0.8 ∝g/kg/day were administered as a continuous subcutaneous infusion over 23 hours. Formulation: AC-2993-F6; lot number: 00-605TP.
Duration of Treatment: 10 days

Reference Therapy, Dose and Mode of Administration, Batch No.: Placebo (same volume as that calculated for 0.4 ∝g/kg/day of AC2993) administered as a continuous subcutaneous infusion over 23 hours.
Formulation: PBO-F12; lot number: 00-0604TE.

Criteria for Evaluation:
Pharmacokinetics: Plasma AC2993 concentrations were assessed to confirm that steady-state concentrations were achieved. Plasma AC2993 concentrations were to be evaluated throughout the 23-hour infusion period for each subject on treatment days (Days 2, 4, 6, 8, and 10).
Pharmacodynamics: The primary pharmacodynamic measure was the effect of AC2993 (0.2, 0.4, 0.6, and 0.8 ∝g/kg/day) and placebo on plasma glucose concentrations over time. Plasma glucose concentrations were to be measured on the first day of randomized study medication and on dosing days, thereafter, (Days 1, 2, 4, 6, 8, and 10) at specified time points throughout the 23-hour infusion period. Secondarily, the effect of AC2993 on the pharmacodynamic measures plasma insulin, plasma glucagon, plasma proinsulin, plasma amylin, (preinfusion on Days 2 through 11) and serum cortisol (four time points during infusion on Days 1 through 11 and two time points at study termination) was to be assessed.
Satiety: The effect of AC2993 on subject satiety (well-sick, satisfied-hungry, and full-empty) was to be evaluated using a visual analog questionnaire.
Safety: Adverse events, clinical laboratory values, vital signs, ECGs, and physical examinations were to be assessed.
Statistical Methods:
Pharmacokinetics: Pharmacokinetic parameters area under the concentration-time curve ($AUC_{(0\text{-}23\ hr)}$), time weighted average concentration (C_{ave}) and maximum observed drug concentration (C_{max}), time of maximum observed concentration (T_{max}) and time of minimum observed concentration (T_{min}) were to be calculated for plasma AC2993 concentrations over the 23-hour infusion period on treatment days (Days 2, 4, 6, 8, and 10). Descriptive statistics were to be summarized by treatment for the evaluable population.
Pharmacodynamics: Individual plasma glucose concentration profiles by treatment were to be plotted for the intent-to-treat population and mean plasma glucose concentration profiles by treatment were to be plotted for the evaluable population. Pharmacodynamic parameters $AUC_{(0\text{-}23\ hr)}$, C_{ave}, C_{max}, and minimum observed drug concentration (C_{min}) for absolute and incremental (the baseline concentration subtracted from the concentration at each time point thereafter) plasma glucose concentrations over the 23-hour infusion period were to be calculated for individual subjects on Days 1, 2, 4, 6, 8, and 10 and summarized descriptively by treatment. T_{max} and T_{min} were to be calculated over the 23-hour infusion period. Pharmacodynamic parameters were also calculated for the prandial and fasting intervals. For the prandial

interval (period from breakfast [~0800 hours; 1 hour] to 1 hour after the evening snack [~2200 hours; 15 hours]), T_{max}, and T_{min} and parameters $AUC_{(0\text{-}15\ hr)}$, C_{ave}, C_{max}, and C_{min} for absolute and incremental plasma glucose concentrations were to be calculated. For the fasting interval (period from the first pharmacokinetic blood collection time after the fast begins [~0000 hours; 17 hours] to the end of infusion [~0600 hours; 23 hours]), parameters $AUC_{(17\text{-}23\ hr)}$, C_{ave}, C_{max}, C_{min}, T_{max}, and T_{min} were to be calculated. Pharmacodynamic parameters for plasma glucose were to be based on the evaluable population.

Plasma insulin, plasma glucagon, plasma proinsulin, plasma amylin (total and nonglycosylated), and serum cortisol were to be listed and summarized descriptively for the evaluable population. In addition, proinsulin/insulin and total amylin/insulin ratios were listed and summarized descriptively.

Satiety: Satiety, as measured per the visual analog scale, was to be summarized descriptively on Day 1 by treatment sequence. Mean satiety well-sick, satisfied-hungry, and full-empty on the visual analog scale were to be summarized for Days 2 to 11 by treatment, relative day (same day/next day) for the evaluable population. In addition, the means and standard errors of each visual analog scale across mealtime assessments on the same day and next day were to be plotted by treatment for the same period and population.

Safety: Adverse events were to be listed and summarized descriptively. Physical examination abnormalities were to be listed. Vital sign data (including blood pressure and heart rate) were listed and summarized descriptively. Electrocardiogram data were listed and summarized descriptively. Clinical laboratory measures were listed and summarized descriptively. Safety analyses were performed for the intent-to-treat population.

SUMMARY - CONCLUSIONS:

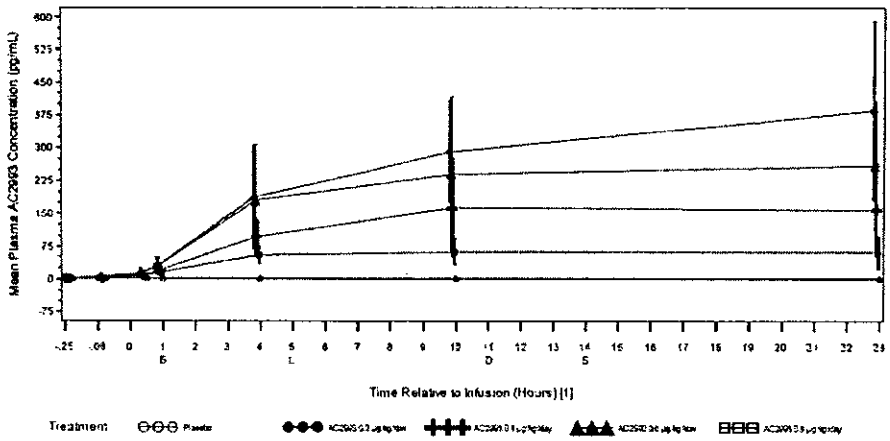
PHARMACOKINETIC RESULTS:

For the four AC2993 doses, mean plasma AC2993 concentrations increased in a dose-dependent manner; however, steady state was not achieved until after at least 4 hours of infusion. The peak mean plasma AC2993 concentrations based on visual examination of the profiles were 62.7 pg/mL (10 hours), 164.2 pg/mL (10 hours), 261.5 pg/mL (23 hours), and 386.2 pg/mL (23 hours) for the 0.2, 0.4, 0.6, and 0.8 ∝g/kg/day treatments, respectively. Pharmacokinetic parameters were calculated from plasma AC2993 concentration profiles. Parameters $AUC_{(0\text{-}23hr)}$, C_{ave}, and C_{max} increased with dose and appeared approximately dose proportional (see table)

Mean (SD) Plasma AC2993 Pharmacokinetic Parameters
(Evaluable Subjects in Study 2993-109 [N = 11])

	AC2993 Treatment			
Parameter/ Mean (SD)/	0.2 µg/kg/day N=11	0.4 µg/kg/day N=11	0.6 µg/kg/day N=10	0.8 µg/kg/day N=10
$AUC_{(0\text{-}23hr)}$ (pg•hr/mL)	1217.8 (611.1)	3053.4 (1878.8)	4873.0 (3116.0)	6212.8 (2722.8)
C_{max} (pg/mL)	70.9 (27.6)	176.5 (108.3)	280.6 (164.9)	391.7 (202.1)
C_{ave} (pg/mL)	54.8 (24.3)	132.8 (81.7)	211.6 (135.6)	270.1 (118.4)

Figure 1: Mean (±SD) AC2993 Concentration-Time Curve by Treatment
(Population Evaluable Subjects in Study 2993-109 [N = 11])



PHARMACODYNAMIC RESULTS:

Plasma Glucose: All four doses of AC2993 markedly reduced mean plasma glucose concentrations compared to placebo at each time point after 3 hours of infusion through infusion completion at 23 hours. Mean plasma glucose concentrations for the AC2993 treatments were similar to placebo treatment during the first few hours of infusion; the reduction of plasma glucose with AC2993 treatment coincided with the rise of plasma AC2993 concentrations, which did not reach steady state for at least 4 hours following the start of the infusion. During the prandial interval (hours 1 to 15 of the infusion), an increase in mean plasma glucose concentrations occurred approximately 1 to 2 hours after meals (breakfast, lunch, dinner); however, even with the post-meal increases, mean plasma glucose concentrations for all AC2993 treatments remained substantially below mean plasma glucose concentrations for placebo treatment. Mean plasma glucose concentrations also remained reduced during the fasting interval (hours 17 to 23 of the infusion) for all AC2993 treatments compared to placebo.

Over the 23-hour time period, all four doses of AC2993 reduced absolute and incremental plasma glucose $AUC_{(0\text{-}23\ hr)}$ compared to placebo (see table).

Plasma Glucose Pharmacodynamic Parameters Based on Absolute and Incremental Concentrations by Treatment: Parametric Analysis
(Evaluable Subjects in Study 2993-109 [N = 11])

	Treatment				
Parameter Variable Statistics	Placebo (N = 11)	AC2993 0.2 µg/kg/day (N = 11)	AC2993 0.4 µg/kg/day (N = 11)	AC2993 0.6 µg/kg/day (N = 10)	AC2993 0.8 µg/kg/day (N = 10)
$AUC_{(0\text{-}23\ hr)}$ (mg·hr/dL)					
Geometric LS Mean (SE)	4598 (268.3)	3697 (245.2)	3564 (219.1)	3418 (213.0)	3222 (214.0)
Geometric 95% C.I.	4084, 5177	3231, 4231	3145, 4038	3012, 3880	2815, 3687
Inc. $AUC_{(0\text{-}23\ hr)}$ (mg·hr/dL)					
LS Mean (SE)	313 (163.9)	-499 (241.6)	-716 (196.9)	-1116 (204.6)	-1292 (242.3)
95% C.I.	-20, 646	-990, -8	-1116, -316	-1532, -701	-1785, -800

Absolute and incremental C_{max} and C_{min} values for plasma glucose were also reduced for all AC2993 treatments compared to placebo. An assessment of plasma glucose values during the prandial (1-15 hr) and fasting intervals (17-23 hr) of each infusion also showed a reduction in absolute and incremental plasma glucose concentrations for all AC2993 treatments compared to placebo.

Plasma Glucagon: After 23 hours of study medication infusion, mean plasma glucagon concentrations were suppressed for all AC2993 treatments (mean change from baseline range: -15.59 pg/mL [0.4 µg/kg/day] to -20.60 pg/mL [0.6 µg/kg/day]) compared to placebo (mean change from baseline: -2.77 pg/mL).

Plasma Insulin: After 23 hours of study medication infusion, mean plasma insulin concentrations had

increased for all AC2993 treatments (mean change from baseline range: 2.27 μU/mL [0.2 μg/kg/day] to 9.68 μU/mL [0.4 μg/kg/day]) compared to virtually no change with placebo treatment (mean change from baseline: 0.05 μU/mL).

Plasma Proinsulin: Mean plasma proinsulin concentrations increased for all doses, however, the increases were less than the increases observed for insulin concentrations.

Plasma Proinsulin/Insulin Ratio: Mean proinsulin/insulin ratios decreased from baseline for all AC2993 treatments compared to placebo with a trend of decreasing ratios with increasing AC2993 doses.

Plasma Total Amylin: Mean total amylin concentrations increased from baseline for all AC2993 treatments (mean change from baseline range: 0.94 pmol/L [0.8 μg/kg/day] to 1.61 pmol/L [0.2 μg/kg/day]) compared to a decrease for placebo (mean change from baseline –0.78 pmol/L).

Plasma Nonglycosylated Amylin: Similar to total amylin, mean nonglycosylated amylin concentrations increased for all doses; as expected, absolute nonglycosylated amylin concentrations were lower than absolute total amylin concentrations.

Plasma Total Amylin/Insulin Ratio: There was negligible change in the mean total amylin/insulin ratio for the four AC2993 treatments compared to placebo indicating that physiological amylin/insulin ratios are preserved.

Serum Cortisol: When evaluated over the 23-hour infusion period, mean serum cortisol concentrations showed a transient increase for the higher doses (0.4 μg/kg, 0.6 μg/kg, and 0.8 μg/kg), but were no different than placebo concentrations near the end of the 23-hour infusion period.

AC2993 Metabolites: Urine samples were taken from 10 subjects (Day 9 and Day 11) for future analysis of AC2993 metabolites. These samples will be tested once an appropriate analytical procedure has been developed and validated. Results will be summarized in separate research reports.

SAFETY RESULTS:
Adverse Events: Of the 12 intent-to-treat subjects, 10 (83.3%) experienced a treatment-emergent adverse event during the study. Of the two subjects who did not have a treatment-emergent adverse event, one completed the study (00155) and one was withdrawn from the study because of an unstable metformin dose (00115). The incidence of adverse events was higher while subjects were receiving AC2993 treatment (10 subjects) compared to placebo (3 subjects). The greatest number of adverse events occurred during the 0.4 μg/kg/day (16 events) and 0.6 μg/kg/day treatments (14 events). The number of adverse events was similar between the 0.2 μg/kg/day (7 events) and 0.8 μg/kg/day (9 events) treatments. The fewest number of adverse events were reported during placebo treatment (3 events). The most common adverse events (i.e., those experienced by at least two subjects receiving any treatment) were: nausea (nine subjects; 75.0%); vomiting (five subjects; 41.7%); neck pain (three subjects; 25.0%); and gastrointestinal upset, flatulence, dizziness, and feeling cold (two subjects each; 16.7% each). Neck pain, weakness, and procedural site reaction were the only adverse events experienced by a subject while receiving placebo treatment (1 subject each; 9.1% each). Nausea, the most frequent adverse event, was experienced by five subjects (50.0%) receiving the 0.6 μg/kg/day AC2993 treatment, five subjects (45.5%) receiving 0.4 ∝g/kg/day, three subjects (30.0%) receiving the 0.8 ∝g/kg/day, and two subjects (16.7%) receiving 0.2 ∝g/kg/day. Vomiting, the second most frequent adverse event, was experienced by three subjects (30.0%) receiving 0.6 ∝g/kg/day, three subjects (27.3%) receiving 0.4 ∝g/kg/day treatment, one subject (10.0%) receiving 0.8 ∝g/kg/day, and one subject (8.3%) receiving 0.2 ∝g/kg/day. There was no clear dose response for nausea and vomiting suggested by these data. Of the 12 intent-to-treat subjects, 9 (75.0%) experienced an adverse event rated as possibly, probably, or definitely related to treatment. The incidence of adverse events classified as possibly, probably, or definitely related to treatment was similar for the 0.4 μg/kg/day (six subjects), 0.6 μg/kg/day (five subjects), and 0.8 μg/kg/day (six subjects) AC2993 treatments. The incidence was lower for the 0.2 μg/kg/day (three subjects) and placebo (one subject) treatments. Of the 49 adverse events reported during the study, 39 (approximately 80%) were considered possibly, probably, or definitely related to study medication by the investigator. All adverse events were

considered mild except one moderate vomiting event (0.4 µg/kg/day AC2993 treatment). There were no occurrences of hypoglycemia during the study.

Deaths: There were no deaths during the study.
Serious Adverse Events: There were no serious adverse events during the study.
Withdrawals Due to Adverse Events: One subject (00110), randomized to Treatment Sequence 2, withdrew from the study due to facial palsy after having received two AC2993 treatments (0.2 µg/kg/day and 0.4 ∝g/kg/day). This event was classified as mild and unrelated to study medication.

Clinical Laboratory Values: Following AC2993 or placebo administration, no clinically meaningful differences were noted in clinical laboratory measures.

Vital Signs, Physical Examination, and 12-Lead Electrocardiogram: No clinically meaningful differences were noted in vital signs, physical examination findings, or ECGs following AC2993 or placebo administration.

CONCLUSION:
Mean plasma AC2993 concentrations increased in a dose-dependent manner; however, steady state was not achieved until after at least 4 hours of infusion. Pharmacokinetic parameters increased with dose and appeared dose-proportional. All four doses of AC2993 (0.2, 0.4, 0.6, and 0.8 µg/kg/day) markedly reduced mean plasma glucose concentrations after 3 hours of infusion through the completion of the infusion at 23 hours compared to placebo. Plasma glucose concentrations for the AC2993 treatments were similar to placebo treatment during the first few hours of the infusion; the reduction of plasma glucose in AC2993-treated subjects coincided withthe rise of plasma AC2993 concentrations. These results demonstrate the effectiveness of AC2993 to lower glucose in preprandial, prandial, and fasting states when delivered as a continuous subcutaneous infusion in subjects with type 2 diabetes mellitus. Furthermore, the results of this study suggest that long-acting release formulations of AC2993 may provide sustained glycemic control.
Twenty-three hours of subcutaneous infusion of AC2993 at doses of 0.2, 0.4, 0.6, and 0.8 µg/kg/day led to:
- increases in mean plasma insulin concentrations;
- reductions in mean plasma glucagon concentrations;
- increases in mean plasma total amylin concentrations;
- decreases in proinsulin/insulin ratio (insulin concentration increased with dose);
- no change in amylin/insulin ratio (both increased with dose);
- no sustained differences in mean serum cortisol concentrations.

Subcutaneous administration of AC2993 (0.2, 0.4, 0.6, and 0.8 µg/kg/day) was well tolerated in subjects with type 2 diabetes mellitus treated with metformin or a thiazolidinedione, either alone or in combination.

2993-110

Title of Study: A Double-Blind, Placebo-Controlled Crossover Study to Examine the Effect of Subcutaneously Administered AC2993 on Fasting Plasma Glucose Concentrations in Subjects with Type 2 Diabetes Mellitus

Phase of Development: 2

Investigators and Study Centers: [redacted]

Publications (References): Kim D, Taylor K, Bicsak T, Wang Y, Aisporna M, Heintz S, Fineman MS, Baron A. Subcutaneous Injection of AC2993 (synthetic exendin-4) Lowered Fasting Glucose Concentrations Through Suppression of Glucagon and Dose Dependent Insulinotropism in Patients With Type 2 Diabetes. Diabetes 2002;51(suppl 2):A104 (abstract 421-P). Kim D, Taylor K, Bicsak T, Wang Y, Aisporna M, Heintz S, Fineman MS, Baron A. AC2993 (synthetic exendin-4) Lowered Fasting Glucose Concentrations Through Suppression of Glucagon and Dose Dependent Insulinotropism in Patients with Type 2 Diabetes. Diabetologia 2002;45(suppl 1):A44.

Studied Period: 06 June 2001 – 24 June 2001

Objectives: Primary Objective: To examine the effect of subcutaneously injected AC2993 on plasma glucose concentrations for 8 hours in fasting subjects with type 2 diabetes. Secondary Objectives: To assess serum insulin, plasma epinephrine, plasma norepinephrine, plasma glucagon, serum cortisol, and serum growth hormone in fasting subjects with type 2 diabetes after subcutaneous injection of AC2993. To assess the pharmacokinetics of AC2993 in fasting subjects with type 2 diabetes after subcutaneous injection of AC2993. To assess the safety and tolerability of AC2993 in fasting subjects with type 2 diabetes after subcutaneous injection of AC2993.

Methodology: Double-blind (investigator and subjects blinded), placebo-controlled, crossover study in subjects with type 2 diabetes mellitus designed to examine the pharmacokinetic and pharmacodynamic effects of subcutaneously injected AC2993. Subjects were randomly assigned to one of four treatment sequences (Treatment Sequence: 1 = ADBC, 2 = BACD, 3 = CBDA, 4 = DCAB; Treatment: A = Placebo, B = 0.05 µg/kg AC2993, C = 0.1 µg/kg AC2993, D = 0.2 µg/kg AC2993). Within each sequence, subjects were to receive four treatments including one dose of placebo and three doses of AC2993 (0.05 µg/kg, 0.1 µg/kg, and 0.2 µg/kg). Subjects were to fast from 2200 hours on Day –1, Day 2, Day 4, and Day 6. On Day 1, Day 3, Day 5, and Day 7, subjects were to receive a single subcutaneous injection of study medication (AC2993 or placebo) at time = 0 (approximately 0700 hours) according to the assigned treatment sequence. No treatment was to be given on Day –1, Day 2, Day 4, Day 6, or at study termination. During the 8 hours following study medication injection, blood samples were to be collected at timed intervals to measure plasma glucose, serum insulin, plasma epinephrine, plasma norepinephrine, plasma glucagon, serum cortisol, serum growth hormone, and plasma AC2993. Serum prolactin was assessed at 1 hour after dosing. Adverse events were reviewed daily starting on Day 1; clinical laboratory measures (hematology, clinical chemistry and urinalysis), a physical examination, and 12-lead electrocardiogram were performed on Day –1 and at study termination; and vital signs were taken on Day –1 and each study day morning through study termination. Subjects were to be discharged after completing study termination procedures, including safety evaluations.

Number of Subjects: The study population consisted of: 14 randomized subjects (i.e., all subjects who were allocated a randomization number), 13 intent-to-treat subjects (i.e., all subjects who received at least one dose of study medication), and 12 evaluable subjects (i.e., all intent-to-treat subjects who completed at least two treatment periods and had adequate data for reliable evaluation of pharmacodynamic parameters of plasma glucose concentrations).

Key Demographics: The intent-to-treat study population consisted of 13 subjects with type 2 diabetes mellitus. The intent-to-treat population was 61.5% male; 84.6% Hispanic, and 15.4% Caucasian. Subjects'

mean age was 49±7.3 years; mean body mass index (BMI) was 32.8±5.77 kg/m2. Mean height and weight were166.0±8.29 cm and **90.6±18.35 kg**, respectively. Subjects randomized into Treatment Sequences 2 and 3 were heavier (mean: 101.3 kg and 96.8 kg, respectively) compared to those subjects randomized into Treatment Sequences 1 and 4 (mean: 80.6 kg and 87.3 kg, respectively). The average duration of diabetes was 3.1±2.93 years; it was comparable among Treatment Sequences 1, 3, and 4 (3.5 to 3.6 years) but was lower among subjects in Treatment Sequence 2 (1.8 years). Mean glycosylated hemoglobin, specific A_{1c} fraction (HbA_{1c}) was 9.8%±1.25 and ranged from 9.2% for subjects in Treatment Sequence 4 to 10.6% in Treatment Sequence 2.

Subject Disposition: Of the 14 subjects randomized, 11 (78.6%) completed the study and 3 (21.4%) withdrew early.

Diagnosis and Main Criteria for Inclusion: A sufficient number of individuals with type 2 diabetes mellitus were to be enrolled in this study to ensure 12 completed subjects. (Note: study finished with 11 completed subjects; 12 evaluable subjects.) Subjects were to be male or infertile females (surgically sterile or postmenopausal) and were to have an HbA_{1c} value of 7.5% to 11%, inclusive, at screening. Subjects' diabetes was to be treated either with diet alone, metformin alone, a thiazolidinedione alone (rosiglitazone or pioglitazone), or with a combination of metformin and one of the thiazolidinediones. Subjects treated with oral been on an assigned diet regimen. A stable diabetes treatment regimen was to have been maintained for at least 3 months prior to screening. Subjects were to continue their regular regimen of specified oral agent therapy during the study.

Test Product; Dose and Mode of Administration; Batch No.: AC2993; 0.05 µg/kg, 0.1 µg/kg, and 0.2 µg/kg via subcutaneous injection; Lot No. 00-0605TP.

Duration of Treatment: 8 days

Reference Therapy, Dose and Mode of Administration, Batch No: Placebo for AC2993, volume equivalent to individual subject's 0.1 µg/kg AC2993 dose, Lot No. 00-0604TE.

Criteria for Evaluation:
Pharmacokinetics: Plasma AC2993 concentration was evaluated over the 8-hour postdose blood-sampling period.
Pharmacodynamics: The primary pharmacodynamic variable was the effect of AC2993 administration on plasma glucose concentrations for 8-hours postdose. Secondary pharmacodynamic analytes were serum insulin, plasma epinephrine, plasma norepinephrine, plasma glucagon, serum cortisol, and serum growth hormone. Pharmacodynamic analytes were evaluated over the 8-hour postdose period. Serum prolactin levels were assessed at 1 hour postdose.

Safety: Adverse events were reviewed daily starting on Day 1; clinical laboratory measures (hematology, clinical chemistry and urinalysis), a physical examination, and 12-lead electrocardiogram were performed on Day –1 and at study termination; vital signs were taken on Day –1 and each study day morning through study termination.

Statistical Methods:
Pharmacokinetics: Pharmacokinetic parameters, including area under the concentration-time curve ($AUC_{(0-8\ h)}$), maximum observed drug concentration (C_{max}), time-weighted average concentration (C_{ave}), time of maximum observed concentration (T_{max}), and terminal elimination half-life ($t_{1/2}$), were calculated from the plasma AC2993 concentration profiles over 8 hours for the evaluable population (N = 12). Descriptive statistics for plasma AC2993 concentrations at each time point were presented by treatment. Individual and mean concentration profiles were plotted by treatment and by treatment sequence.

Pharmacodynamics: Pharmacodynamic parameters $AUC_{(0-8\ h)}$, C_{max}, minimum observed drug concentration (C_{min}), C_{ave}, T_{max}, and time of minimum observed concentration (T_{min}) were calculated for the absolute and

incremental (the baseline concentration subtracted from the concentration at each time point thereafter) plasma glucose concentrations over 8 hours. For all secondary pharmacodynamic parameters (serum insulin, plasma epinephrine, plasma norepinephrine, plasma glucagon, serum cortisol, and serum growth hormone), $AUC_{(0\text{-}8\ h)}$, C_{max}, C_{ave}, and T_{max} were calculated for the absolute and incremental concentrations over 8 hours.
Pharmacodynamic parameter calculations were performed for the evaluable population (N=12). Descriptive statistics for these analytes at each time point were presented by treatment. Descriptive statistics of change from baseline for serum prolactin concentrations were summarized. Individual and mean concentration-time curves were plotted by treatment.

Safety: Adverse events were summarized by presenting subject incidence and the number of events in each system organ class and preferred term defined by the Medical Dictionary for Regulatory Activities (MedDRA™). All adverse events occurring during or after the administration of randomized study medication beginning on Day 1, through study termination (or early termination, if applicable) were summarized. Descriptive statistics of changes from baseline for clinical chemistry, hematology, urinalysis, physical examinations, and 12-lead electrocardiograms were summarized. Descriptive statistics of changes in vital signs from baseline by visit and treatment sequence were presented.

SUMMARY - CONCLUSIONS:
PHARMACOKINETIC RESULTS:
Mean plasma AC2993 concentrations increased in relation to dose from baseline to a maximum concentration at 2 hours for all AC2993 doses. At the 2-hour time point, mean AC2993 concentrations were 100.8 pg/mL, 205.2 pg/mL, and 359.2 pg/mL, for the 0.05 µg/kg, 0.1 µg/kg and 0.2 µg/kg doses, respectively, compared to placebo at 1.3 pg/mL. Pharmacokinetic plots for individual subjects were consistent with the mean curves with a clear dose-dependent pattern apparent for every subject. $AUC_{(0\text{-}8\ h)}$, C_{ave}, and C_{max} values appeared to be dose-proportional. Mean T_{max} and $t_{1/2}$ values were similar among the AC2993 doses.

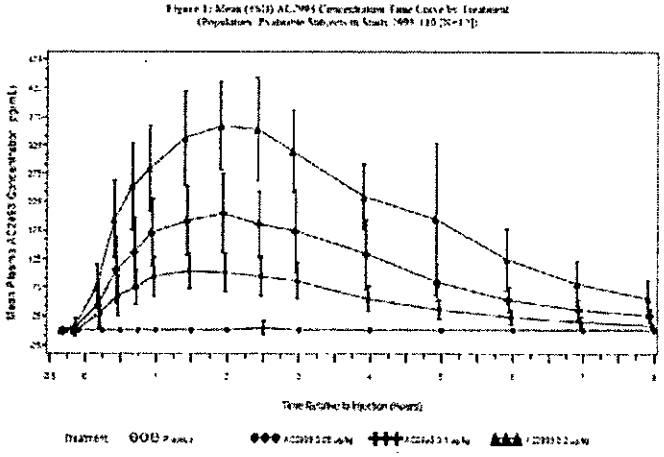


Table 7: Plasma AC2993 Pharmacokinetic Evaluation
(Population: Evaluable Subjects in Study 2993-110 [N = 12])

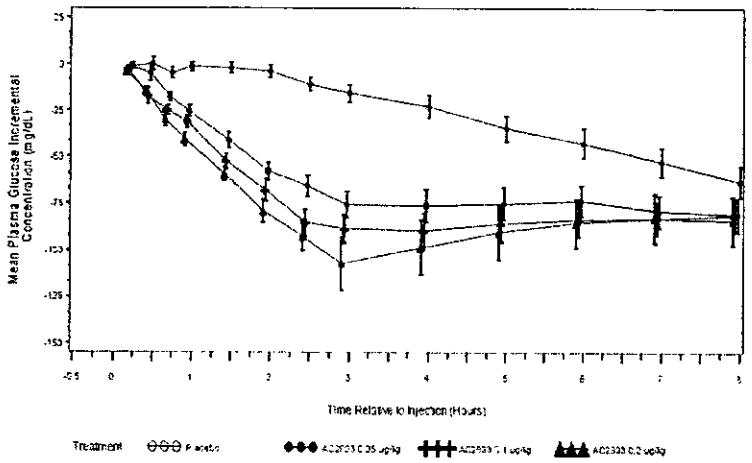
Parameter, Mean±SD	AC2993 Treatment		
	0.05 µg/kg (N = 12)	0.1 µg/kg (N = 12)	0.2 µg/kg (N = 12)
$AUC_{(0-8\ h)}$ (pg•h/mL)	425.4 ± 121.56	871.7 ± 295.36	1649.8 ± 346.80
C_{max} (pg/mL)	114.4 ± 32.32	216.1 ± 65.40	393.7 ± 97.30
C_{ave} (pg/mL)	54.0 ± 16.1	112.1 ± 35.5	214.5 ± 52.24
T_{max} (h)	1.83 ± 0.752	2.12 ± 0.628	2.50 ± 1.087
$t_{1/2}$ (h)	1.47 ± 0.213	1.61 ± 0.377	1.66 ± 0.573

Cross-References: Supporting Data Summary 2.1.1 and Appendix 3.11.2.2

PHARMACODYNAMIC RESULTS:

Fasting Plasma Glucose: All three doses of AC2993 (0.05 µg/kg, 0.1 µg/kg, and 0.2 µg/kg) markedly reduced fasting plasma glucose concentrations in a dose-dependent manner during the 8-hour time period. With AC2993 treatment, there was a 38 mg/dL to 55 mg/dL greater reduction in baseline corrected average fasting plasma glucose concentrations compared to the decrease observed with placebo treatment. The mean fasting plasma glucose nadir occurred between 3 and 4 hours after administration of AC2993. At 3 hours postdose, mean incremental fasting plasma glucose concentrations were –75.7 mg/dL, -88.6 mg/dL, and -107.0 mg/dL for AC2993 doses 0.05 µg/kg, 0.1 µg/kg, and 0.2 µg/kg, respectively. Similar values were observed at 4 hours postdose with mean incremental fasting glucose concentrations of -76.2 mg/dL, -89.7 mg/dL, and –98.5 mg/dL for AC2993 doses 0.05 µg/kg, 0.1 µg/kg, and 0.2 µg/kg, respectively. For placebo, the mean incremental fasting plasma glucose concentrations were -15.9 mg/dL at 3 hours and -23.0 mg/dL at 4 hours. Fasting plasma glucose concentrations remained below baseline at 8 hours postdose. Fasting plasma glucose pharmacodynamic parameters $AUC_{(0-8\ h)}$, C_{ave}, C_{max}, and C_{min} decreased in a dose-dependent manner for AC2993 treatments compared to placebo.

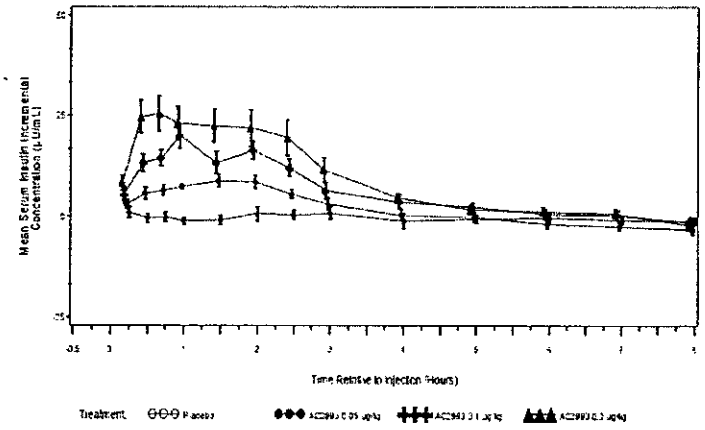
Figure 2: Mean (±SE) Incremental Fasting Plasma Glucose Concentration-Time Curve by Treatment
(Population: Evaluable Subjects in Study 2993-110 [N = 12])



Fasting Serum Insulin: There was a dose-dependent increase in mean incremental fasting serum insulin concentrations for the three AC2993 treatments (0.05 µg/kg, 0.1 µg/kg, and 0.2 µg/kg) compared to placebo within the first few hours after dosing. By 2 hours postdose, mean fasting incremental serum insulin concentrations for all AC2993 treatments had peaked. Thereafter, mean fasting incremental serum insulin concentrations began to decrease, and by 4 hours postdose they approached baseline for all AC2993 treatments. The time frame of the observed peak and subsequent decrease of fasting serum insulin

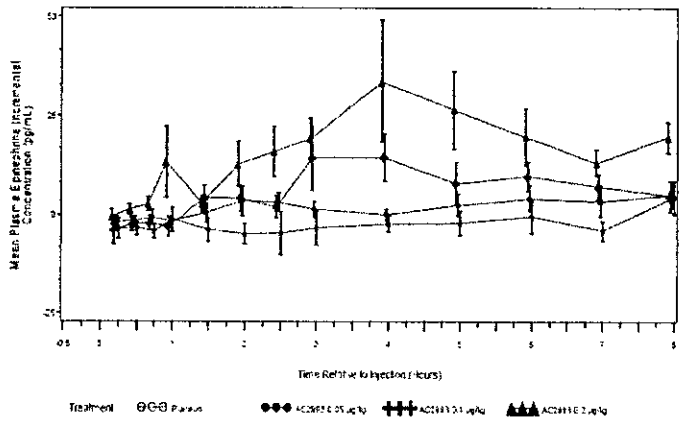
concentrations coincided with the time frame of the nadir for fasting glucose concentrations. After 4 hours postdose, little difference was observed between mean incremental fasting serum insulin concentrations for the AC2993 treatments and placebo. However, the glucose-dependent insulinotropic nature of AC2993 was still apparent because similar serum insulin concentrations were maintained in response to significantly lower plasma glucose concentrations compared to those seen with placebo. Mean incremental serum insulin concentrations peaked earlier for higher doses. Mean incremental serum insulin concentrations peaked at 45 minutes, 1 hour, and 1.5 hours for AC2993 doses 0.2 µg/kg, 0.1 µg/kg, and 0.5 µg/kg, respectively. Corresponding mean incremental serum insulin concentrations at these time points were 25.6 µU/mL, 20.0 µU/mL, and 8.8 µU/mL, for the 0.2 µg/kg, 0.1 µg/kg, and 0.5 µg/kg doses, respectively. Fasting serum insulin pharmacodynamic parameters $AUC_{(0\text{-}8\ h)}$, C_{ave}, and C_{max} increased in a dose dependent manner for AC2993 treatments compared to placebo.

Figure 3: Mean (±SE) Incremental Fasting Serum Insulin Concentration-Time Curve by Treatment (Population: Evaluable Subjects in Study 2993-110 [N=12])

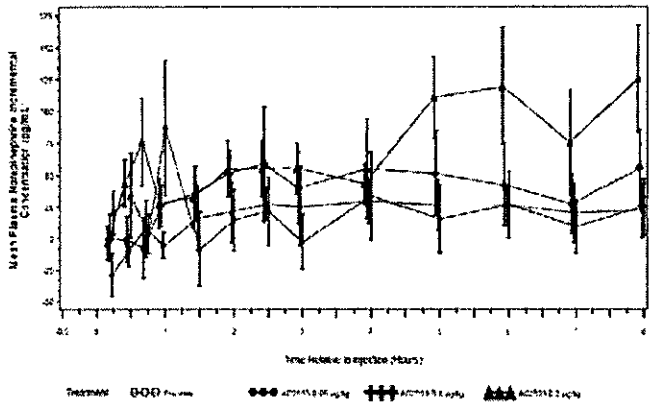


Fasting Plasma Epinephrine: An apparent dose-dependent increase in mean fasting incremental plasma epinephrine concentrations was observed for the 0.1 µg/kg and 0.2 µg/kg AC2993 treatments. The greatest effect occurred between 3 to 6 hours postdose for the 0.1 µg/k and 0.2 µg/kg AC2993 treatments. Mean incremental plasma epinephrine concentrations for the 0.05 µg/kg AC2993 treatment did not to differ from placebo.

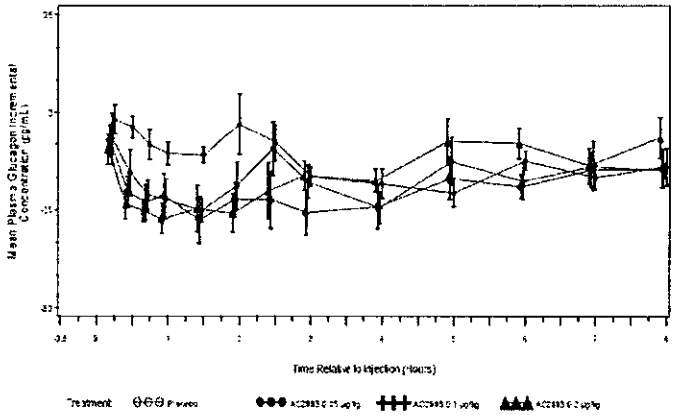
Figure 4: Mean (±SE) Incremental Fasting Plasma Epinephrine Concentration-Time Curve by Treatment (Population: Evaluable Subjects in Study 2993-110 [N=12])



Fasting Plasma Norepinephrine: An apparent increase in mean fasting plasma norepinephrine concentrations was observed for the 0.1 µg/kg and 0.2µg/kg doses.

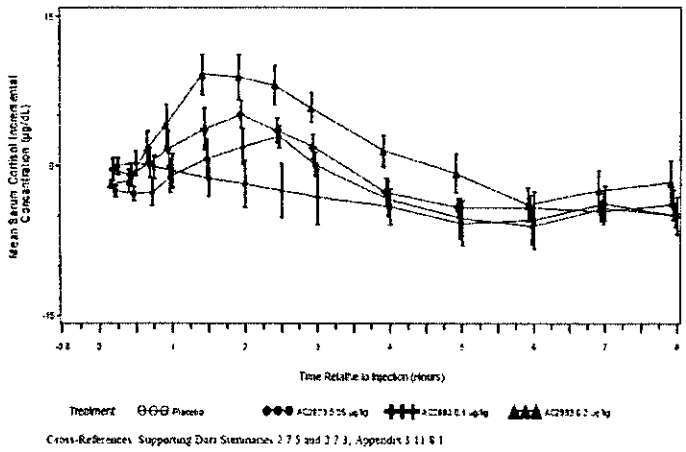


Fasting Plasma Glucagon: Mean incremental fasting plasma glucagon concentrations appeared to be suppressed within the first 3 hours for all AC2993 treatments (0.05 µg/kg, 0.1 µg/kg, and 0.2 µg/kg) compared to placebo. After 3 hours postdose, little difference in fasting plasma glucagon concentrations was observed among the AC2993 treatments and placebo.



Fasting Serum Cortisol: A dose-dependent transient increase in mean incremental fasting serum cortisol concentrations was observed for all three AC2993 treatments (0.05 µg/kg, 0.1 µg/kg, and 0.2 µg/kg) for the first 3 hours postdose. After approximately 4 hours postdose there was no difference in mean incremental fasting serum cortisol concentrations between the AC2993 treatments and placebo.

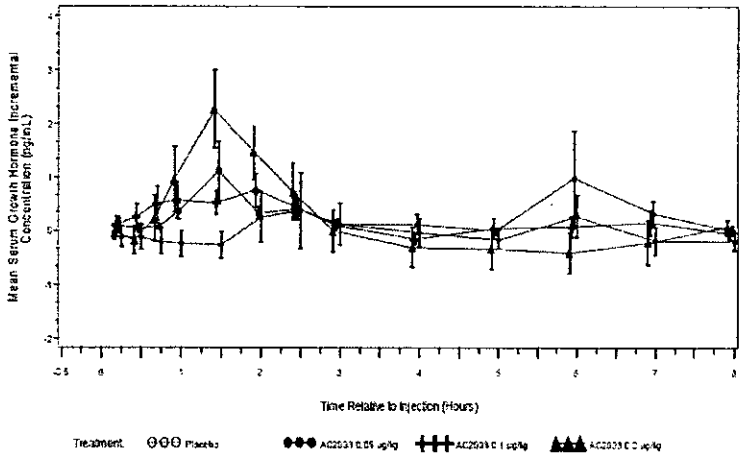
Figure 7: Mean (±SE) Incremental Fasting Serum Cortisol Concentration-Time Curve by Treatment
(Population: Evaluable Subjects in Study 2993-110 [N=12])



Cross-References: Supporting Data Summaries 2.7.5 and 2.7.3, Appendix 5.11.6.1

Fasting Serum Growth Hormone: An apparent transient increase in mean incremental fasting serum growth hormone concentrations was observed 1 to 2 hours postdose for all AC2993 treatments compared to placebo.

Figure 8: Mean (±SE) Incremental Fasting Serum Growth Hormone Concentration-Time Curve by Treatment
(Population: Evaluable Subjects in Study 2993-110 [N=12])



Fasting Serum Prolactin: No trends were observed for serum prolactin concentrations.

SAFETY RESULTS:

Adverse Events: There were a total of 28 treatment-emergent adverse events experienced by 10 subjects (76.9%) throughout the study. Of the 28 adverse events, 23 were reported by eight subjects (61.5%) during AC2993 treatment and 5 were reported by four subjects (30.8%) during placebo treatment. The greatest number of treatment-emergent adverse events were associated with the 0.2 ∝g/kg AC2993 dose (six subjects [46.2%], 11 events); there were similar numbers of adverse events among the other three treatments (four subjects [30.8%], five events for placebo; four subjects [30.8%], six events each for the 0.05 µg/kg and 0.1 µg/kg AC2993 doses). The most common treatment-emergent adverse events (i.e., those experienced by at least two subjects receiving any treatment) were headache, vomiting, abdominal pain, diarrhea, and nausea.

Headache (eight events) and vomiting (five events) were experienced by four subjects (30.8%) each. One of the five events of vomiting occurred at the 0.1 µg/kg dose and the other four events occurred at the 0.2 µg/kg dose. Abdominal pain, diarrhea, and nausea were experienced by two subjects (15.4%) each, with both events of nausea experienced at the 0.2 µg/kg AC2993 dose. All adverse events were rated as mild with the exception of one event of moderate headache. Of 28 treatment emergent adverse events, 15 were considered by the investigator to be possibly, probably, or definitely related to study medication. All other events were considered not related or unlikely to be related to study medication. Most events considered possibly, probably, or definitely related to treatment were associated with the 0.2 µg/kg AC2993 dose (five subjects [(38.5%], eight events).

Deaths: There were no deaths during the study.
Serious Adverse Events: There were no serious adverse events during the study.
Withdrawals Due to Adverse Events: No subject withdrew from the study due to an adverse event.

Clinical Laboratory Values: No unexpected changes were observed for this study population in clinical laboratory values; no trends of clinical importance were apparent.
Vital Signs, Physical Examination, and 12-Lead Electrocardiogram: Mean blood pressure values decreased over the course of the study. This is not unexpected per the study design (domiciled subjects). No clinically meaningful differences were noted in vital signs, electrocardiograms, or physical examination findings following AC2993 or placebo administration.

CONCLUSION: AC2993 (0.05 µg/kg, 0.1 µg/kg, and 0.2 µg/kg) effectively lowered fasting plasma glucose concentrations in a dose-dependent manner over 8 hours. With AC2993 treatment, there was a 38 mg/dL to 55 mg/dL reduction in baseline corrected average fasting plasma glucose concentrations compared to the decrease observed with placebo treatment. The period of greatest glucose reduction coincided with peak serum insulin concentrations and maximal suppression of glucagon.
Subcutaneous administration of AC2993 (0.05 µg/kg, 0.1 µg/kg, and 0.2 µg/kg) was well tolerated by subjects with type 2 diabetes mellitus treated with metformin alone or in combination with a thiazolidinedione. There were no safety concerns.

2993-111

Title of Study: A Triple-Blind, Placebo-Controlled Crossover Study to Examine the Effects of Intravenously Administered AC2993 on Insulin Secretion and Counterregulation During Euglycemia and Insulin-Induced Hypoglycemia in Healthy Volunteers

Phase of Development: 2

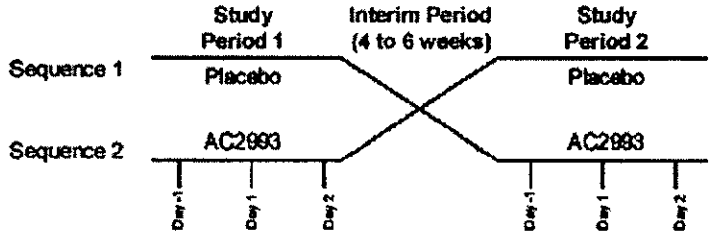
Investigators and Study Centers: Ole Schmitz, MD, Centre for Clinical Pharmacology, University of Aarhus, DK-8000 Aarhus C, Denmark.

Publication (Reference): Brock B, Degn, Juhl CB, Djurhuus C, Grubert J, Han J, Love K, Simitzi J, Nielsen L, Schmitz O. Evidence of Glucose-Dependent Insulin Secretion and Unaltered Counter-Regulation during Hypoglycemia after Intravenous Infusion of Exenatide (Synthetic Exendin-4). Diabetes Metabolism 2003; 29: Abstract 1787.

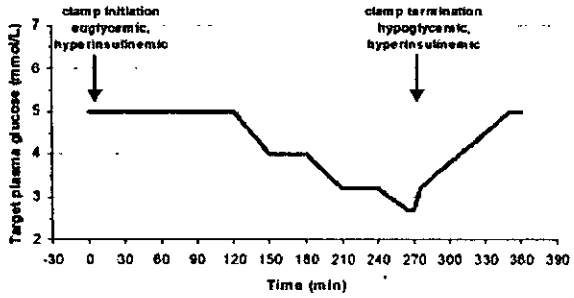
Studied Period: 22 August 2002 - 9 December 2002.

Objectives: Primary Objectives: To assess the effects of AC2993 delivered via continuous intravenous infusion to healthy subjects on the counterregulatory response to hypoglycemia by quantitating changes in circulating concentrations of glucagon, growth hormone, cortisol, free fatty acids, epinephrine, and norepinephrine. To assess the effects of AC2993 delivered via continuous intravenous infusion on insulin secretion during euglycemia and various levels of hypoglycemia in healthy subjects. Secondary Objective: To examine the effects of AC2993 delivered via continuous intravenous infusion on the recovery of glucose concentrations from hypoglycemia upon termination of the glucose clamp.

Methodology: This single-center, randomized, triple-blind, placebo-controlled crossover study in healthy volunteers was designed to examine the effect of intravenously administered AC2993 on insulin secretion and counterregulatory responses during insulin-induced hypoglycemia. Each subject was to undergo intravenous (IV) infusions of AC2993 and placebo to be administered for 360 minutes on the second day of a three-day study period on two separate occasions. Eligible subjects were to be housed in the study unit for 3 days (2 nights) during each of the study periods and were to receive the randomized study medication on Day 1 of each study period. Following admission to the unit, subjects were to begin fasting (with water as desired) and were to continue fasting through the next day (Day 1) until 6 hours following the initial infusion of study medication. Subjects were to be randomly assigned to one of two treatment sequences in this crossover study, each of which included a 360-minute infusion of AC2993, a 360-minute infusion of placebo, and a 4-to 6-week interim period as shown in the following diagram:



AC2993 or the equivalent volume of placebo was to be infused (0.066 pmol/kg/min) starting at time 0 and continued at a constant rate for 360 minutes. A euglycemic hyperinsulinemic clamp, followed by a stepwise hypoglycemic clamp was to be carried out from 0-270 minutes as demonstrated in the following schematic:



The plasma glucose concentration was to be targeted to ~ 5 mmol/L from time 60-120 minutes (euglycemic phase); and fall in progressive increments during the hypoglycemic phase; ~ 4 mmol/L from time 120-180 minutes, and ~3.2 mmol/L from time 180-240 minutes; the plasma glucose concentrations were to be maintained by the glucose clamp technique at the target concentration during the last 30 minutes of each step period. During the 240-270 minutes period, the plasma glucose concentration was to be targeted to ~2.7 mmol/L, where it was to be maintained for 5 minutes. At 270 minutes, insulin infusion and glucose clamp were to be terminated and plasma glucose was to be increased to 3.2 mmol/L to ensure subject safety; subsequent recovery from that point was to be assessed for a further 90 minutes. The time to achieve a plasma glucose concentration of at least 4 mmol/L was to be recorded. The variable glucose infusion may have been continued if needed to prevent the plasma glucose concentration from dropping below 3.2 mmol/L. Blood samples were to be collected throughout the 390-minute period (-30 minutes to 360 minutes) for determination of concentrations of circulating glucose, insulin, glucagon, growth hormone, cortisol, C-peptide, epinephrine, norepinephrine, free fatty acids, and AC2993.

Number of Subjects: Twelve subjects were randomized into the study.

Key Demographics: All twelve randomized subjects were male and Caucasian. The mean age of the population was 27.5 years. Mean weight and the mean body mass index (BMI) at screening were 78.7 kg and 23.3 kg/m2, respectively.

Subject Disposition: Eleven of the 12 randomized subjects completed the study. One subject randomized to the placebo-AC2993 treatment sequence withdrew early due to an adverse event (abnormal liver function tests) during placebo treatment in Period 1. The event was classified as moderate in intensity and probably not related to study medication.

Diagnosis and Main Criteria for Inclusion: Subjects were to be healthy males or females who were surgically sterile or postmenopausal, aged 22 to 50 years, and have a BMI of 20 to 30 kg/m2. Subjects were to have no personal or immediate family history of diabetes mellitus (including impaired glucose tolerance, impaired fasting glucose, and gestational diabetes) and were to have met the inclusion/exclusion criteria. Additionally, because severe nausea could cause stress to the subject and confound interpretation of AC2993 effects on counterregulatory hormones, any subject that experienced severe nausea during either of the infusion periods was to complete early termination procedures.

Test Product, Dose and Mode of Administration, Batch No.: AC2993, infusion at 0.066 pmol/kg/min (360 minutes). Lot No. 00-0606TP.

Duration of Treatment: Seven weeks from the time the subject was enrolled in the first study period to the time the subject completed study termination on Day 2 of the second study period.

Reference Therapy, Dose and Mode of Administration, Batch No: Placebo, infusion at the same rate as AC2993 (360 minutes). Lot No: 00-0604TE.

Criteria for Evaluation:
Pharmacokinetics: Plasma AC2993 concentrations were to be evaluated throughout each 360-minute infusion period. Blood samples for pharmacokinetic testing were to be collected at 11 time points (-15, 0, 15, 30, 45, 60, 120, 180, 240, 300, and 360 minutes).

Pharmacodynamics: The primary pharmacodynamic measures, intended to assess the effects of AC2993 on the counterregulatory response to hypoglycemia, were to include insulin secretory rates via C-peptide kinetic modeling, and measurement of glucagon (-30, -20, -10, and 0 minutes, and every 15 minutes thereafter for the duration of the 360-minute infusion period), growth hormone, cortisol, norepinephrine, epinephrine, and free fatty acid concentrations (-30, -15, 0, 60, 120, 150, 180, 210, 240, 255, 270, 285, 300, 315, 330, and 360 minutes). The secondary pharmacodynamic measure, intended to assess the effects of AC2993 on the recovery of glucose concentrations from hypoglycemia upon termination of the glucose clamp from time 270 minutes to 360 minutes. Also to be recorded was the time to recover to a plasma glucose concentration of at least 4 mmol/L from the 3.2 mmol/L target at 270 minutes. Blood samples were collected on Day 1 of each study period.

Safety: Adverse events, clinical laboratory values, vital signs, ECGs, and physical examinations were to be assessed.

Statistical Methods:
Pharmacokinetics: AC2993 concentrations at each time point were summarized descriptively by treatment. The individual and mean concentration profiles were plotted by treatment. The pharmacokinetic parameters $AUC_{(0\text{-}360\ min)}$, $C_{ave(0\text{-}360\ min)}$, $C_{max(0\text{-}360\ min)}$,$AUC_{(120\text{-}360\ min)}$, and $C_{ave(0\text{-}360\ min)}$,were listed by treatment. Descriptive statistics, including number of subjects (n), mean, standard deviation, geometric mean, standard error of the geometric mean, coefficient of variation (CV), minimum, and maximum, were presented for all of the pharmacokinetic parameters by treatment.

Pharmacodynamics: The insulin secretion rates were estimated by mathematical analysis of plasma C-peptide concentrations using a two compartment model. The mean insulin secretion rates and the incremental insulin secretion rates for each glycemic step were summarized descriptively. The AC2993 treatment effects on the mean insulin secretion rates and the incremental insulin secretion rates during each glycemic step were examined by a mixed effect model that included treatment (2 levels), treatment sequence (2 levels), and period (2 levels) as fixed effects, and subject-within-sequence as a random effect. The least squares (LS) means and standard errors were derived. The 95% confidence intervals were constructed from the LS means and the standard errors for each treatment. To be considered statistically significant, the 95% confidence interval for the difference should not have included zero and the confidence interval for the ratio should not have included 1. The mean values of the counterregulatory measurements (glucagon, growth hormone, cortisol, norepinephrine, epinephrine, and free fatty acids) for each glycemic step were analyzed in the same manner as for insulin secretion rate.

Analyses of the Recovery From Hypoglycemia: The ability to recover from hypoglycemia during AC2993 treatment versus placebo treatment was determined by the concentration-time profile of plasma glucose from time 270 minutes to 360 minutes and the time to achieve a plasma glucose concentration of at least 4 mmol/L during that period. Glucose nadir and other counterregulatory measurements were assessed. The AUC and C_{ave} for all pharmacodynamic parameters over the 270-360 min sampling period was summarized descriptively by treatment. The descriptive statistics for these pharmacodynamic parameters included n, mean, standard deviation, geometric mean, standard error of the geometric mean, minimum, and maximum. The $AUC_{(270\text{-}360\ min)}$ and $C_{ave(270\text{-}360\ min)}$ data for all pharmacodynamic parameters were loge-transformed and analyzed using a similar mixed effect model as described in the primary analysis. The counterregulatory measurements over the 270- to 360-minute sampling period were summarized descriptively.

Safety: Adverse events were summarized by presenting subject incidence and the number of events in each system organ class and in each preferred term defined by the Medical Dictionary for Regulatory Activities (MedDRA™ version 5) by treatment. Treatment-emergent adverse events (TEAEs) were defined as those

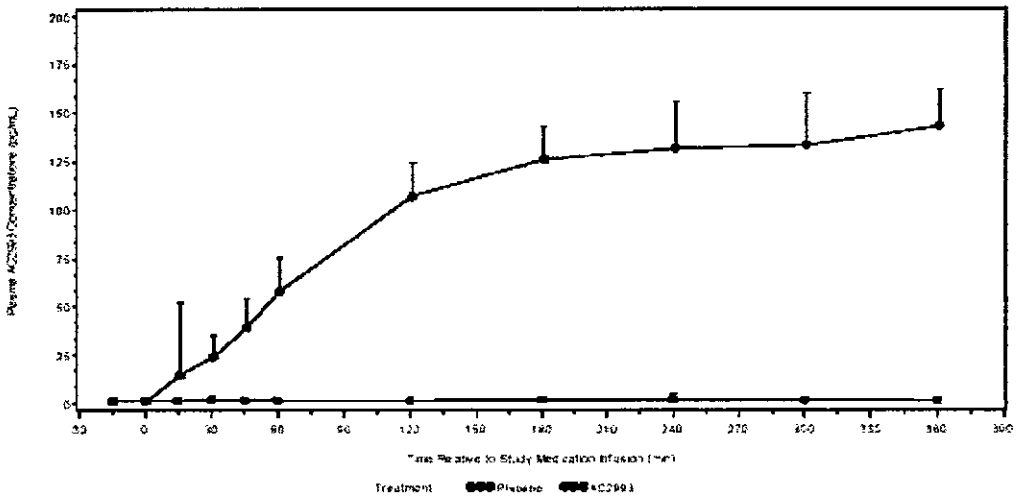
occurring on or after the randomized infusion of study medication on Day 1 and Day 2 of both study periods, and were assigned by treatment and summarized. Adverse events that occurred on or after the date of consent through Study Period 1, Day -1, and during the wash out period (4-6 weeks) through Study Period 2, Day -1 were classified as pretreatment (non-treatment-emergent) and were listed only. Clinical chemistry, hematology, and urinalysis values were summarized descriptively. Vital signs and ECG data were summarized. Data for physical examinations were listed.

SUMMARY - CONCLUSIONS:

PHARMACOKINETIC RESULTS:

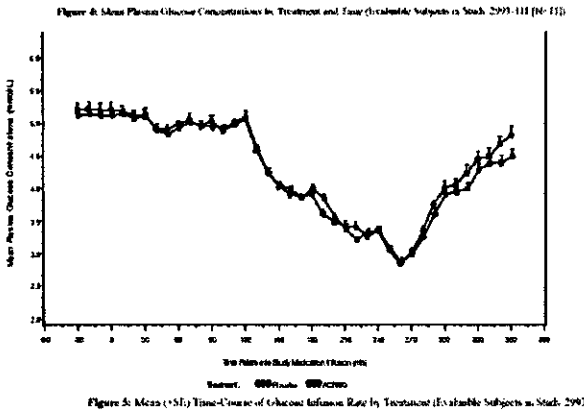
Mean plasma AC2993 concentrations showed an ascending trend for the first 120 minutes of AC2993 infusion. Therapeutic AC2993 concentrations (> 50 pg/mL) were acheived within the first 60 minutes of AC2993 infusion. Steady-state concentrations of approximately 130 pg/mL (within the therapeutic range) were achieved at approximately 120 mins and maintained for the remainder of the study.

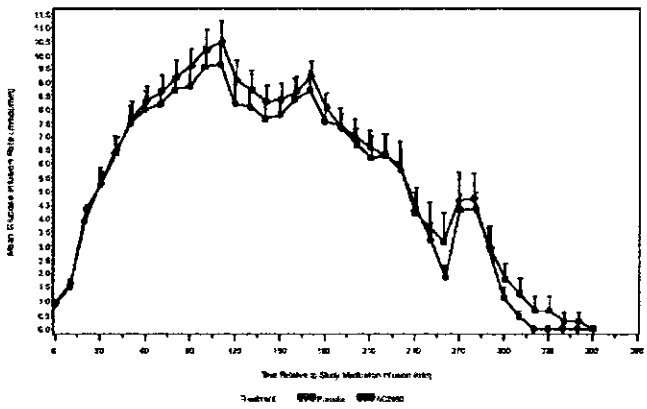
Figure 3: Mean (SD) Plasma AC2993 Concentration-Time Curve by Treatment (Evaluable Subjects in Study 2993-111 [N=11])



PHARMACODYNAMIC RESULTS:

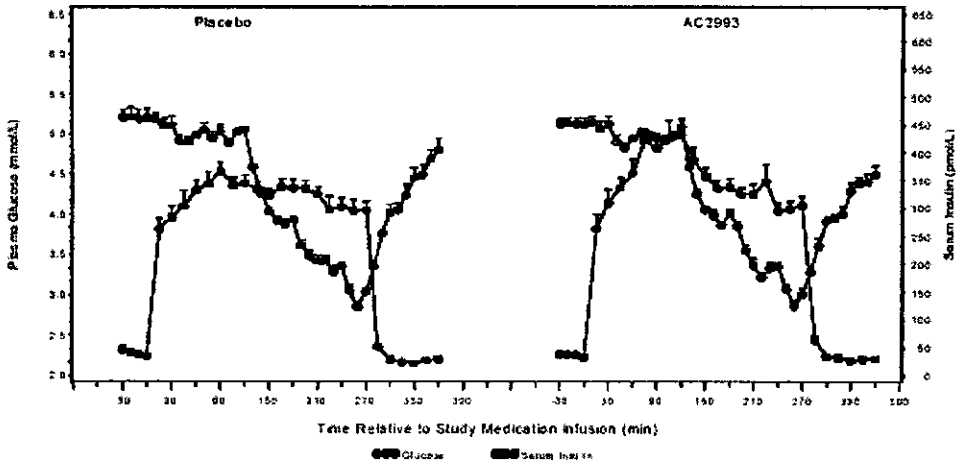
Plasma Glucose: Glucose concentrations for the placebo and AC2993 treatments were similar over the entire 360 minute treatment period. Target glucose concentrations of approximately 5 mmol/L during 90-120 min, 4 mmol/L during 120-180 min, and 3.2 mmol/L (180-240 min) were maintained during the last 30 minutes of each step. At the onset of the recovery period from insulin-induced hypoglycemia (270 to 360 minutes), the insulin infusion was terminated and plasma glucose concentrations were increased to 3.2 mmol/L to ensure subject safety; recovery was assessed for a further 90 minutes. The variable glucose infusion may have been continued if needed to prevent the plasma glucose concentrations from dropping below 3.2 mmol/L. The total amount of glucose infused during the recovery period for each treatment arm was similar (12695.21 mmol/L, AC2993 vs. 10380.78 mmol/L, placebo). Since the 95% confidence interval for the difference was (-3596.18, 7868.22) and included zero, this difference was not statistically significant.





Serum Insulin Secretion Rates: Mean serum insulin secretion rates were derived from the standard parameters for C-peptide distribution and clearance from the C-peptide concentration profile. Prior to infusion of study medication (-30 to 0 min), the mean insulin secretion rate was similar for both treatments. Following infusion of AC2993, at glucose concentrations of approximately 5 mmol/L (90-120 min), the mean insulin secretion rate was approximately 3.5 times higher with AC2993 treatment (LS mean: 352.53 pmol/min) compared with placebo treatment (LS mean: 99.66 pmol/min) demonstrating the insulinotropic effect of AC2993. The difference between the treatments was statistically significant with the LS mean for the difference of 252.88 pmol/min. The 95% confidence interval for the difference did not include zero (158.67, 347.08). As glucose concentrations decreased from 5 mmol/L to 4 mmol/L, the mean insulin secretion rate decreased during both treatments but the decrease was most marked during AC2993 treatment (LS mean: 59.70 pmol/min at 150-180 min). As glucose concentrations continued to decrease, the mean insulin secretion rates declined progressively and were similar to those observed with placebo treatment. There were no statistically significant differences in insulin secretion rates between the treatments during hypoglycemia (glucose concentrations ranging from 3.2 mmol/L to 4.0 mmol/L). During the recovery period (270-360 min) similar increases in the insulin secretion rates were observed for both treatments (62.78 pmol/min, AC2993 vs. 49.90 pmol/min, placebo).

Figure 6: Mean Serum Insulin Concentration-Time Curves by Treatment During the Glycemic Steps (Evaluable Subjects in Study 2993-111 [N=11])



Plasma Glucagon: Mean glucagon concentrations were similar for both treatments prior to infusion of study medication (-30 to 0 min). The mean glucagon concentration was lower with AC2993 treatment compared with placebo at glucose concentrations of approximately 5 mmol/L (14.91 ng/L, AC2993 treatment vs. 28.40 ng/L, placebo treatment; 90-120 min). Glucagon concentrations rose in response to hypoglycemia with both AC2993 and placebo treatment. At glucose concentrations of approximately 4 mmol/L (150-180 min), the mean glucagon concentrations increased for both treatments, with lower concentrations still observed with AC2993 treatment. This difference was statistically significant (geometric LS mean of 26.86 ng/L, AC2993 vs. 39.07 ng/L, placebo) with the geometric LS mean ratio of 0.69. The 95% confidence interval for the ratio did not include 1 (0.53, 0.89). At a glucose concentration of approximately 3.4 mmol/L (210 min), slightly higher concentrations of glucagon were observed with AC2993 treatment until 270 minutes. The difference at the 240-270 min time period was statistically significant (geometric LS mean at the 240 min, 255 min, and 270 min time points was 205.86 ng/L, AC2993 vs. 157.36 ng/L, placebo) with the geometric LS mean ratio of 1.28 and a 95% confidence interval for the difference which did not include zero (1.02, 1.61). At 270 min (glucose concentration of approximately 3 mmol/L) when the fixed rate insulin infusion was terminated and plasma glucose concentrations were rapidly raised to ε 3.2 mmol/L, glucagon concentrations declined rapidly in both treatments achieving similar concentrations at 300 min (geometric LS mean: 233.91 ng/L at 270 min vs. 77.64 ng/L, at 300 min for AC2993; 177.27 ng/L, at 270 min vs. 78.55 ng/L, at 300 min for placebo). There were no statistically significant differences between treatments for AUC (0-360min), AUC (270-360 min), Cave (0-360 min), Cave(270-360 min), and Tmax (0-360 min).

Serum Growth Hormone, Plasma Norepinephrine, Plasma Epinephrine, and Serum Free Fatty Acids: There were no statistically significant differences between treatments in mean serum growth hormone, plasma norepinephrine, epinephrine, and serum free fatty acids during various glucose concentrations over the 360 min treatment period.

Serum Cortisol: Mean serum cortisol concentrations were similar between treatments prior to infusion of study medication (-30 to 0 min). Higher cortisol concentrations were observed with AC2993 treatment at glucose concentrations ranging from approximately 5 mmol/L to 2.7 mmol/L (60 to 270 min). The difference in serum cortisol concentrations between treatments at glucose concentrations of approximately 5 mmol/L (90-120 min) and 4 mmol/L (150-180 min) was statistically significant, with the geometric LS mean ratio of 1.29 and 1.31. The range of the 95% confidence interval for the ratio did not include 1 (1.01, 1.65) and (1.16, 1.48) for the 90-120 min and 150-180 min, respectively. Mean serum cortisol concentrations peaked at glucose concentrations of approximately 3.5 mmol/L for both treatments and declined with increasing glucose concentrations during the recovery period. The transient rise

in cortisol has been observed in previous studies with AC2993 treatment. AUC (0-360min) and Cave (0-360 min) were significantly higher with AC2993 treatment compared with placebo (AUC: 117958.52 nmol•min/L, AC2993 treatment vs. 105879.11 nmol•min/L, placebo treatment; Cave: 327.66 nmol/L AC2993 treatment vs. 294.11 nmol/L, placebo treatment). There were no statistically significant differences in cortisol between treatments for AUC(270-360 min), Cave (270-360 min), Cmax (0-360 min), and Tmax (0-360 min).

SAFETY RESULTS:
Adverse Events: No notable differences in adverse event reporting were observed between both treatments. A total of four subjects (33.3%) experienced five treatment-emergent adverse events during the study. Three (25.0%) were receiving placebo treatment at the time of the event and one (8.3%) was receiving AC2993 treatment. All three adverse events experienced during placebo treatment were considered as mild or moderate in intensity by the investigator. The one event of nausea experienced by a subject during AC2993 treatment was considered mild. The most common events exeprienced were nausea and headache (2 subjects; 16.7%). One subject receiving placebo and one receiving AC2993 experienced nausea. Both events of headache were experienced by subjects when they were receiving placebo treatment.

Deaths: There were no deaths during the study.

Serious Adverse Events: There were no serious adverse events during the study.

Withdrawals Due to Adverse Events: One subject withdrew from the study due to abnormal liver function tests on Day 2 of Period 1 following placebo treatment. The event was classified as moderate in intensity and probably not related to study medication. The subject did not receive AC2993 treatment. Clinical Laboratory Values: No clinically meaningful differences were noted in clinical laboratory measures following AC2993 or placebo administration except for the one subject who withdrew due to abnormal liver function tests.

Vital Signs, Physical Examination, and 12-Lead Electrocardiogram: No clinically meaningful differences were noted in vital signs, physical examination findings, or ECGs following AC2993 or placebo administration. A slight increase in resting heart rate was observed for subjects treated with AC2993 compared with placebo. The mean (SD) change in resting heart rate from preinfusion Day 1 for periods 1 and 2 were -0.33 (3.386) bpm, placebo vs. 6.50 (3.271) bpm, AC2993 (Period 1) and 2.00 (5.550) bpm, placebo vs. 9.00 (7.176) bpm, AC2993 (Period 2), respectively. No subject experienced an adverse event due to this change.

CONCLUSION: Continuous infusion of AC2993 (0.066 pmol/kg/min; 0.4 µg/kg/day) was well tolerated in healthy volunteers. No safety concerns were identified. The study clearly demonstrated the glucose-dependent insulinotropic action of AC2993 in healthy volunteers as evidenced by a 3 to 3.5-fold increase in the insulin secretion rate with AC2993 treatment at glucose concentrations of 5 mmol/L. The insulin secretion rate decreased markedly at glucose concentrations of approximately 4.5 mmol/L. When plasma glucose concentrations were at or below 4 mmol/L, the insulinotropic effect of AC2993 was negligible as compared with placebo. The counterregulatory response as measured by glucagon, epinephrine, norepinephrine, cortisol, and growth hormone concentrations remained intact during hypoglycemia with AC2993 treatment. As a result, the recovery time from hypoglycemia was the same for each treatment indicating that AC2993 does not impair the ability to reverse insulin induced hypoglycemia.

2993-118

Title of Study: A Randomized, Open-Label, Four-Way Crossover Study to Examine the Bioavailability of AC2993 Injected Subcutaneously at Three Anatomical Sites in Subjects With Type 2 Diabetes Mellitus

Investigators and Study Centers: Multicenter (3 investigators, 3 study centers)

Publication (Reference): Calara F, Taylor K, Han J, Aisporna M, Zabala E, Carr E, et al. Effect of injection site on relative bioavailability of Exenatide (synthetic exendin-4). *Clin Pharmacol Ther.* 2004;75:P58. Abstract PII-25

Studied Period: 04 November 2002 (First Subject Dosed) to 21 February 2003 (Last Subject's Final Visit/Procedure)

Phase of Development: 2

Objectives: Primary Objectives: To determine the relative bioavailability of exenatide injected subcutaneously at three anatomical sites in subjects with type 2 diabetes mellitus. To determine the absolute bioavailability of exenatide injected subcutaneously at three anatomical sites in subjects with type 2 diabetes mellitus. Secondary Objective: To assess the safety and tolerability of exenatide injected subcutaneously at three anatomical sites in subjects with type 2 diabetes mellitus.

Methodology: Open-label, four-way crossover study in subjects with type 2 diabetes mellitus designed to determine the relative and absolute bioavailability of exenatide administered by subcutaneous (SC) injection at three anatomical sites. Each day during the 4-day treatment period of this inpatient study, subjects were to receive one of four treatments: a SC injection of exenatide (10 µg) in the abdomen, arm, or thigh; or an intravenous (IV) bolus dose of exenatide (1 µg). The exenatide 10 µg SC treatment in the abdomen was to be used as the reference treatment to determine the relative bioavailability of exenatide 10 µg SC treatments in the arm and thigh. The IV bolus dose was to be used as the reference treatment to determine the absolute bioavailability of the SC treatments. Subjects were to be randomly assigned to one of four treatment sequences, and were to receive treatments in the order specified by their assigned sequence. The four treatment sequences were to be ABCD, CADB, DCBA, and BDAC, where treatment A = exenatide 10 µg SC (abdomen); B = exenatide 10 µg SC (arm); C = exenatide 10 µg SC (thigh); D = exenatide 1 µg IV (arm vein). The glomerular filtration rate (GFR) for individual subjects was to be measured using a radioiodinated (^{125}I) iothalamate clearance method. GFR measurement was to allow the exploration of the relationship between the pharmacokinetics of exenatide and renal elimination.

Number of Subjects: The study population consisted of 28 randomized subjects (i.e., all subjects who were allocated a randomization number), 28 intent-to-treat subjects (i.e., randomized subjects who received at least one dose of exenatide), and 25 evaluable subjects (i.e., randomized subjects who completed all 4 days of the 4-day treatment period in compliance with the protocol and had adequate blood samples for reliable evaluation of the primary pharmacokinetic parameter).

Key Demographics and Baseline Characteristics: The intent-to-treat study population consisted of 28 subjects with type 2 diabetes mellitus. The composition of the intent-to-treat population was as follows: 78.6% were male; 57.1% were Caucasian, 35.7% were Black, and 7.1% were Hispanic. Subjects' mean ± SD age was 56.2 ± 8.1 years. Mean height was 173.5 ± 8.70 cm, mean weight was 100.2 ± 20.84 kg, and mean body mass index (BMI) was 33.0 ± 5.14 kg/m2. The average duration of diabetes was 7.8 ± 10.15 years (mean range, 4.5 years to 11.9 years). Mean glycosylated hemoglobin, specific A_{1c} fraction (HbA_{1c}) was 8.0 ± 1.7%. A total of 10 subjects (35.7%) received one or more concomitant medications for the treatment of type 2 diabetes. The following types of antidiabetic medications were received by the specified number and percentage of subjects (intent-to-treat population [N = 28]) during the study: biguanides (5 subjects, 17.9%), sulfonylureas (6 subjects, 21.4%), or biguanide and sulfonylurea combinations (2 subjects, 7.1%).

Subject Disposition: Of 28 randomized subjects, 25 subjects (89.3%) completed the study and 3 subjects (10.7%) withdrew early.

Diagnosis and Main Criteria for Inclusion: According to the protocol, approximately 24 subjects with type 2 diabetes mellitus were to be included in the study. The main criteria for inclusion were type 2 diabetes treatment regimen (metformin, a sulfonylurea, a combination of metformin and a sulfonylurea, and/or diet modification and exercise); sex (males or postmenopausal females); age (18 to 65 years, inclusive); BMI (27 kg/m2 to 45 kg/m2, inclusive); fasting plasma glucose (< 280 mg/dL); and HbA_{1c} (Υ<= 12%). Subjects who received insulin therapy within 3 months prior to screening were to be excluded.

Test Product; Dose and Mode of Administration; Formulation No., Lot No.: Exenatide, 0.25 mg/mL; 10 µg SC injection, 1 µg intravenous bolus; AC2993-F8, 01-0302WP.

Duration of Treatment: Four days.

Reference Therapy, Dose and Mode of Administration, Batch No: None

Criteria for Evaluation:
Pharmacokinetics:
Relative Bioavailability: The bioavailability of exenatide 10 µg SC, administered at three anatomical sites (abdomen, arm, and thigh), was to be compared in subjects with type 2 diabetes mellitus. The exenatide 10 µg SC treatment administered in the abdomen (specifically, the anterior abdominal wall, the injection location for exenatide treatment in clinical studies to date) was designated as the reference treatment for the comparison. Plasma exenatide concentrations were to be assessed at selected time points during a 10-hour period following each treatment.
Absolute Bioavailability: An exenatide 1 µg IV bolus dose was used as a reference to determine the absolute bioavailability of exenatide 10 µg SC treatments administered at three anatomical sites (abdomen, arm, and thigh). Plasma exenatide concentrations were to be assessed at selected time points for a 10-hour period following treatment.
Safety: An adverse event review and vital sign measurements were to be performed daily (Day -1 through Study Termination); clinical laboratory measures (hematology, clinical chemistry, and urinalysis) were to be performed on Day -1 and at Study Termination; and a physical examination and ECG were to be performed at Study Termination. During the 10-hour pharmacokinetic sampling period, study-site staff were to monitor blood glucose concentrations using finger-stick blood glucose measurements in the event that a subject reported symptoms consistent with hypoglycemia.

Statistical Methods:
Pharmacokinetics:
Key pharmacokinetic parameters $AUC_{(0\text{-inf})}$ (primary measure) and C_{max} (secondary measure) were calculated from plasma exenatide concentrations, summarized as descriptive statistics, and compared using parametric analysis. In addition, $AUC_{(0\text{-}600\ min)}$, T_{max}, and $t_{1/2}$ were calculated and descriptively summarized.
Relative Bioavailability: The relative bioavailability of exenatide 10 µg SC, administered at three anatomical sites (abdomen, arm, and thigh), was assessed by comparing $AUC_{(0\text{-inf})}$ for the treatments. Specifically, the bioavailability of SC treatments in the arm and thigh relative to the abdomen was to be estimated by the ratios of the geometric least squares (LS) means of $AUC_{(0\text{-inf})}$ (90% confidence interval for the ratio of the geometric LS means). C_{max} for the SC treatments was also compared.
Absolute Bioavailability: Prior to summary and analysis, $AUC_{(0\text{-inf})}$ for the 1 µg IV bolus dose of exenatide was multiplied by a factor of 10 to adjust for the dose differential between the IV bolus treatment and the 10 µg SC treatments. The absolute bioavailability of exenatide following treatment at each of the three SC injection sites was estimated by the ratios of the geometric LS means of $AUC_{(0\text{-inf})}$ between each SC site and the IV bolus dose of exenatide (95% confidence intervals for ratios of the geometric LS means were calculated). Of note, three subjects (29609, 29606, 30609) were observed to have biologically implausible or otherwise erroneous data for pharmacokinetic measurements at some time points. A full description of the excluded data is provided in Section 3.7.2.1 in the body of the report. Parametric statistics were calculated both including and excluding these data. Clearance, volume of distribution, and GFR (corrected and uncorrected) were summarized for the evaluable population. Of note, one subject had a high outlier clearance value (subject 30609, clearance = 91.9 L/h, compared with the clearances for all other subjects

[Min, Max: 3.68 L/h to 27.16 L/h]). Descriptive summaries were generated both including and excluding this subject.

Safety: Adverse events were summarized by presenting subject incidence and event frequency in each system organ class and in each preferred term defined by Medical Dictionary for Regulatory Activities (MedDRA™), by treatment. Treatment-emergent adverse events, defined as those events occurring on or after Day 1 through Study Termination (end of Day 4), were assigned to treatment and summarized. Chemistry, hematology, urinalysis, concomitant medications, vital signs, and ECG data were summarized descriptively. Physical examination data were listed.

SUMMARY - CONCLUSIONS:

PHARMACOKINETIC RESULTS:

Relative Bioavailability: An evaluation of the pharmacokinetics of exenatide after subcutaneous administration at three anatomical sites (abdomen, arm, and thigh) showed that the site of injection did not substantially influence the pharmacokinetic profile of exenatide.

Relative Bioavailability of Exenatide 10 µg Subcutaneous Treatments (Population: Evaluable Subjects in Study 2993-118 [N = 25])

Parameter[1]	Treatment	
Statistics [1]	Arm	Thigh
$AUC_{(0\text{-}inf)}$		
Geometric LS Mean Ratio	0.93	0.97
Geometric 90% CI Ratio	(0.819, 1.048)	(0.857, 1.096)
C_{max}		
Geometric LS Mean Ratio	0.91	0.88
Geometric 90% CI Ratio	(0.849, 1.152)	(0.752, 1.020)

[1] Reference treatment: exenatide 10 µg SC (abdomen)

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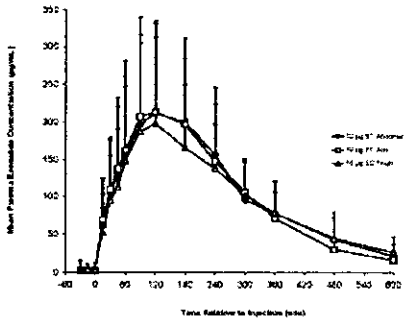
Mean plasma exenatide concentration-time curves were congruous for exenatide 10 µg SC treatments administered at three anatomical sites (abdomen, arm, and thigh).

Mean (+SD) Plasma Exenatide Concentration-Time Curves for Subcutaneous Treatments Population: Evaluable Subjects in Study 2993-118 [N=25]



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Plasma exenatide concentration-time curves for individual subjects are generally uniform among the exenatide 10 µg SC treatments. Low intrasubject (within subject) variability for SC treatments is evidenced by an intrasubject geometric coefficient of variation (geometric CV) of 26% for AUC(0-inf) obtained from the mixed-effect model.

Pharmacokinetic parameters AUC(0-inf), Cmax, Tmax, and t1/2 were calculated from the profile of plasma exenatide concentration values for each SC treatment and descriptively summarized. Key pharmacokinetic parameters (mean AUC(0-inf) and mean Cmax) were comparable among the exenatide 10 µg SC treatments at three anatomical sites (abdomen, arm, and thigh). Mean AUC(0-inf) was 71910.23 pg.min/mL (abdomen), 64813.60 pg.min/mL (arm), and 67775.14 pg.min/mL (thigh). Mean Cmax was 250.52 pg/mL (abdomen), 245.44 pg/mL (arm), and 220.12 pg/mL (thigh). Results indicate that the bioavailability (i.e., the rate and extent of absorption) of exenatide after SC administration in the arm or thigh is essentially the same as that after SC administration in the abdomen.

Absolute Bioavailability: Estimates of absolute bioavailability for SC treatments are provided in the following table.

Absolute Bioavailability of Exenatide 10 µg SC Treatments
Population: Evaluable Subjects in Study 2993-118 [N=25])

	Exenatide 10 µg SC Treatment		
Parameter/ Statistics[1]	Abdomen	Arm	Thigh
$AUC_{(0\text{-}inf\ min)}$			
Geo. LS Mean Ratio	1.21	1.13	1.18
Geo. 95% CI Ratio	(0.956, 1.534)	(0.891, 1.429)	(0.930, 1.491)

[1] Reference treatment: exenatide 1 µg IV bolus

While these results suggest a high absolute bioavailability, results above 1.00 (100% bioavailability) are implausible. Such variability in the IV bolus data is contrary to theoretical expectations and likely attributable to methodological issues related to administration of the IV dose; therefore, no conclusions may be drawn. Clearance, Glomerular Filtration Rate, and Volume of Distribution: Although the distribution was highly variable due to the IV bolus dose assessments being unreliable, total clearance and GFR were observed to have a similar trend; median clearance was 9.47 L/h and median uncorrected GFR was 8.21 L/h. In general, individuals with a higher measured GFR tended to have a higher calculated clearance suggesting that exenatide elimination is largely attributable to renal clearance. This observation is consistent with available preclinical data. Median Vd for the IV bolus dose was 21.84 L.

SAFETY RESULTS:
Adverse events were recorded for the intent-to-treat population (N = 28). A total of 19 subjects (67.9%) experienced at least one treatment-emergent adverse event during the study. The most common adverse events were nausea (10 subjects, 35.7%), headache (7 subjects, 25.0%), vomiting (6 subjects, 21.4%), and dizziness (5 subjects, 17.9%). Adverse events were primarily associated with the 10 µg SC treatments and were balanced among the anatomical injection sites. Two subjects (22901, 22907) experienced moderate hypoglycemia associated with exenatide 10 µg SC treatment. These events were detected by finger-stick blood glucose measurements performed by the investigator. Both subjects recovered with concomitant therapy and continued in the study.

Deaths: There were no deaths during the study.

Serious Adverse Events: Three subjects (22902, 22903, 22904) experienced serious, severe study medication overdoses. Overdoses were 10-fold (exenatide 100 µg SC) relative to the planned dose. Effects noted secondary to the overdoses included severe nausea, severe vomiting, and rapidly declining blood glucose concentrations. One of the three overdosed subjects (22903) experienced severe hypoglycemia. All received concomitant medications, including an antiemetic and continous IV infusion of 5% dextrose solution. The intensity of secondary overdose effects were correlated with plasma exenatide concentrations; the most severe effects occurred when plasma exenatide concentrations were highest. The intensity of secondary overdose effects subsided as plasma exenatide concentrations declined. All subjects recovered without complication and withdrew from the study. These overdoses are the highest exenatide overdoses to date. Withdrawals Due to Adverse Events: Three subjects (22902, 22903, 22904) experienced serious, severe study medication overdoses that led to withdrawal from the study (described in the context of Serious Adverse Events).

Clinical Laboratory Values: No clinically notable changes between baseline and study termination were observed in mean hematology, chemistry, and urinalysis values.
Vital Signs, Physical Examination, and Electrocardiogram: There were no notable effects on vital sign measurements (temperature, respiratory rate, sitting systolic blood pressure, sitting diastolic blood pressure, and heart rate) physical examination findings, or ECG results upon administration of protocol-specified doses of exenatide (10 µg SC and 1 µg IV). An acute and transient elevation in hemodynamic measures (sitting systolic blood pressure, sitting diastolic blood pressure, and heart rate) was observed for subjects who received exenatide overdoses (100 µg SC). Consistent with the observed elevation of hemodynamic measures, acute and transient sinus tachycardia (not clinically significant) was detected by ECG.

CONCLUSION: The bioavailability (i.e., the rate and extent of absorption) of exenatide after SC injection in the thigh or arm is shown in this study to be essentially the same as the bioavailability observed after SC injection in the abdomen. Absolute bioavailability could not be assessed based on results of this study. In general, treatment with exenatide 10 µg SC appeared to be well-tolerated. Results of this study indicate that subcutaneous injection of exenatide in the thigh or arm should not compromise efficacy or safety compared with subcutaneous injection of exenatide in the anterior abdominal wall.
Date of the report: 28 January 2004

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Number of Subjects: The study population consisted of 40 randomized subjects (i.e., all subjects allocated a randomization number), 40 intent-to-treat (ITT) subjects (i.e., all subjects who received at least one dose of randomized study medication [exenatide or placebo]), and 39 evaluable subjects (i.e., all ITT subjects who completed at least two treatment periods in compliance with the protocol).

Key Demographics: The ITT study population consisted of 40 healthy subjects. The ITT population was 52.5% female and 87.5% Hispanic. The mean age of the subject population was 40.6 ± 10.3 years. Mean weight was 74.3 ± 10.3 kg, and mean body mass index (BMI) was 26.7 ± 3.0 kg/m$_2$. Demographic and baseline characteristics appeared to be well balanced across treatment sequences.

Subject Disposition: Of the 40 randomized subjects, 39 (97.5%) completed all study procedures and visits (Screening, Day 1 to Day 6, and Study Termination) and 1 (2.5%) subject withdrew early.

Diagnosis and Main Criteria for Inclusion: Healthy male or female subjects 18 to 65 years of age with a body mass index (BMI) of 20 kg/m$_2$ to 35 kg/m$_2$, inclusive, at Visit 1 (Screening).

Test Product, Dose and Mode of Administration, Batch No.: Exenatide, 0.25 mg/mL; 10 µg SC injection; pen-cartridge device [redacted] administration of SC injection; AC2993-F8, 02-0901KP.

Duration of Treatment: Total study duration was estimated to be 7 days, not including the interval between Screening (Visit 1) and Day -1 (Visit 2), an interval that was not to exceed 14 days.

Reference Therapy, Dose and Mode of Administration, Batch No: placebo; 0.04 mL per subject; pen-cartridge device [redacted] administration of SC injection; PBO-F12, 02-0304KE. [redacted] adult strength elixir (500 mg/15 mL); 30.0 mL per subject; PO administration; Lot number: 0045-0500-08.

Criteria for Evaluation:
Primary Study Endpoints:
Plasma Acetaminophen Pharmacokinetics: The primary study endpoints included the area under the plasma acetaminophen concentration-time curve from 0 to 12 h ($AUC_{(0\text{-}12\ h)}$), the average mean plasma acetaminophen concentration (C_{ave}), the peak plasma acetaminophen concentration (C_{max}), the time to the maximum plasma acetaminophen concentration (T_{max}), and the terminal half-life ($t_{1/2}$) of plasma acetaminophen concentrations. Plasma Exenatide Pharmacokinetics: Plasma exenatide pharmacokinetic parameters included the area under the plasma exenatide concentration-time curve from 0 to 8 h ($AUC_{(0\text{-}8\ h)}$), the average mean plasma exenatide concentration (C_{ave}), the peak exenatide concentration (C_{max}), the duration from the time of exenatide dosing to the time of the first maximum observed concentration (T_{max}), and the terminal half-life ($t_{1/2}$) of plasma exenatide concentrations.

Safety: Safety and tolerability were assessed by adverse events, hematology, chemistry, urinalysis, concomitant medication use, vital signs, physical examination, and 12-lead electrocardiogram.

Statistical Methods:
Plasma Acetaminophen Pharmacokinetic Analyses: Plasma acetaminophen pharmacokinetic analyses were summarized using the evaluable population. Plasma acetaminophen concentrations at each sampling point were listed and summarized descriptively (n, mean, standard deviation [SD], median, minimum, and maximum). All plasma acetaminophen pharmacokinetic parameters were listed and summarized descriptively by treatment. Descriptive statistics for plasma acetaminophen $AUC_{(0\text{-}12\ h)}$, C_{ave}, and C_{max} included: untransformed data (n, mean, SD, median, CV, minimum, and maximum); natural log transformed data (mean and SD); and transformed data on the original scale (geometric mean and standard error [SE]). Descriptive statistics for plasma acetaminophen T_{max} and $t_{1/2}$ included: n, mean, SD, median, minimum, and maximum. Plasma Exenatide Pharmacokinetic Analyses: Plasma exenatide pharmacokinetic analyses were similar to those performed for acetaminophen pharmacokinetics.
Safety: All safety data were analyzed using the ITT population. Safety data were listed and summarized descriptively (n, mean, SD, median, minimum, and maximum).

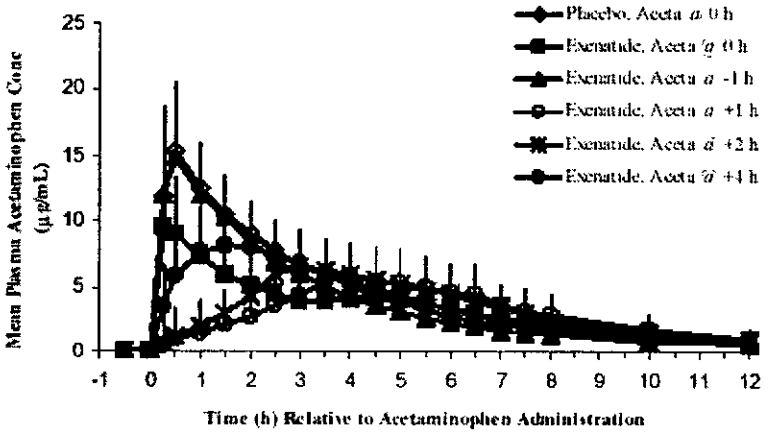
Changes in the Planned Analyses: For plasma acetaminophen pharmacokinetic parameters, 95% confidence intervals for the least square means (LS means) were derived from the mixed-effect model as opposed to 90% confidence intervals as described in the study protocol. The 90% confidence intervals for the LS means mentioned in the protocol was a typographical error. The study protocol stated that a sufficient number of subjects were to be screened to achieve 30 subjects who would complete all treatment periods (five subjects per treatment sequence). To ensure precise evaluation of exenatide's effects on acetaminophen absorption, however, if a subject vomited within one hour of acetaminophen ingestion on a treatment day, the PK data from that day were excluded from the analyses. Thus, additional subjects were randomized (total of 40) to ensure that each treatment had at least 30 usable PK profiles collected.

PLASMA ACETAMINOPHEN PHARMACOKINETIC RESULTS:

Mean Plasma Acetaminophen Concentration-Time Profiles:

To evaluate the effect of exenatide administration on acetaminophen pharmacokinetics, mean plasma acetaminophen concentration-time profiles following acetaminophen administration at 0 h with placebo and at 0, -1, +1, +2, +4 h relative to exenatide dosing are graphically depicted below.

Mean (+SD) Plasma Acetaminophen Concentration-Time Curve by Treatment Population: Evaluable (N=39)



Aceta = acetaminophen

Plasma acetaminophen pharmacokinetic parameters are presented by treatment in Table 9.

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Table 9: Plasma Acetaminophen Pharmacokinetic Parameters by Treatment
Population: Evaluable Subjects in Study 2993-121 (N=39)

Parameter Statistic	Placebo Aceta 0 h	Exenatide Aceta -1 h	Exenatide Aceta 0 h	Exenatide Aceta +1 h	Exenatide Aceta +2 h	Exenatide Aceta +4 h
	N=39	N=39	N=39	N=39	N=39	N=39
$AUC_{(0-12\ h)}$ (µg•h/mL) [1]						
n	39	39	37	34	39	39
Mean (SD)	52.6 (14.4)	47.0 (13.0)	41.6 (14.0)	40.6 (12.0)	39.8 (12.4)	45.0 (13.8)
Median	50.3	44.4	40.0	40.3	39.7	43.8
Geometric Mean (SE)[2]	50.7 (2.2)	45.2 (2.0)	39.1 (2.4)	38.7 (2.1)	37.8 (2.1)	42.9 (2.2)
Min, Max	[redacted]					
C_{max} (µg/mL)						
n	39	39	37	34	39	39
Mean (SD)	4.4 (1.2)	3.9 (1.1)	3.5 (1.2)	3.4 (1.0)	3.3 (1.0)	3.7 (1.2)
Median	4.2	3.7	3.3	3.4	3.1	3.7
Geometric Mean (SE)[2]	4.2 (0.2)	3.8 (0.2)	3.3 (0.2)	3.2 (0.2)	3.1 (0.2)	3.6 (0.2)
Min, Max	[redacted]					
$C_{max,1}$ (µg/mL)						
n	39	39	37	34	39	39
Mean (SD)	16.7 (4.9)	16.9 (4.8)	10.6 (4.6)	7.3 (2.5)	7.7 (2.5)	9.8 (3.0)
Median	16.4	15.9	9.9	6.7	7.4	10.0
Geometric Mean (SE)[2]	16.0 (0.8)	15.3 (0.8)	9.8 (0.7)	6.9 (0.4)	7.3 (0.4)	9.3 (0.5)
Min, Max	[redacted]					
T_{max} (h)						
n	39	39	37	34	39	39
Mean (SD)	0.6 (0.3)	0.6 (0.3)	0.9 (1.6)	4.2 (4.2)	3.3 (1.2)	1.6 (1.0)
Median	0.5	0.5	0.5	4.0	3.0	1.5
Min, Max	0.3, 1.5	0.3, 1.5	0.3, 6.0	1.0, 6.5	0.5, 6.5	0.5, 5.0
$t_{1/2}$ (h)						
n	39	39	37	34	39	39
Mean (SD)	2.5 (0.5)	2.9 (1.1)	3.0 (1.1)	2.6 (0.9)	2.5 (0.6)	2.9 (1.0)
Median	2.4	2.6	2.7	2.5	2.4	2.7
Min, Max	[redacted]					

Note: Study medication (exenatide 10 µg or placebo) was administered at 0 h, 15 minutes prior to breakfast.
Treatments represent the timing of acetaminophen (1000 mg) administration relative to study medication administration.
[1] Time is relative to acetaminophen administration
[2] Geometric Mean (X) = exp(mean(log X)), Geometric SE (X) = Geometric Mean * SE (log X)

Following co-administration of acetaminophen with placebo 15 minutes prior to the meal, mean plasma acetaminophen concentrations increased rapidly, and reached the peak concentration (15.3 µg/mL) at approximately 0.5 h. Following acetaminophen administration at -1 h relative to exenatide administration, mean plasma acetaminophen concentrations increased rapidly, reached peak concentrations at approximately 0.5 h after acetaminophen dosing (14.8 µg/mL), and steadily declined thereafter, with concentrations approaching minimal detectable limits at 12 h. The maximum acetaminophen concentrations for the -1 h treatment was attained prior to injection of exenatide or ingestion of the meal, thus, the pharmacokinetic profile for this treatment was similar to that of placebo. Following acetaminophen and exenatide co-administration at 0 h, early acetaminophen plasma concentrations were reduced compared to placebo, yet substantial plasma concentrations of acetaminophen were achieved by 0.5 h. The mean maximum plasma acetaminophen concentration was reached at 0.25 h (9.6 µg/mL). The concentration-time profiles observed for acetaminophen administration at +1, +2, and +4 h post-exenatide dosing showed acetaminophen plasma concentrations in the absorptive phase were reduced compared to placebo. The mean plasma acetaminophen concentrations at the 0.25 h post dose time point in the +1, +2, and +4 h post-exenatide groups were 0.54 µg/mL, 0.76 µg/mL, and 3.47 µg/mL, respectively.

The greatest reduction in mean maximum plasma concentration and longest prolongation of time to reach maximum plasma concentration, compared to placebo (0 h) were in the +1 and +2 h post-exenatide dosing groups. The mean maximum plasma acetaminophen concentration following acetaminophen administration at +1 and +2, post-exenatide dosing was reached at 4.0 h (5.8 µg/mL), and 3.0 h (6.6 µg/mL) respectively. A smaller effect was observed when acetaminophen was administered 4 hours after exenatide injection (mean maximum plasma concentration was reached at 1.5 h [8.2 µg/mL]). The effect of exenatide to slow the rate of absorption of acetaminophen appeared to be limited to the initial 4-hour period following exenatide dosing. Thereafter (4.0 to 12.0 h), similar plasma acetaminophen concentrations were observed for all exenatide groups compared with placebo.

Plasma Acetaminophen Pharmacokinetic Parameters:

Plasma Acetaminophen $AUC_{(0-12\ h)}$. Acetaminophen extent of exposure, defined as $AUC_{(0-12\ h)}$, was reduced by no more than 25% when acetaminophen was administered at varying times (0, -1, +1, +2, +4 h) in relation to exenatide dosing in comparison to when acetaminophen was co-administered with placebo. Plasma acetaminophen $AUC_{(0-12h)}$ means ranged from 39.8 µg.h/mL to 47.0 µg.h/mL across exenatide

treatments, and were contained within the range of individual AUCs observed when placebo was administered with acetaminophen (0 h).

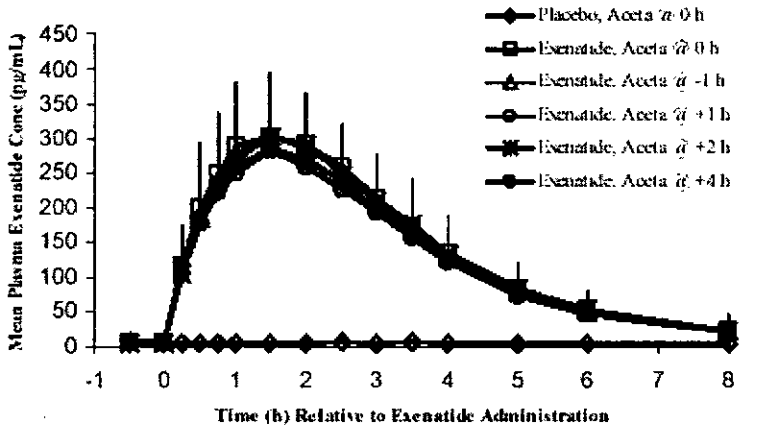
Plasma Acetaminophen C_{ave}. There were minimal effects of exenatide treatment on acetaminophen C_{ave} values. Mean plasma acetaminophen C_{ave} ranged from 3.3 µg/mL to 3.9 ∝g/mL when acetaminophen was administered at 0, -1 h, +1 h, +2 h, +4 h relative to exenatide administration and 4.4 ∝g/mL when placebo was co-administered with acetaminophen (0 h).

Plasma acetaminophen C_{max}. Mean plasma acetaminophen C_{max} values were similar following administration of acetaminophen one hour prior to exenatide administration (16.0 µg/mL) and when acetaminophen was co-administered with placebo (16.7 µg/mL). Mean plasma acetaminophen C_{max} was reduced by 36.5% when acetaminophen was co-administered at 0 h with exenatide (10.6 µg/mL), and by 56.3% (7.3 µg/mL) and 53.9% (7.7 µg/mL) when administered one or two hours following exenatide injection. Acetaminophen administration 4 hours after exenatide injection resulted in a smaller reduction (41.4%) of C_{max} (9.8 µg/mL) in comparison to when acetaminophen was administered one or two hours following exenatide injection.

Plasma Acetaminophen T_{max}. Mean plasma acetaminophen T_{max} values were the same following administration of acetaminophen one hour prior to exenatide administration (0.6 h) and when acetaminophen was co-administered with placebo (0.6 h). Mean plasma acetaminophen T_{max} was prolonged to 4.2 h, 3.3 h, and 1.6 h when acetaminophen was ingested +1, +2, or +4 hours following exenatide dosing.

Terminal Elimination Half-life. The mean terminal elimination half-life of plasma acetaminophen was unchanged, ranging from 2.5 to 3.0 h when administered at varying times in relation to exenatide administration, compared to 2.5 h when administered with placebo (0 h).

Mean (+SD) Plasma Exenatide Concentration-Time Curve by Treatment Population: Evaluable (N=39)



SAFETY RESULTS:

Adverse Events: Treatment-emergent adverse events were defined as events that began on or after study medication dosing time on Day 1. The overall incidence of treatment-emergent adverse events for the ITT population (N=40) ranged from 41.0% to 67.5% in the exenatide dosing arms compared to 2.6% in the placebo dosing arm. The most frequently reported treatment-emergent adverse event was nausea, with the incidence ranging from 25.6% to 52.5% during treatments when exenatide was administered compared to 0.0% when placebo was administered. Other commonly reported treatment-emergent adverse events included vomiting (range 12.8% to 30.0%), dizziness (range 2.5% to 7.5%), and headache (range 5.1% to 10.3%) during exenatide treatment. Nearly all treatment-emergent adverse events were assessed as treatment-related. The overall incidence of treatment-related adverse events ranged from 41.0% to 67.5% in exenatide treatments, compared to 0.0% in the placebo treatment.

Adverse events were associated primarily with the administration of exenatide and acetaminophen in comparison with placebo and acetaminophen administration and were generally balanced among

acetaminophen administration times. The incidence of nausea and vomiting appeared to be related to the administration times of exenatide and acetaminophen.

SAFETY RESULTS (Continued):
Adverse Events (Continued): Nausea and vomiting occurred at a higher frequency when acetaminophen was administered before exenatide (-1 h) and when exenatide and acetaminophen were co-administered (0 h) in comparison to acetaminophen administration at +1, +2, and +4 h following exenatide dosing. The incidence of nausea was 47.5%, 52.5%, 38.5%, 33.3%, and 25.6% when acetaminophen was administered at -1, 0, +1, +2, and +4 h in relation to exenatide dosing. The incidence of vomiting was 27.5%, 30.0%, 23.1%, 15.4%, and 12.8% when acetaminophen was administered at -1, 0, +1, +2, and +4 h in relation to exenatide dosing. As the post-exenatide interval of acetaminophen administration increased, the frequency of nausea and vomiting decreased. All treatment-emergent adverse events, with the exception of the one event of moderate nausea that led to withdrawal, were assessed as mild in intensity by the investigator. Deaths, Serious Adverse Events, and Withdrawals Due to Adverse Events: There were no deaths or serious adverse events reported in this study. One subject withdrew from the study due to an adverse event of nausea.

Clinical Laboratory Values: There were no unexpected changes in clinical laboratory values. Three subjects had abnormal laboratory values considered clinically significant by the investigator. These abnormal laboratory values included: decreased hemoglobin, hematocrit, elevated urine blood, urine leukocytes, urine WBCs, urine epithelial cells, and urine bacteria, none of which were likely to be due to study medication. Vital Signs, Physical Examinations, and 12-lead Electrocardiogram: Within each study group, no clinically meaningful or unexpected changes were reported in vital signs, physical examinations, or 12-lead ECGs.

CONCLUSIONS:
Effect of exenatide on acetaminophen pharmacokinetics. Exenatide appeared to affect the rate of absorption of acetaminophen when administered with exenatide or during the 4-hour period after exenatide dosing; i.e., acetaminophen C_{max} was lowered (36.5% to 56.3%), and T_{max} was prolonged (0.3 to 3.6 h). The largest reduction in $AUC_{(0\text{-}12\ h)}$, observed in the +2 h treatment, was less than 25%; this difference is judged to be not clinically relevant. The largest effects on acetaminophen absorption were observed when acetaminophen was ingested 1-2 hours following exenatide injection. The changes in absorption appeared to show a trend to return to baseline (placebo) conditions by 4 hours. No effect was observed when acetaminophen was ingested one hour prior to exenatide injection. These results suggest that changes in the rate of absorption of orally administered concomitant medications are likely to be minimized if administration occurs at least 1 h prior to exenatide administration or is postponed until approximately 4 h after exenatide administration.

Safety. Co-administration of oral acetaminophen at varying times in relation to exenatide dosing appeared to be fairly well tolerated in healthy subjects. There appeared to be an increase in gastrointestinal adverse events when acetaminophen was administered 1 hour before exenatide and when acetaminophen and exenatide where co-administered (0 h). As the post-exenatide interval of acetaminophen administration increased, the frequency of gastrointestinal adverse events decreased.

Reviewer's comments:
The reviewer agrees with the sponsor that the rate of absorption of orally administered drugs may be slowed by concurrent treatment of exenatide. Patients should be advised to take oral drugs at or before exenatide use (-1 to 0 hours) to avoid reduced the rate of absorption.

2993-122

Title of Study: A Phase 2, Randomized, Single-Blind, Single-Center Crossover Study to Examine the Effects of Exenatide on First-Phase Insulin Release in Subjects with Type 2 Diabetes Mellitus.

Investigators and Study Centers: [redacted]

Publication (Reference): None

Phase of Development: 2

Studied Period: 12 September 2003 through 7 November 2003

Objectives: Primary Objective: To assess the effects of exenatide on first-phase insulin release in subjects with type 2 diabetes mellitus. Secondary Objective: To assess the effects of exenatide on second-phase insulin release in subjects with type 2 diabetes mellitus.

Methodology: Following enrollment, Group 1 subjects (type 2 diabetes) were domiciled for 4 days/3 nights and Group 2 subjects (healthy controls; reference group) were domiciled for 2 days/1 night. Group 1 subjects were randomly assigned to one of two treatment sequences (AB or BA, where A = saline and B = exenatide). On separate days (Day 2 and Day 4), separated by a one-day wash-out period (Day 3), each Group 1 subject received an intravenous (IV) insulin infusion to reduce plasma glucose to euglycemic concentrations, followed by an infusion of either exenatide (0.05 µg/min for the first 30 min followed by 0.025 µg/min steady-state) or saline in a randomized order. Group 2 subjects received only saline infusions. An intravenous glucose tolerance test (IVGTT) was administered to subjects in both groups during the infusions of exenatide or saline to assess first- and second-phase insulin release in response to a glucose stimulus.

Number of Subjects: 26 (26 intent-to-treat, 25 evaluable)

Subject Disposition: The intent-to-treat (ITT) population comprised 26 subjects: 14 Group 1 and 12 Group 2. Of those, 25 (96.2%) subjects completed the study and 1 (3.8%) was withdrawn early due to an adverse event (AE) (increased white blood cell [WBC] count). The evaluable population comprised 25 (96.2%) subjects who completed infusion procedures on Day 2 (Group 1 and Group 2) and Day 4 (Group 1): 13 subjects in Group 1 and 12 in Group 2.

Key Demographics: The majority of subjects in Groups 1 and 2 were male (78.6% and 75.0%); all subjects were Caucasian. The mean age for Group 1 subjects was 55.5 years and 57.3 years for Group 2 subjects. The mean duration of diabetes for Group 1 subjects was 3.7 years and the mean HbA_{1c} was 6.7%, which was consistent with a population of subjects with well-controlled diabetes. By design, groups were approximately balanced with respect to body mass index (BMI) and other baseline characteristics.

Diagnosis and Main Criteria for Inclusion: Potential Group 1 study subjects were to have type 2 diabetes for at least 3 months treated with diet and exercise modification alone or in combination with metformin or an alpha-glucosidase inhibitor, a fasting plasma glucose of < 200 mg/dL (11.1 mmol/L), and HbA_{1c} 6.0% to 8.5%, inclusive.

Diagnosis and Main Criteria for Inclusion (continued): Group 2 subjects were to be healthy adults without a personal or immediate family history of diabetes mellitus, impaired glucose tolerance, impaired fasting glucose, or gestational diabetes, with normal glucose tolerance defined by plasma glucose concentrations < 140 mg/dL (7.8 mmol/L) at 2h following oral ingestion of 75 g glucose given following a fast of at least 8h, and no clinically significant laboratory test values. All subjects were to be male or female volunteers, 35 to 70 years of age, with BMI ranging from 25 kg/m^2 to 35 kg/m^2.

Test Product, Dose and Mode of Administration, Batch No.: Exenatide, 0.25 mg/mL; formulation AC-2993-F8; lot number 02-0805KP.

Duration of Study: 4 days (4 days, Group 1; 2 days, Group 2).

Reference Therapy, Dose and Mode of Administration, Batch No.: Saline

Criteria for Evaluation: Efficacy: The primary efficacy measure for examining the effect of exenatide was first-phase insulin release (FPIR). Secondary efficacy measures included second-phase insulin release (SPIR), glucose disappearance constant (K_g), and insulin secretion rate (ISR). Pharmacokinetics: Blood samples were drawn for measurement of plasma exenatide on Day 2 and Day 4 for subjects in Group 1 only. Time points for blood samples (relative to IVGTT at t = 0 min) were -195 min, -180 min, -165 min, -150 min, -120 min, -90 min, -60 min; immediately prior to the IVGTT at 0 min, and following IVGTT at 60 min and 120 min. The blood sample at –180 min was drawn prior to exenatide infusion. Pharmacodynamics: Pharmacodynamic measures included insulin, C-peptide, glucose, proinsulin, and glucagon concentrations. Blood samples were drawn on Day 2 and Day 4 at –195 min, -180 min, -120 min, -60 min, -30 min, -15 min, -10 min, -5 min; immediately prior to the IVGTT at 0 min, 2 min, 4 min, 6 min, 8 min, 10 min, 12 min, 15 min, 20 min, 30 min, 45 min, 60 min, 90 min, and 120 min. The blood sample at -180 min was drawn prior to exenatide and saline infusions. Safety: Safety was assessed by examination of data for adverse events, clinical laboratory measures, physical examination findings, vital signs, and electrocardiogram (ECG) findings.

Statistical Methods: Efficacy: Efficacy data were presented for 25 subjects in the evaluable population. FPIR was calculated using the trapezoidal rule as the incremental area relative to the basal insulin concentration during the first 10 min after the subject received the IVGTT. The basal insulin concentration was the mean value of insulin concentrations obtained between –15 min and 0 min prior to IVGTT. SPIR was calculated in a similar manner as FPIR, as the incremental area from basal concentration from 10 min to 120 min after IVGTT. Within group comparisons were made using mixed effects analysis of variance (ANOVA); between group comparisons were made using fixed effects ANOVA. Pharmacokinetics: Pharmacokinetic parameters for plasma exenatide were calculated using the standard noncompartmental method, parameters included $AUC_{(-180\ to\ 120\ min)}$, $AUC_{(0\ to\ 120\ min)}$, $C_{ave\ (-180\ to\ 120\ min)}$, $C_{ave\ (0\ to\ 120\ min)}$, $C_{max\ (180\ to\ 120\ min)}$, and $C_{max\ (0\ to\ 120\ min)}$. Pharmcodynamics: Pharmacodynamic parameters for insulin, glucagon, proinsulin, C-peptide, and glucose concentrations included $AUC_{(0\ to\ 10\ min)}$, $AUC_{(10\ to\ 120\ min)}$, $AUC_{(0\ to\ 120\ min)}$, $C_{ave\ (0\ to\ 10\ min)}$, $C_{ave\ (10\ to\ 120\ min)}$, $C_{ave\ (0\ to\ 120\ min)}$, $C_{min\ (0\ to\ 10\ min)}$, $C_{min\ (10\ to\ 120\ min)}$, $C_{min\ (0\ to\ 120\ min)}$, $C_{max\ (0\ to\ 10\ min)}$; $C_{max\ (10\ to\ 120\ min)}$, $C_{max\ (0\ to\ 120\ min)}$, and $T_{max\ (0\ to\ 10\ min)}$, $T_{max\ (10\ to\ 120\ min)}$, $T_{max\ (0\ to\ 120\ min)}$. All pharmacokinetic and pharmacodynamic parameter calculations required a minimum of three nonmissing values. Safety: Safety analyses were performed on data for the ITT population. Treatment-emergent adverse events were defined as those occurring or worsening after the start time of exenatide or saline infusions on Day 2. Adverse events that occurred between Day 2 infusion start time, inclusive, and Day 4 infusion start time, exclusive, were assigned to the treatment administered on Day 2. Adverse events occurring on or after Day 4 study medication infusion start time were assigned to the treatment administered on Day 4. Treatment-emergent adverse events were summarized by system organ class and preferred term, intensity, and relationship to study medication. Adverse events were coded using the Medical Dictionary for Regulatory Activities (MedDRA™) version 5.0 and WHO DRUG dictionary, version 1st Quarter 2002. Hypoglycemic adverse events were listed; treatment assigned to hypoglycemic adverse events followed the same method of assignment used for general adverse events. Descriptive statistics and change from baseline to study termination were presented by treatment sequence for clinical chemistry, hematology, and numerical urinalysis data. Shift tables of baseline clinical laboratory test values versus study termination were summarized. Vital signs and electrocardiograms were summarized and compared descriptively with baseline measurements, and physical examination data were listed.

SUMMARY OF RESULTS: EFFICACY: FPIR and SPIR: Elevation of plasma exenatide concentrations to the therapeutic range (> 50 pg/mL) resulted in a 4-fold increase in FPIR (0 to 10 min), restoring the impaired glucose-stimulated FPIR in subjects with type 2 diabetes. Exenatide concentrations maintained at the therapeutic range significantly improved glucose-stimulated FPIR in subjects with type 2 diabetes (LS mean: 675 mU·min/L [Group1 exenatide infusion] versus 164 mU·min/L [Group 1 saline infusion]; p = 0.0002) to levels observed in healthy subjects (675 mU·min/L [Group 1 exenatide infusion] versus 443 mU·min/L [Group 2 without exenatide], p = 0.1149). A significant increase in SPIR was also observed

in type 2 diabetes subjects (6916 mU•min/L [Group 1 exenatide infusion] versus 2027 mU•min/L [Group 1 saline infusion], p = 0.0002) and when compared to healthy subjects (6916 mU•min/L [Group 1 exenatide infusion] versus 2055 mU•min/L [Group 2], p = 0.0029). Insulin Secretion Rate (ISR) and Glucose Disappearance Constant (K_g): Exenatide did not directly stimulate insulin secretion when glucose concentrations were in the euglycemic range during the 180 min infusion prior to IVGTT. Following IVGTT, the mean (SD) ISR at 4 min for Group 1 subjects during exenatide infusion peaked rapidly to 23.4 (11.73) pmol•kg-1• min-1 and was higher than Group 2 (17.2 (9.55) pmol•kg-1• min-1) subjects. Elevations in second-phase insulin release occurred primarily from 10 to 90 min. Plasma glucose concentrations were elevated following administration of the IV glucose bolus and decreased to secretion rates observed in healthy subjects as plasma glucose concentrations diminished over time.

Figure 3: Mean (+SE) Plasma Glucose Concentration Time Curve by Group and Treatment (Population: Evaluable Subjects in Study 2093-122 [N = 13, Group 1; N = 12, Group 2])

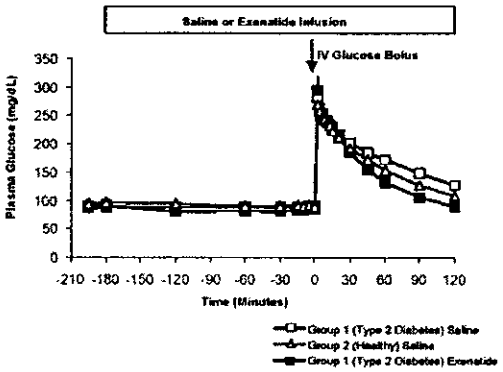


Figure 4: LS Mean (+SE) First-Phase Insulin Release (Population: Evaluable Subjects in Study 2093-122 [N= 25])

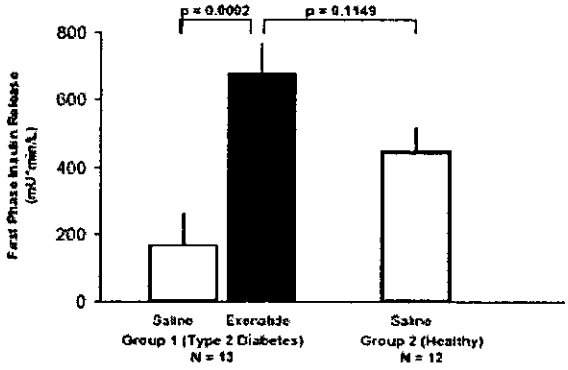


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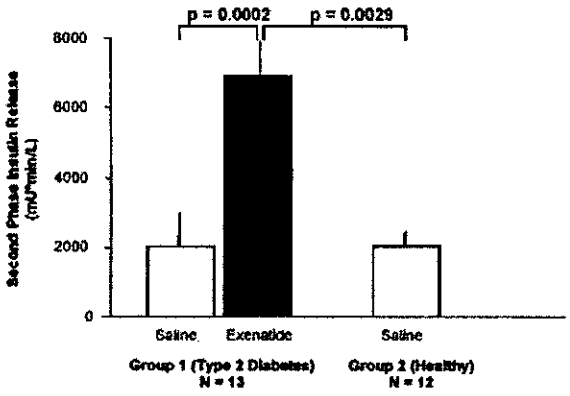
Figure 5: LS Mean (+SE) Second-Phase Insulin Release
(Population Evaluable Subjects in Study 2993-122 [N = 25])



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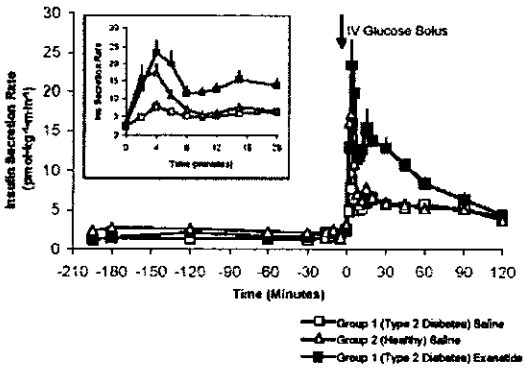
Insulin secretion rates were derived from the standard parameters for C-peptide distribution and clearance from the C-peptide concentration profiles. During the 180 min infusion period prior to IVGTT, the mean insulin secretion rate was similar for Group 1 during infusions of exenatide and saline, but was slightly higher in Group 2 subjects. Following IVGTT, a rapid rise in insulin secretion rate was observed in all three groups. Insulin secretion rates initially peaked at 4 min to 23.4 (11.73) pmol•kg^{-1}•min^{-1} for Group 1 subjects during infusion of exenatide compared with 7.8 (5.21) pmol•kg^{-1}•min^{-1} for Group 1 during infusion of saline and 17.2 (9.55) pmol•kg^{-1}•min^{-1} for Group 2.

Figure 6: Mean (+SE) Insulin Secretion Rate
(Population Evaluable Subjects in Study 2993-122 [N = 13 Group 1, N = 12, Group 2])



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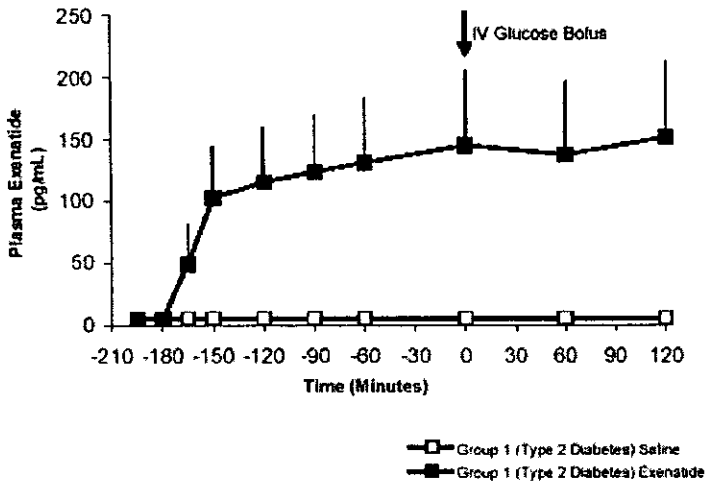
PHARMACOKINETICS: Mean plasma exenatide concentration rose rapidly and reached therapeutic levels (> 50 pg/mL) within 20 min after the start of the exenatide infusion and continued to increase for 30 min. Mean concentrations gradually increased to 131 pg/mL for 150 min until glucose stimulation and remained relatively constant (131 to 152 pg/mL) until cessation of exenatide infusion.

Figure 2: Mean (+SD) Plasma Exenatide Concentration
(Population: Evaluable Group 1 Subjects in Study 2993-122 [N = 13])



SAFETY: Hypoglycemia (4 Group 1 subjects, 28.6%) and nausea (2 Group 1 subjects, 14.3%) were the most frequent treatment-emergent adverse events. Of the 4 hypoglycemic events that occurred in Group 1 subjects, only one event occurred during the exenatide infusion; the other three episodes occurred during the insulin infusion prior to the administration of exenatide. The event was considered mild in intensity and related to study medication by the investigator; the subject recovered without intervention. Two Group 1 subjects experienced 1 mild and 2 moderate nausea events that were considered possibly or probably related to study treatment; 2 of the events occurred during the exenatide infusion. None of the events was considered severe or resulted in withdrawal from the study. No adverse changes in clinical laboratory test values, vital signs, physical examination findings, or electrocardiograms (ECGs) were associated with exenatide treatment.

Deaths: No deaths were reported during this study.

Serious Adverse Events: No serious adverse events were reported during this study.
Withdrawals Due to Adverse Events: One subject was withdrawn due to an adverse event (increased WBC count) that occurred prior to exenatide infusion and was considered unrelated to study treatment by the investigator.

Clinical Laboratory Values: No adverse changes in clinical laboratory test values were associated with exenatide treatment.
Vital Signs, Physical Examinations, and Electrocardiograms: No clinically meaningful changes in vital signs, physical examination findings, or ECGs attributable to exenatide treatment were noted during the study.

CONCLUSIONS:

- In subjects with type 2 diabetes treated with diet and exercise alone or in combination with metformin or α-glucosidase inhibitors, intravenous infusion of exenatide resulted in restoration of impaired first-phase insulin secretion as evidenced by a four-fold increase in plasma insulin $AUC_{(0\ to\ 10\ min)}$ and a three-fold increase in insulin secretion rate (at 4 min post glucose bolus) compared to saline. First-phase insulin secretion during IV exenatide infusion was similar to or greater than that observed in Group 2 subjects (healthy controls) administered saline infusions.
- In subjects with type 2 diabetes treated with diet and exercise alone or in combination with metformin or α-glucosidase inhibitors, intravenous infusion of exenatide resulted in improvements in glucose-stimulated second-phase insulin secretion as evidenced by a 3.5-fold increase in plasma insulin $AUC_{(10\ to\ 120\ min)}$ and a 2.4-fold increase in peak insulin secretion rate (15 min post glucose bolus)

compared to saline. These improvements resulted in higher second-phase insulin secretion than that observed in healthy control subjects receiving saline.

(Hypoglycemia and nausea were the most frequent adverse events occurring in Group 1 (type 2 diabetes) subjects.

- One treatment-emergent hypoglycemic event occurred during the exenatide infusion and was considered related to study treatment; the event was mild in intensity and no treatment intervention was required. Three hypoglycemic events occurred prior to the infusion of study medication and were resolved by adjustment of the insulin infusion rates.
- Two Group 1 (type 2 diabetes) subjects experienced 3 moderate nausea adverse events that were considered possibly or probably related to study treatment; 2 of the events occurred during the exenatide infusion and one of those subjects also reported a mild nausea event during the saline infusion.

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H8O-EW-GWAB

Title: Single Subcutaneous Dose Pharmacokinetics of LY2148568 in Subjects with Renal Dysfunction

Investigators: [redacted]

Study Centers: The study was conducted at three centres in Belgium.

Dates of Study: 06 May 2003 to 27 October 2003.

Clinical Phase: Phase I.

Objectives: Primary Objective: To evaluate the pharmacokinetics of exenatide in subjects with mild or moderate renal dysfunction or end-stage renal disease (ESRD) after a single subcutaneous dose, compared to healthy subjects with normal renal function. Secondary Objective: To assess the safety and tolerability of exenatide in healthy subjects and those with mild or moderate renal dysfunction or ESRD after a single subcutaneous dose.

Methodology: This was an open-label, parallel, single-dose study. It was planned that up to 32 subjects, split into four groups of up to eight subjects, would complete the study. The measurement of serum creatinine at screening using the Cockroft-Gault equation was used to estimate creatinine clearance for subjects in Groups 1 to 3, and this value was used to assign subjects to Groups 1 to 3 as detailed below:

Group 1 (control group): Subjects with normal renal function (estimated creatinine clearance: >80 mL/min).
Group 2: Subjects with mild renal dysfunction (estimated creatinine clearance: 51 to 80 mL/min).
Group 3: Subjects with moderate renal dysfunction (estimated creatinine clearance: 31 to 50 mL/min).
Group 4: Subjects with ESRD, and who had required haemodialysis for at least 1 month prior to screening.
Subjects in Group 1 were to be age- and gender-matched to subjects in Groups 2 to 4 as far as was practically possible.

Number of Subjects: A total of 31 subjects entered and completed the study. Of these, 8 subjects were healthy (Group 1) and 8, 7 and 8 subjects were assigned to Group 2 (mild renal dysfunction), Group 3 (moderate renal dysfunction) and Group 4 (ESRD), respectively.

Diagnosis and Inclusion

Criteria:
Male or female subjects aged between 25 and 80 years (inclusive), with normal renal function, mild renal dysfunction, moderate renal dysfunction, or ESRD requiring haemodialysis for at least 1 month prior to screening.

Dosage and Administration: Test Product: Single doses of 5 µg (Group 3 [5 subjects] and Group 4) or 10 µg (Group 1, Group 2, and Group 3 [2 subjects]) exenatide, provided as a sterile solution in cartridges (0.25 mg/mL). Lot number 02-0805KP.

Duration of Treatment: A single subcutaneous dose of exenatide was administered on Day 1 approximately 15 minutes prior to a standardised breakfast. Criteria for Evaluation: Safety-- Adverse events, vital signs (supine and standing blood pressure and heart rate), 12-lead ECG, body weight, physical examinations, clinical laboratory evaluations, and plasma/blood glucose assessment.
Pharmacokinetic-- Blood samples were collected for the measurement of exenatide concentrations.
Pharmacodynamic-- Not applicable.
Methods: Bioanalytical-- Plasma samples were analysed for exenatide using an immunoenzymetric assay.
Pharmacokinetic-- Noncompartmental pharmacokinetic analyses were used to evaluate plasma exenatide concentration-time data.
Exenatide pharmacokinetics in each of the renally impaired

groups were compared to data from subjects with normal renal function.
Statistical-- The dose-weight normalised pharmacokinetic parameters AUC0-∞ and Cmax were log-transformed and analysed by analysis of variance. The ratios of geometric least square means between each of the renally impaired groups and the healthy group were calculated along with their 90% confidence intervals.

Results and Conclusions:
Mean plasma exenatide concentration-time profiles across each of the treatment groups are shown in Figure GWAB 11.1 below. The mean pharmacokinetic profile following administration of 10 µg exenatide in moderately impaired subjects is not illustrated in Figure GWAB 11.1 due to the small number of subjects

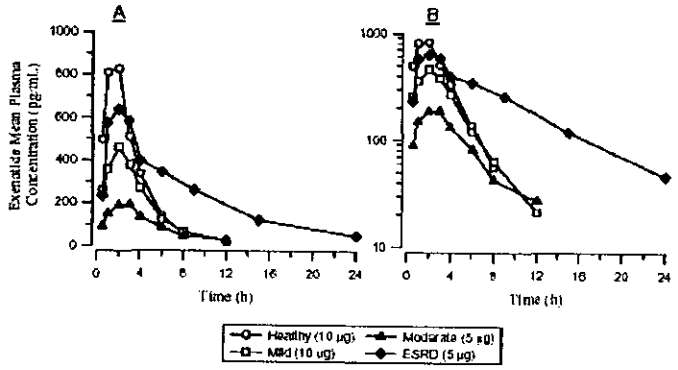

Figure GWAB.11.1. Comparison of Mean Plasma Exenatide Time Profiles by Treatment (Panel A: Linear scale; Panel B: Semi Logarithmic Scale).

Table xx. Mean noncompartmental pharmacokinetic parameters for plasma exenatide by treatment group

Parameter	Geometric Mean (CV%)				
	Healthy	Mild impairment	Moderate impairment		ESRD
N	8	8	5	1	8
Dose (µg)	10	10	5	10	5
Creatinine Clearance [b] (mL/min)	83-156	60-78	34-50		4-11
Tmax [c] (h)	2.0 (1.0 – 3.0)	2.0 (0.52 – 3.0)	2.50 (1.0 – 3.0)		2.0 (1.0 – 4.0)
Cmax (pg/mL)	821 (61.0)	470 (24.6)	202 (19.9)	352.6	601 (69.4)
(pg/mL)/(µg/kg) [d]	5940 (50.4)	3560 (12.9)	3100 (15.0)	3100 (15.0)	7600 (55.5)
AUC0-t [e] (pg·h/mL)	2880 (32.0)	2030 (19.4)	1070 (12.6)	1960	5060 (43.9)
(pg·h/mL)/(µg/kg) [d]	20800 (22.8)	15400 (26.4)	16500 (11.4)	16500 (11.4)	64000 (31.3)
CLp/F(L/h)	3.41 (31.4)	4.80 (17.4)	4.35 (15.2)	4.79	0.929 (42.2)
(L/h/kg)	0.0471 (22.1)	0.0634 (25.9)	0.0563 (8.98)	0.0563 (8.98)	0.0147 (28.8)
Vz/F(L)	7.11 (40.2)	14.7 (21.9)	19.5 (49.8)	24.1	7.97 (43.9)
(L/kg)	0.0983 (30.5)	0.194 (14.9)	0.257 (49.4)	0.257 (49.4)	0.126 (37.0)
t1/2 f	1.45	2.12	3.16		5.95
(h)	(0.944 to 2.02)	(1.56 to 3.36)	(1.82 to 7.01)		(4.27 to 7.58)

N = number of subjects included in means; ESRD = End-Stage Renal Disease; [a] Subject 222 was excluded as an outlier from all statistical evaluations; [b] Cockroft-Gault creatinine clearance at screening (range); [c] Median (range); [d] Dose-weight normalized

parameter; [e] Sample collection intervals were up to 12 hours for Healthy, up to 18 hours for Mild and Moderate, and up to 60 hours for ESRD subjects; [f] Mean (range).

Figure GWAB.11.2 illustrates the relationship between plasma exenatide clearance and creatinine clearance

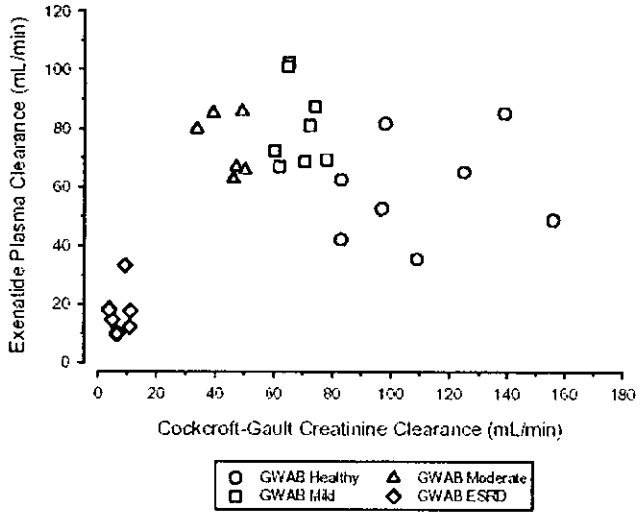

Figure GWAB.11.2. Relationship between Plasma Exenatide Clearance and Creatinine Clearance.

Table xx. Comparison of dose-weight normalised AUC0-∞ and Cmax between healthy control group and mild, moderate and ESRD groups

Dose-Weight Normalised Parameter	Group	LS Gmean	Ratio of LS GMean Group (2, 3 or 4)/Healthy	90% CI on Ratio
AUC0-∞ (pg·h/mL)/(mg/kg)	Healthy	19917.11		
	Mild	16036.41	0.81	(0.66, 0.98)
	Moderate	19258.16	0.97	(0.77, 1.21)
	ESRD	67101.74	3.37	(2.80, 4.06)
Cmax (pg/mL)/(mg/kg)	Healthy	5392.13		
	Mild	3649.98	0.68	(0.49, 0.93)
	Moderate	3507.42	0.65	(0.45, 0.94)
	ESRD	7433.74	1.38	(1.01, 1.88)

The ratios of the geometric means of dose-weight normalized AUC0-∞ between the healthy group and the mild, moderate and ESRD groups were 0.81, 0.97 and 3.37, respectively, and the ratios for dose-normalized Cmax were 0.68, 0.65 and 1.38, respectively. The 90% CIs for the ratios indicate that the increase in AUC0-∞ and Cmax in the ESRD group were statistically significant. AUC0-∞ in the mild and moderate
groups was similar to the healthy subject group, although Cmax was slightly lower. This is consistent with the graphical analyses that indicated a substantial change in clearance only in the ESRD group. Overall, these analyses suggest that exenatide clearance estimates in subjects with mild to moderate renal impairment were similar to those in the healthy subject group. Exenatide clearance was significantly reduced in subjects with ESRD, thus BID dosing of 5 µg in ESRD subjects would be likely to result in increases in exposure that would be associated with poor tolerability.

Summary:

•Exenatide clearance estimates in subjects with mild to moderate renal dysfunction were similar to those in the control group.

• Exenatide clearance reduced from a mean estimate of 4.8 L/h in subjects with mild renal impairment to 0.9 L/h in subjects with ESRD.

•Administration of a single subcutaneous dose of exenatide appeared to be safe in all groups, and was well tolerated in subjects with mild (10 μg) and moderate (5 and 10 μg) renal dysfunction compared to healthy controls. Exenatide was not well tolerated in subjects with ESRD (5 μg).

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H8O-EW-GWAE

Title: A Pharmacodynamic Interaction Study to Evaluate the Effects of Exenatide on Lisinopril in Hypertensive Subjects

Investigators: [redacted]

Study Centres: The study was conducted at two centres in the UK.

Dates of Study: 16 June to 25 November 2003.

Clinical Phase: Phase I.

Objectives: Primary Objective: To evaluate the effect of exenatide on the blood pressure response to lisinopril in subjects with mild to moderate hypertension. Secondary Objectives: To assess the safety and tolerability of concomitant administration of lisinopril and exenatide. To evaluate the influence of exenatide on the plasma pharmacokinetics of lisinopril.

Methodology: A subject- and investigator-blind, placebo-controlled, randomized, two-period, two-sequence crossover, drug interaction study.

Number of Subjects: It was planned to enrol up to 30 subjects, with a total of at least 18 subjects required to complete the study (9 per treatment sequence). A total of 22 subjects entered the study and 19 subjects completed the study. Three subjects were withdrawn after completing Treatment Period 1.

Diagnosis and Inclusion
Criteria:
Male or female subjects, aged 18 years or over, with mild to moderate hypertension and on established lisinopril therapy (for at least 30 days prior to the first dose administration).

Dosage and :Administration:
Test Product: Exenatide: 10 µg twice-daily (BID), administered subcutaneously. Provided as a sterile solution in cartridges (0.25 mg/mL). Batch number 371064 (Amylin batch 02-0805KP). Co-administered Drug Lisinopril: Subjects continued to take their prescribed lisinopril therapy (daily dose of 5 to 20 mg) for the duration of the study.

Reference Therapy

Placebo (the same formulation as the test product, with exenatide omitted): BID, administered subcutaneously. Batch number 162012 (Amylin batch 02-0304KE).

Duration of Treatment: Exenatide or placebo: 1 day.

Criteria for Evaluation: Safety-- Adverse events, vital signs (supine, sitting and standing blood pressure and heart rate), 12-lead ECG, physical examination and clinical laboratory evaluations.

Pharmacokinetic-- Blood samples were collected in each treatment period over a 24-hour period following the lisinopril dose on Day 1 for the measurement of plasma lisinopril concentrations. A blood sample was collected for the measurement of plasma exenatide concentrations approximately 2 hours following the morning dose of exenatide.

Pharmacodynamic-- Diastolic and systolic blood pressure measured by ABPM. Methods: Bioanalytical-- Plasma samples were analyzed for lisinopril using a validated LC/MS/MS method. Additional plasma samples were analyzed for exenatide using an immunoenzymetric assay. Pharmacokinetic-- Noncompartmental pharmacokinetic analysis methods were used to analyze the lisinopril plasma concentration-time data on Day 1 of each treatment period.

Pharmacodynamic-- In each treatment period, ambulatory blood pressure and heart rate monitoring was conducted for 24 hours post exenatide/placebo dosing. The 24-hour mean for diastolic and systolic blood pressure was computed. Statistical-- The natural logarithm of lisinopril dose and weight normalizedAUCτ,ss and Cmax,ss were analyzed with a mixed effects model. Ninety percent confidence intervals (CIs) for the ratio of the geometric least squares (LS) means between the two treatments were calculated. Inter- and intra-subject CV% were calculated for AUCτ,ss and Cmax,ss. The median of tmax,ss differences was listed. The primary pharmacodynamic variables for statistical analysis were mean systolic and diastolic blood pressure over 24 hours adjusted for the baseline. The two treatments were compared using a linear mixed effects model. LS mean differences between treatments were calculated along with the 95% CIs. The secondary variables, 24-hour weighted mean for systolic and diastolic blood pressure, were analysed in a similar fashion.

Summary and Conclusions:

• Concomitant administration of exenatide did not change the 24-hour mean systolic and diastolic blood pressure of hypertensive subjects stabilised on lisinopril therapy. No statistically significant differences in lisinopril steady-state exposure (Cmax,ss and AUCτ,ss) were observed when dosed concomitantly with exenatide or placebo. Concomitant administration of exenatide resulted in a minor delay in reaching peak plasma steady-state lisinopril concentrations. Median tmax,ss was delayed by approximately 2 hours (increased from a median value of 6 to 8 hours) in the presence of exenatide. Subcutaneous doses of 10 μg BID exenatide, administered concomitant to an established dose of lisinopril, were safe and fairly well tolerated by mild to moderate hypertensive male and female subjects.

H8O-FW-GWAF

Title: Effect of Exenatide Administration on the Pharmacokinetics of Digoxin in Healthy Male Subjects.

Investigator: [redacted]

Study Centers: This was a single-centre study

Dates of Study: 20 May to 1 July 2003

Clinical Phase: Phase I

Objectives: Primary Objective: To determine the effects of chronic exenatide dosing on the pharmacokinetics of digoxin at steady-state in healthy male subjects; Secondary Objective: To assess the safety and tolerability of co-administration of exenatide and digoxin.

Methodology: An open-label, fixed sequence, drug interaction study

Number of Subjects: It was planned to study 24 subjects, with a total of at least 14 subjects required to complete the study. A total of 23 subjects were enrolled in the study and 21 subjects completed the study: Subject 14 was withdrawn due to an adverse event considered to be gastrointestinal infection prior to dosing with exenatide, and Subject 17 withdrew for personal reasons.

Diagnosis and Inclusion Criteria: Overtly healthy males aged between 21 and 50 years (inclusive)

Dosage and Administration: Test Product: Exenatide: 10 µg BID on Days 8 to 12, provided as sterile solution in cartridges (0.25 mg/mL), Lot number 371064 (Amylin lot 02-0805KP)

Co-administered Drug: Digoxin: 0.5 mg BID on Day 1, 0.25 mg QD on Days 2 to 12, provided as Lanoxin® capsules (0.25 mg), Lot number 775103

Duration of Treatment: Exenatide: 5 days; Digoxin: 12 days

Criteria for Evaluation:
Safety--adverse events, vital signs (supine blood pressure and pulse rate), 12-lead ECG, digoxin trough levels, and clinical laboratory evaluations

Pharmacokinetic--Blood samples were collected on Days 7 and 12 over a 24-hour period for the measurement of plasma digoxin concentrations. Urine was collected over a 24-hour period on Days 7 and 12 for the measurement of digoxin amounts. Blood samples were collected on Days 11 and 12 for the measurement of plasma exenatide concentrations approximately 2 hours following the exenatide dose.

Pharmacodynamic--Not applicable.

Methods: Bioanalytical--Heparinised plasma samples and urine samples were analyzed for digoxin using validated radioimmunoassay methods. Additional plasma samples were analyzed for exenatide using an immunoenzymetric assay. Pharmacokinetic--Noncompartmental analysis methods were used to determine standard pharmacokinetic parameters of digoxin when administered alone and concomitantly with exenatide.

Statistical--Cmax,ss, Cmin,ss and AUCτ,ss were log-transformed and analyzed using a linear mixed effects model. Confidence intervals (90%) of the ratio between the two treatments were calculated. Inter- and intra-subject CV% were calculated for Cmax,ss and AUCτ,ss. The median of tmax,ss differences was listed.

Results:

Figure GWAF.11.1. Arithmetic Mean (±SE) Digoxin Plasma Concentration-Time Profiles Following Steady-State Dosing of 0.25 mg QD Digoxin Alone or in the Presence of Steady-State Dosing of 10 µg Exenatide BID Administered Subcutaneously.

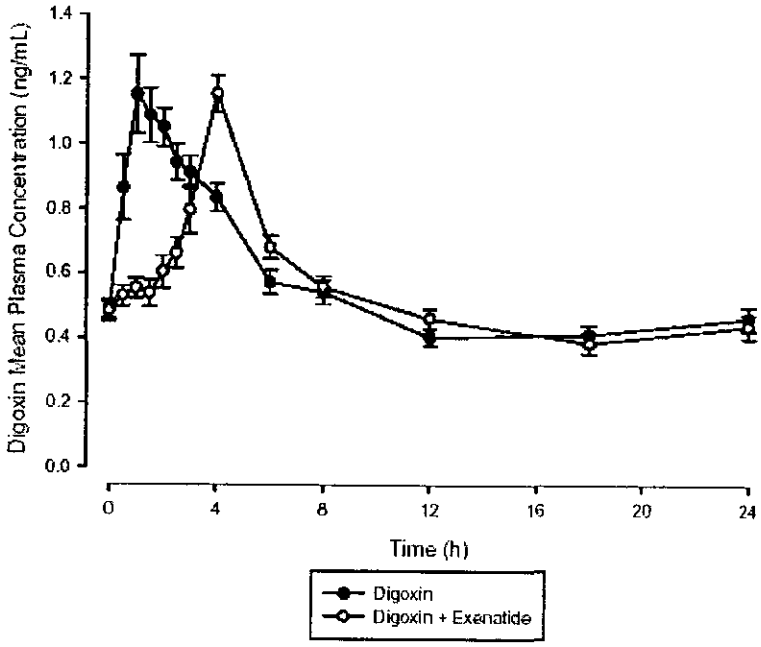


Table GWAF.11.2. Statistical Comparison of Digoxin AUCτ,ss, Cmin,ss and Cmax,ss for Digoxin + Exenatide (Day 12) and Digoxin (Day 7)

Parameter	LS Geometric Mean		LS Geometric Mean Ratio	
	Digoxin + exenatide	Digoxin	Digoxin + exenatide/ Digoxin	90% CI
AUCτ,ss (ng·h/mL)	12.11	12.78	0.95	(0.90, 1.00)
Cmin (ng/mL)	0.32	0.34	0.94	(0.87, 1.03)
Cmax (ng/mL)	1.15	1.40	0.82	(0.75, 0.89)

Twice-daily subcutaneous administration of 10 µg exenatide did not produce a statistically significant change in digoxin Cmin,ss or AUCτ,ss. The 90% CI for the geometric mean ratio of Cmax,ss ranged from 0.75 to 0.89, with the estimated ratio 0.82, and was therefore slightly below the prospectively defined equivalence range of (0.8, 1.25). However, digoxin Tmax was delayed for a median value of 2.5 hours when administered concomitantly with exenatide.

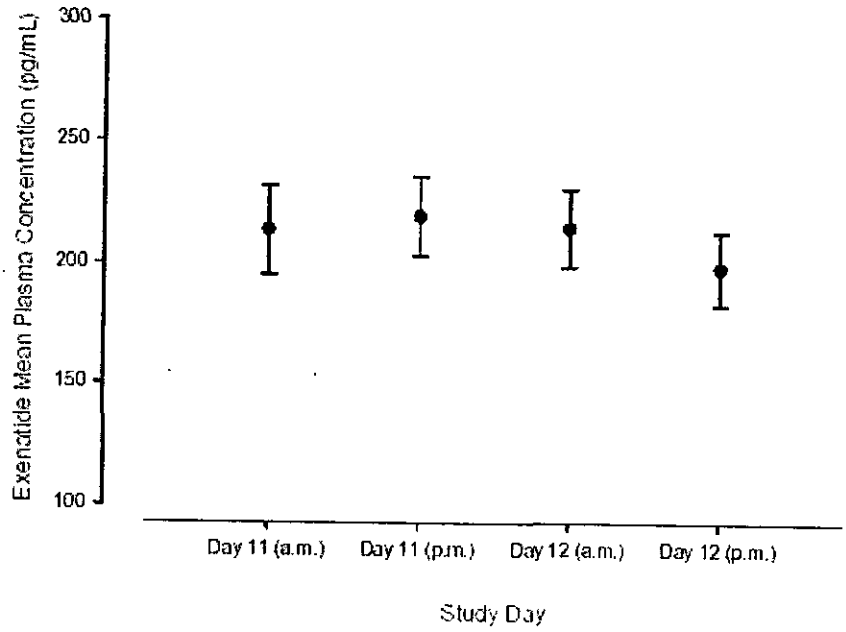
Estimates of renal digoxin clearance with and without exenatide co-administration are summarized (Table GWAF.11.5). These estimates were comparable, indicating that exenatide co-administration did not affect the renal clearance of digoxin.

Table GWAF.11.5. Summary of Geometric Means (CV%) of the Urinary Digoxin Pharmacokinetic Parameters in the Absence and Presence of Exenatide BID

Parameters	Digoxin Alone (Day 7)	Digoxin + Exenatide (Day 12)
N	20	19
fe	0.351 (40.3)	0.340 (34.3)
$CL_{R,SS\ (L/h)}$	7.06 (42.6)	6.91 (35.5)
$CL_{R,SS\ (L/h/kg)}$	0.0971 (42.7)	0.0969 (35.3)

The mean plasma concentrations of exenatide at 2 hours post exenatide dose on Days 11 and 12 are shown in Figure GWAF.11.4 below. The similarity of plasma exenatide concentrations on Days 11 and 12 suggests that exenatide had attained steady-state by Day 11.

Figure GWAF.11.4. Arithmetic Mean (±SE) Exenatide Plasma Concentrations 2 hours Following Steady-State Exenatide Dosing of 10 μg BID in the Presence of 0.25 mg QD Digoxin.



Summary and Conclusions:

- When co-administered with exenatide, no dose adjustment of digoxin is required.
- Co-administration of subcutaneous exenatide (10 μg BID) with oral digoxin (0.25 mg QD) did not produce a statistically significant change in the overall 24-hour steady-state exposure (AUCτ,ss) to digoxin and Cmin,ss. Digoxin urinary pharmacokinetic parameters (CLR,ss and fe) were not altered in the presence of exenatide.
- Co-administration of exenatide caused a 17% decrease in mean digoxin Cmax,ss (1.4 to 1.16 ng/mL) and an increase in digoxin tmax,ss (median increase of approximately 2.5 hours). Although the decrease in Cmax,ss was statistically significant, it was not clinically relevant: peak concentrations were still within the therapeutic concentration range in all of the individual subjects.
- The post-absorptive phase of the steady-state digoxin concentration-time profile following administration of oral digoxin was not altered by subcutaneous administration of exenatide.

- Subcutaneous doses of 10 μg BID exenatide, co-administered with oral doses of 0.25 mg QD digoxin for 5 days, were safe and fairly well tolerated in this study.
- The incidence of new adverse events considered to be related to exenatide decreased throughout the study on each subsequent exenatide dosing day, consistent with induction of tolerance to exenatide side effects with repeated dosing.

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Study H8O-EW-GWAG

Title: The Effect of Exenatide on the Pharmacokinetics of a Single Dose of Lovastatin in Healthy Subjects.

Investigator: [redacted]

[redacted]

Study Centre: This was a single-centre study.

Dates of Study: 11 May to 01 August 2003.

Clinical Phase: Phase I.

Objectives: Primary Objective: To evaluate the effect of exenatide on the single dose pharmacokinetics of lovastatin in healthy subjects. Secondary Objectives: To assess the safety and tolerability of exenatide alone and when given concurrently with lovastatin in healthy subjects. To characterize the pharmacokinetics of exenatide in healthy subjects.

Methodology: An open-label, fixed sequence, drug interaction study.

Number of Subjects: It was planned to enrol 25 subjects, with a total of at least 20 subjects required to complete the study. A total of 22 subjects were enrolled in the study and 20 subjects completed the study: Subject 19 withdrew his consent to participate following his second dose of exenatide on Day 2, and Subject 15 was lost to follow-up following dosing with lovastatin on Day 1.

Diagnosis and Inclusion Criteria:
Overtly healthy males or females aged between 18 and 70 years (inclusive).

Dosage and Administration: Test Product: Exenatide: 10 µg BID on Days 2, 3 and 4 provided as sterile solution in cartridges (0.25 mg/mL). Lot number 371064 (Amylin lot 02-0805KP).

Co-administered Drug: Lovastatin: 40 mg on Days 1 and 4, provided as MEVACOR ® tablets (40 mg). Lot number L1143.

Duration of Treatment: Exenatide: 3 consecutive days.

Lovastatin: 2 separate days.

Criteria for Evaluation: Safety—Adverse events, vital signs (supine, sitting and standing blood pressure and heart rate), 12-lead ECG, and clinical laboratory evaluations.

Pharmacokinetic—Blood samples were collected on Days 1 and 4 for the measurement of plasma lovastatin concentrations. Blood samples were collected on Day 3 and after the morning dose of exenatide on Day 4, for the measurement of plasma exenatide concentrations.

Pharmacodynamic--Not applicable.

Methods: Bioanalytical—Plasma samples were analyzed for lovastatin using a validated LC/MS/MS method. Additional plasma samples were analyzed for exenatide using an immunoenzymetric assay. Pharmacokinetic—Non compartmental analysis methods were used to determine standard pharmacokinetic parameters of lovastatin when administered alone and concomitantly with exenatide (Day 1 and Day 4, respectively).

Non compartmental steady-state pharmacokinetic parameters of exenatide were assessed from exenatide plasma concentration-time data collected on Day 3. Sparse plasma exenatide measurements on Day 4 were used to document exposure of exenatide and were listed descriptively.

Statistical—Cmax and AUC0-∞ were log-transformed and analyzed using a linear mixed effects model. Ninety % confidence intervals of the ratio between two treatments were calculated. Inter- and intra-subject CV% were calculated for Cmax and AUC0-∞. Median of tmax differences was listed.

Results:

Figure xx. Lovastatin plasma concentration vs. time profiles (arithmetic mean ± SE) after administration of a single dose of lovastatin (40 mg) given alone (Day 1) or concomitantly with exenatide (Day 4) (Panel A: linear scale; Panel B: semi logarithmic scale).

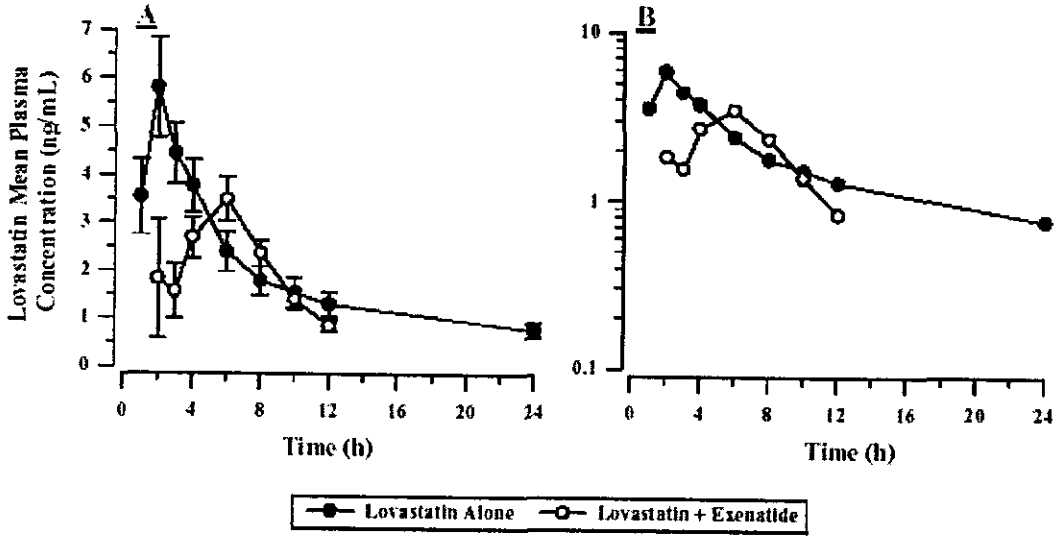


Table GWAG.11.2. Comparison of AUC0-∞ and Cmax for Lovastatin + Exenatide (Day 4) and Lovastatin (Day 1)

Parameter	LS Geometric Mean		LS Geometric Mean Ratio	
	Lovastatin + exenatide	Lovastatin	Lovastatin + exenatide/ Lovastatin	90% CI
AUC 0-∞ (ng·h/mL)	25.32 (11.57%)	42.22 (10.85%)	0.60	(0.50, 0.71)
Cmax (ng/mL)	3.91 (12.33%)	5.42 (11.25%)	0.72	(0.57, 0.91)

Co-administration of exenatide caused statistically significant decreases in both mean lovastatin AUC 0-∞ and Cmax by 40% and 28%, respectively.

The steady-state mean plasma concentrations of exenatide on Day 3 after repeated administration of 10 μg doses are shown in Figure xx, and in Table xx, exenatide non compartmental pharmacokinetic parameters are summarized.

Figure xx. Mean (± SD) plasma exenatide concentration versus time profiles at steady-state (Day 3) after subcutaneous administration of 10μg BID (Panel A: linear scale; Panel B: semi logarithmic Scale).

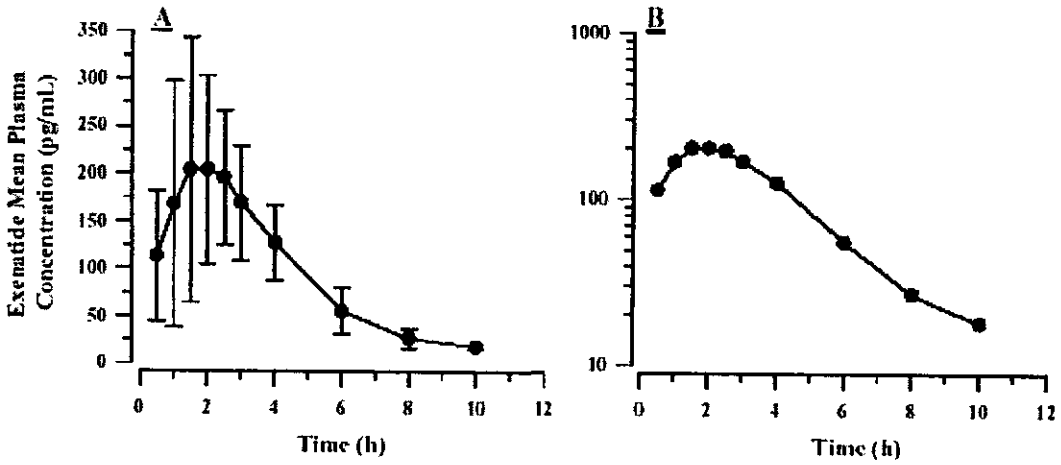


Table xx. Pharmacokinetic parameters (geometric mean, CV%) of exenatide at steady-state in healthy subjects

Parameter	Geometric Mean (CV%)
N	19
Cmax (pg/mL)	218 (46.8)
$AUC_{\tau,ss}$ (pg·h/mL)	878 (31.2)
$Tmax_{,ss}$ (h)	2.5 (1.00 – 3.00)
CLp,ss/F (L/h)	11.4 (31.2)
Vss/F (L)	43.3 (47.2)
t1/2 (h)	1.78 (1.24 to 3.28)

Steady-state pharmacokinetics of exenatide was consistent with previous studies in healthy subjects and patients with type 2 diabetes. Therefore, lovastatin did not alter the pharmacokinetics of exenatide.

Summary and Conclusions:

- Co-administration of exenatide caused statistically significant decreases in both mean lovastatin AUC0-∞ and Cmax, of approximately 40% and 28%, respectively.
- Co-administration of exenatide caused a delay in lovastatin absorption, reflected by an increase in median tmax of approximately 4 hours.
- Steady-state pharmacokinetics of exenatide were consistent with previous studies in healthy subjects and patients with type 2 diabetes.
- Subcutaneous doses of 10 μg BID exenatide were safe and fairly well tolerated when administered for 2 days alone and concomitantly with lovastatin on a third day.
- The overall incidence of new adverse events considered to be related to exenatide decreased throughout the study. This decrease was predominantly due to a decrease in the number of gastrointestinal disorders with repeat exenatide dosing.

Review's comments:

Patients who are treated with lovastatin should be aware that lovastatin AUC and Cmax will be reduced by 40% and 28% when exenatide is added on in therapy. Dose adjustment of lovastatin should be considered.

H8O-EW-GWAJ

Title: Exenatide: Effect of Injection Time on Post-prandial Glycaemia in Patients with Type 2 Diabetes Mellitus.

Investigator: [redacted]

Study Center: This was a single-center study.

Dates of Study: 13 August 2003 to 15 September 2003.

Clinical Phase: Phase I.

Objectives: Primary Objective: To evaluate the effect of time of administration of subcutaneous exenatide relative to a meal on post-prandial glycaemic control in subjects with Type 2 diabetes. Secondary Objective: To evaluate the safety and tolerability of subcutaneous exenatide in patients with Type 2 diabetes mellitus.

Methodology: An open-label, placebo-controlled, randomised, fixed sequence, six-way crossover study.

Number of Subjects: Eighteen subjects entered and 17 subjects completed the study. Subject 11 withdrew consent and was withdrawn from the study on Day 2 after receiving two doses of 10 □g exenatide.

Diagnosis and Inclusion
Criteria:
Sixteen subjects were male and two were female with Type 2 diabetes mellitus controlled by diet/exercise or oral hypoglycaemic agent(s). All subjects were Caucasian Type 2 diabetics, with age, height and body weight ranging from 44 to 68 years, 161 to 196 cm, and 62.0 to 121.8 kg, respectively. Five subjects used tobacco products (ranging from 3 to 20 cigarettes, cigars or roll-ups per day) and 16 subjects drank alcohol (ranging from 2 to 58 units per week).

Dosage and Administration: Test Product Single doses of 10 µg exenatide, provided as a sterile solution in cartridges (0.25 mg/mL). Batch number 3710674 (Amylin batch 02-0805KP).

Reference Therapy: Placebo (same formulation as the test product, with exenatide omitted). Batch number 162012 (Amylin batch 02-0304KE).

Duration of Treatment: Each subject was to receive 5 subcutaneous single doses of exenatide (administered at -60, -15, 0, 30 and 60 minutes relative to the start of a standard breakfast), and one subcutaneous dose of placebo administered 15 minutes prior to the start time of a standard breakfast over six consecutive days (Days 1 to 6).

Criteria for Evaluation:
Safety- Adverse events, vital signs (supine, sitting and standing blood pressure and heart rate), 12-lead ECG, and clinical laboratory evaluations.

Pharmacokinetic- Not applicable.

Pharmacodynamic- Blood samples for the measurement of plasma glucose and plasma insulin concentrations were obtained for all subjects during each study period for 60 minutes prior to and up to 360 minutes following a meal.

Methods: Bioanalytical - Plasma samples were analysed for glucose using a hexokinase method. Pharmacodynamic - Noncompartmental analysis methods were used to determine pharmacodynamic parameters such as the area under the plasma glucose curve (AUC0-6 h), the minimum (Cmin) and maximum (Cmax) plasma glucose concentrations for up to 6 hours following a meal. Parameters were

calculated for both the incremental (baseline-adjusted) and absolute plasma glucose concentration profiles. The duration of post-prandial glucose excursion above baseline (Tdur) was reported from the incremental glucose profile. Plasma insulin data were analysed graphically and descriptively.

Statistical - Incremental AUC0-6 h, incremental Cmax and incremental Cmin were analysed using a linear mixed effects model. Ninety-five percent confidence intervals for the difference between each treatment (time of dosing relative to meal) and the placebo were calculated.

Results:

Table GWAJ.11.1 shows that the greatest absolute glucose mean AUC0-6 h, Cmax and Cmin were observed for the placebo group. In the exenatide treatment groups, both AUC0-6 h and Cmax exhibited a fairly consistent increase from the –60 minutes to the +60 minutes dose administration relative to the meal (Treatments B to F). The opposite trend, a consistent decrease in mean Cmin, was observed across these treatments.

Table GWAJ.11.1. Absolute Plasma Glucose Pharmacodynamic Parameters by Treatment

	Treatment					
Pharmacodynamic Parameters	A Placebo	B -60 min	C -15 min	D 0 min	E 30 min	F 60 min
N_{PD}	16	15	16	15	16	16
$AUC_{0-6\ h}$ (mg·min/dL)						
Arithmetic Mean	53800	40300	40800	41300	43700	42200
Arithmetic SD	13200	7120	8250	7420	9520	9780
Minimum						
Maximum						
C_{max} (mg/dL)						
Arithmetic Mean	237	158	161	169	219	225
Arithmetic SD	50.7	31.4	32.1	40.9	47.9	52.9
Minimum						
Maximum						
C_{min} (mg/dL)						
Arithmetic Mean	91.9	75.5	70.7	67.2	61.9	55.4
Arithmetic SD	21.8	16.2	19.6	15.2	18.7	12.7
Minimum						
Maximum						

Figure GWAJ.11.1. Comparison of Mean Post-prandial Absolute Plasma Glucose Profiles Across Treatments.

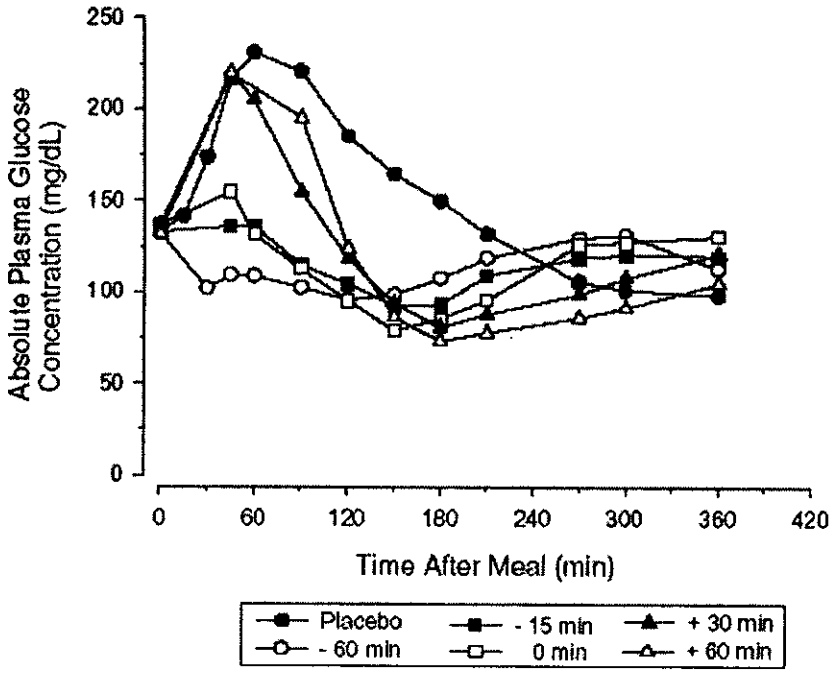
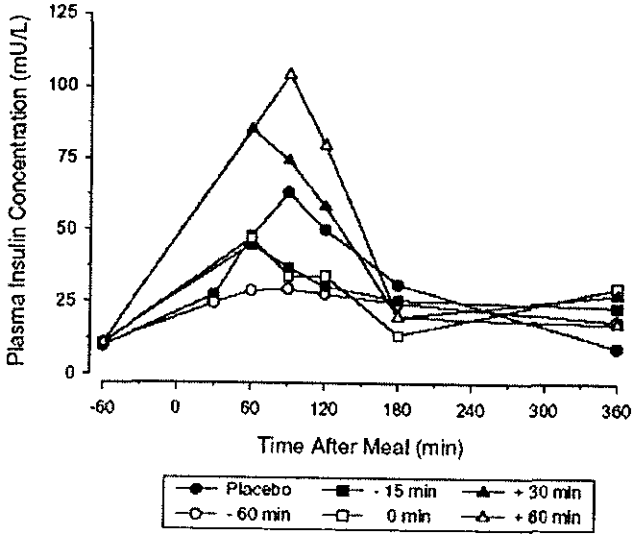


Table GWAJ.11.1. Absolute Plasma Glucose Pharmacodynamic Parameters by Treatment

Pharmacodynamic Parameters	Treatment A Placebo	B -60 min	C -15 min	D 0 min	E 30 min	F 60 min
N_{PD}	16	15	16	15	16	16
$AUC_{0\text{-}6\ h}$ (mg·min/dL)						
Arithmetic Mean	53800	40300	40800	41300	43700	42200
Arithmetic SD	13200	7120	8250	7420	9520	9780
Minimum						
Maximum						
C_{max} (mg/dL)						
Arithmetic Mean	237	158	161	169	219	225
Arithmetic SD	50.7	31.4	32.1	40.9	47.9	52.9
Minimum						
Maximum						
C_{min} (mg/dL)						
Arithmetic Mean	91.9	75.5	70.7	67.2	61.9	55.4
Arithmetic SD	21.8	16.2	19.6	15.2	18.7	12.7
Minimum						
Maximum						

Figure GWAJ.11.6 illustrates the mean plasma insulin concentrations across treatments. Means were not calculated or plotted for sampling times where less than two-thirds of the subjects had quantifiable concentrations. An illustration of the mean insulin profiles with all evaluable data is provided in Section 14.2.3, Figure 55.



In the treatment groups where exenatide was administered prior to or simultaneously with the meal (at –60, -15 and 0 minutes), mean insulin plasma concentrations appear to be reduced compared to placebo. Whereas the treatment groups with post-meal administration of exenatide (at +30 and +60 minutes) exhibited mean insulin plasma concentrations that were increased relative to placebo, possibly due to the higher post-prandial glucose concentrations for these treatments. These observations are consistent with the known mechanism of action of exenatide which results in a glucose-dependent insulin release.

Summary and Conclusions:

•Each of the exenatide treatments demonstrated improved glycaemic control compared to placebo. For the exenatide treatments, the peak post-prandial glucose concentration was lower following administration prior to the meal or at the time of the meal, compared to administration after the meal.

•For each exenatide treatment, the baseline-adjusted exposure (incremental AUC0-6 h) for post-prandial glucose was significantly reduced compared to placebo.

•Baseline-adjusted post-prandial maximum glucose concentrations (incremental Cmax) were significantly lower for all treatments except for the 60 minutes post-meal administration, which could not be distinguished from placebo.

•Baseline-adjusted post-prandial minimum glucose concentrations (incremental Cmin) were significantly lower for all treatments compared to placebo.

•The median duration of the post-prandial glucose excursion above baseline (Tdur) for each of the exenatide treatments was less than that following placebo. There was a trend towards an increase in median Tdur following administration of exenatide from 60 minutes prior to the meal to administration 60 minutes after the meal.

•Subcutaneous single doses of 10 µg exenatide were safe and fairly well tolerated when administered with a meal or up to 60 minutes before a meal in subjects with Type 2 diabetes mellitus.

•The optimal timing of exenatide administration is within 60 minutes prior to a meal. The timing of dosing may be adjusted within this 60 minute pre-prandial period based on individual glycaemic levels and

convenience. Administration of exenatide up to 60 minutes after a meal should be with caution as some subjects may be at risk of low blood glucose concentrations

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POPULATION PK

1. What were the pharmacokinetic characteristics of a single dose of exenatide following subcutaneous (SC) administration in type 2 diabetes?

The mean single dose pharmacokinetic parameters of exenatide were estimated from the Combined, Single-dose database (TY2P12SD). Following SC administration, exenatide was rapidly absorbed and peak concentration was reached at 2.14 hour. Exenatide was rapidly eliminated with a mean terminal half-life of 2.4 hour. The mean apparent clearance (CL/F) was 9.1 L/h and the mean apparent volume of distribution (V/F) was 28.3 L.

Single-dose pharmacokinetic parameters of exenatide from six Phase 1 and Phase 2 studies including Studies 2993-102, -103 (Day 1), -104 (Part 2), -107 (Day 1), -110, and -118 (SC treatment arms) were combined into a Combined, Single-Dose database (TY2P12SD). Multiple parameter estimates from the same individual were considered discrete data in the analysis. Studies 2993-102, -103, -110, and -118 involved pharmacokinetic sampling for relative longer duration (8 to 15 hours post dose) compared with the other two studies 2993-104 (5-hour post dose) and 2993-107 (6-hour post dose). Therefore, the CL/F and V/F values were only calculated for these studies. Considering the relative short period of time of plasma sampling, the half-life values for studies 2003-104 and 2993-107 might not be determined as accurate as the studies where sampling times were relatively longer. However, the half-life values obtained from these two studies were not quite different from the other studies. Therefore, the data from all six studies were used to estimate the mean half-life values. The by-study summary statistics including geometric mean (10^{th} to 90^{th} percentile) for single dose pharmacokinetic parameters of exenatide are presented in **Table 1**.

Table 1. Geometric Mean (10^{th} to 90^{th} percentile) of Pharmacokinetic Parameters of Single Dose Exenatide following SC Administration from Individual Studies (TY2P12SD)

Study	AUC0-inf ((pg.h/mL)/(ug/kg))	Cmax ((pg/mL)/(ug/kg))	Clearance (L/h)	Volume (L)	T1/2 (h)
102	9098 (6702-11526)	1618 (780-2277)	9.71 (7.85-12.38)	47.90 (32.12-81.72)	3.34 (2.33-5.29)
103	11367 (9001-13547)	2256 (1759-3026)	7.22 (5.33-9.48)	23.51 (16.96-35.57)	2.26 (1.61-3.53)
104	13203 (8831-19989)	2089 (1570-2910)	--	--	3.20 (1.68-6.33)
107	--	1904 (1168-3223)	--	--	2.40 (1.28-4.60)
110	8795 (6342-12360)	2067 (1380-3112)	10.20 (7.04-15.97)	22.54 (14.48-39.23)	1.53 (1.17-2.37)
118	10303 (6081-19114)	2097 (1052-3904)	9.66 (5.19-18.11)	27.51 (15.44-64.16)	1.97 (1.36-3.15)

The Proc Mixed procedure in SAS was used for the noncompartmental meta-analysis. A linear mixed effects model was fitted in which the study effect was modeled as a random effect. The within-study subject effect was also modeled as a random effect. Summary statistics are provided in **Table 2**.

Table 2. Summary of Exenatide Single Dose Pharmacokinetic Parameters: Geometric Mean (10^{th} to 90^{th} Percentiles) of Exenatide Following SC Administration (TY2P12SD)

Parameter	Geometric Mean	10^{th} to 90^{th} percentile	Interstudy CV%	Intrasubject CV%	Intersubject CV%
Tmax (hr)[2]	2.14	1.57-3.54	--	--	--
Vz/F (L)[1]	28.27	15.47-62.50	29.11	36.91	34.81
CL/F (L/hr)[1]	9.07	6.15-15.86	13.90	22.14	30.08
T1/2 (hr)[2]	2.35	1.35-4.52	27.87	42.45	21.14

1. Four studies (2993-102, 2993-103, 2993-110, and 2993-118) were included in the analysis. Number of patients is 67.

2. Number of patients is 118.

Results showed that the mean apparent volume of distribution of exenatide was 28.3 L. The mean apparent clearance was 9.1 L/h and the mean half-life was 2.4 h. The mean Tmax was 2.14 hr.

2. Was the dose-proportionality established for exenatide?

Dose-proportionality was established for AUC0-inf over the dose range of 5 ug to 10 ug. The Cmax values were less than proportional.

Doses ranging from 0.01 ug/kg to 0.4 ug/kg were evaluated in clinical studies with exenatide. The dose-proportionality was evaluated for Cmax and AUC0-inf over the therapeutic range of 5 ug to 10 ug using a power model. Study and within-study subject were included in the model as random effects. The Combined, Single-dose Database (TY2P12SD) was used. The dose, in ug units, was used in this analysis. Results of the power model analysis are presented in **Table 3**.

Table 3. Power Model Analysis of Dose-Proportionality of Exenatide AUC0-inf and Cmax values over the range of 5 ug to 10 ug using TY2P12SD database.

PK Parameter	Dose (µg)	Power Model Equation	Predicted Geometric Mean PK Parameter Value	Ratio of Dose Normalized Geometric Means (90% CI) [c]	Conclusion Over Dose Range [d]
$AUC_{0-\infty}$ (pg-h/mL)	5	$(127.29 \times D)^{0.96}$	595.41	0.97 (0.93, 1.02)	Yes
	10		1157.11		
C_{max} (pg/mL)	5	$(34.31 \times D)^{0.79}$	122.88	0.87 (0.82, 0.91)	Yes
	10		212.86		

Abbreviations: $AUC_{0-\infty}$ = area under the concentration-time curve from 0 to infinity, CI = confidence interval, C_{max} = maximum concentration, D = dose, PK = pharmacokinetic

[a] Power Model from full dataset (Appendix 2.7.2.5.1)

[b] Dose-proportionality (predicted geometric means and ratios) assessed on 5-µg to 10-µg dose range

[c] Ratio of model-predicted geometric mean values for high to low dose, normalized for dose

[d] Dose-proportionality was concluded over the dose range if the 90% CI for ratio of dose normalized geometric means was entirely contained within 0.7 and 1.43.

Data Source: Combined Single-dose Database

The estimated exponents of the power model equations for AUC0-inf and Cmax were 0.96 and 0.79, respectively. The sponsor did not include the 90% CI in the original NDA submission. Via email (Feb. 14, 2005), the sponsor provided the 90% CI values that were 0.8910 to 1.0261 and 0.7137 to 0.8716, respectively, for the exponents of the power models of AUC0-inf and Cmax. Therefore, dose proportionality was concluded for AUC0-inf over the dose range of 5 ug to 10 ug. The Cmax values were less than proportional. The sponsor concluded dose proportionality for both AUC0-inf and Cmax based on the 90% CI for the ratios of dose-normalized geometric means being between 0.70 and 1.43, which was not acceptable.

3. What covarites affected the pharmacokinetics of exenatide?

Population pharmacokinetic analyses (NONMEM) have demonstrated statistically significant effects of body weight and anti-exenatide antibody status on clearance, body weight and antibody titer ratio on volume of distribution, and gender on rate of absorption.

The final population PK model describing the pharmacokinetics of exenatide was a one-compartment model with first-order elimination and a nonlinear absorption modeled as a combination of a Michaelis-

Menten process plus a linear absorption rate. The nonlinear absorption rate constant depended on the amount of drug remaining to be absorbed.

The mean (SD) apparent clearance (CL/F) and apparent volume of distribution (V/F) were 9.11 (4.72) L/hr and 64 (102) L, respectively. The population mean CL/F increased approximately 3.7-fold as weight increased from 50 to 160 kg for both anti-exenatide antibody-negative and positive subjects (4.9 to 18.1 L/hr and 2.4 to 8.9 L/hr, respectively). The antibody-positive subjects had approximately half the typical CL/F value relative to subjects who were antibody-negative. The population mean V/F increased approximately 3.7, 3.0, 2.0, and 1.3-fold as weight increased from 50 to 160 kg for anti-exenatide antibody-negative subjects and subjects with titer ratios of 5, 25, and ≥ 125, respectively.

CL/F stratified by antibody status, gender, and weight less than or greater than the median (95 kg) showed the median CL/F value ranged from 8.2 to 10.8 L/hr and 4.3 to 8.3 L/hr for antibody-negative and -positive patients, respectively. The median V/F for each of the strata ranged from 22 to 36 L and 72 to 118 L for antibody-negative and -positive subjects, respectively. Considering the negative antibody status for the noncompartmental meta-analysis, the results of this population analysis was consistent with the noncompartmental meta-analyses where the mean CL/F and V/F were 9.1 L/hr and 28.3 L, respectively.

The population pharmacokinetic model development is briefly described as follows:

A total of 4870 exenatide concentrations obtained from 242 patients from ten trials including Studies 2993-102, -103, 104 (Part 2), -105, -107, -110, -112, -113, -115, and -118 were included in the final population pharmacokinetic analysis. Among them, 90 patients were from phase 1 studies and 152 patients from Phase 2 and 3 studies. Among the patients from phase 2 and 3 studies, approximately 46% patients had anti-exenatide anti-body-positive observation. Overall, sixty-five percent of the patients were male and the mean age of the population was 54 years with a range of 22 to 73. Patient weight varied from 50 to 162 kg with a mean of 94 kg and the mean creatinine clearance was 95 mL/min with a range of 42 to 297 mL/min. In addition, 53%, 14%, and 30% of the population was Caucasian, Black, and Hispanic, respectively. Twenty-eight percent of the patients received sulfonylureas and 55% received metformin concomitantly with exenatide.

The one-compartment model with linear elimination and a combination of linear and non-linear absorption was previously developed in the interim analysis using data from 4 studies including Studies 2993-102, -103, -104 (Part 2), and -105. In the interim analysis, a one-compartment model with first-order elimination and first-order or zero absorption were also evaluated. The selection of non-linear absorption was based on the goodness-of-fit (GOF) plots. However, the change in the minimum value of the objective function (MVOF) was not statistically significant. This model was further evaluated using the data from ten trails. Again, based on the trends of GOF plots, the model including the non-linear components of the absorption (Equation 1) was selected as the structural model.

Equation 1:

$$Ka = \frac{KaMax}{Ka_{50} + A(1)} + KaL$$

Where:

Ka:	the absorption rate constant
KaMax (ug/hr):	the maximum absorption rate of the nonlinear component
Ka50:	the drug amount in the depot compartment required to achieve 50% of the maximum absorption rate of the nonlinear components
A(1) (ug):	the amount of drug remaining to be absorbed from the depot compartment
KaL (1/hr):	the linear absorption rate constant.

The influence of anti-exenatide antibody on the pharmacokinetics of exenatide was evaluated first using a forward selection approach ($\alpha = 0.05$). The impact of anti-exenatide antibody absence on CL/F and the effect of titer ratio as a piece-wise linear function on V/F were incorporated based on significant decrease in MVOF as well as decrease in the inter-individual variability (IIV) in the parameter of interest. The apparent clearance was estimated to be 4.86 L/hr for anti-exenatide antibody-positive subjects and was estimated to be 9.72 L/hr (100% increase) for negative subjects. V/F was estimated to be 35, 40, 60, and 160 L for titer ratios of 0, 5, 25, and 125 and greater, respectively.

Following the evaluation of the influence of anti-exenatide antibody presence (ANTI), various patient demographics including gender, race, age, weight (WTKG), height, ideal body weight (IBW), percent of ideal body weight (%IBW), body mass index (BMI), and body surface area (BSA), and various clinical chemistries including serum creatinine (SCr), alkaline phosphatase (ALP), alanine aminotransferase (ALT), albumin (ALB), gamma-glutamyl transferase (GGT), total bilirubin (TBIL), aspartate aminotransferase (AST), and creatinine clearance (CrCL) were tested using forward selection process ($\alpha = 0.05$). Based on the significant decrease in MVOF and decrease in IIV of parameter of interest, effect of gender and GGT on KaL, effects of ideal body weight, percent ideal body weight, and CrCL on CL/F, and effects of weight and CrCL on V/F were incorporated to the model.

The exponential error model was originally used in the full multivariable model. An additive residual variability model was evaluated and the results showed that the precision of many parameter estimates became much weaker. Therefore, the exponential error model for the IIV of all parameters was retained. The model with the covariance of all etas estimated was evaluated. The covariances of all etas were poorly estimated. Therefore, the model was tested in which the estimates of all etas covariances were removed. The results showed no apparent difference in GOF plots and improved precision of KaMax and Ka50. Thus, an exponential error model for the IIV of all parameters was kept in the full multivariable model without the estimation of eta covariances.

All covariates included in the multivariable model were further evaluated using a backward elimination process ($\alpha = 0.001$). The effect of CrCL on V/F and CL/F were dropped because they contributed less than 10.83 change in the MVOF. All remaining covariates including %IBW, IBW, and ANTI on CL/F, WTKG and antibody titer on V/F, and GGT and gender on KaL were statistically significant.

Consequently, the effect of concomitant medications including sulfonylureas and metformin on CL/F were evaluated. The presence of both sulfonylureas and metformin was significant ($p<0.05$). However, incorporating the effect of sulfonylureas or metformin caused the IIV of CL/F increase. Therefore, the effect of sulfonylureas and metformin on CL/F was not incorporated into the model.

The model was further simplified by eliminating the effect of IBW and %IBW $\geq$ 180% on CL/F and added the effect of weight on CL/F based on the decrease in the IIV of CL/F. The effect of GGT on KaL was removed because it appeared that the significance of the relationship was being driven by three extreme observations. The revised model was the final pharmacokinetic model with effect of antibody and weight on CL/F, effect of antibody titer and weight on V/F and effect of gender on KaL. Parameter estimations and standard errors for the final pharmacokinetic model are presented (**Table 4**).

Table 4. Parameter Estimates and Standard Errors for the Final Pharmacokinetic Model

Parameter	Final Parameter Estimate		Magnitude of Interindividual Variability	
	Population Mean	%SEM	Estimate (%CV)	%SEM
Ka Max (µg/hr)[4]	2.67	59.2		
Ka50 (µg)[4]	3.56	49.4		
KaL (1/hr)[3]	0.237	36.6	135.65	65.2
CL/F (L/hr)[2]	4.51	14.9	55.50	19.5
V/F (L)[1]	168	20.6	64.5	22.0
CL/F Shift – No Anti.[2]	1.03	33.9		
V/F Slope for Titer ≤ 125[1]	1.08	25.6		
KaL Shift - SEXF	0.679	38.3		
CL Power – WTKG	1.12	16.5		
V Power - WTKG	0.205	24.6		
RV (SD-Log Unit)	0.32	7.9		

MVOF=-4455.110

[1] Population mean parameters V/F and V/F slope for titer ≤ 125 were highly correlated $r^2 \geq 0.8$.

[2] Population mean parameters CL/F and CL/F shift No Antibody were highly correlated $r^2 \geq 0.8$.

[3] Population mean parameters KaL and IIV of KaL were highly correlated $r^2 \geq 0.8$.

[4] Population mean parameters Ka Max and IIV of Ka50 were highly correlated $r^2 \geq 0.8$.

KaMax (59.2% SEM), Ka50 (49.4%SEM) and IIV of KaL (65.2%SEM) were not well estimated. The IIV of KaL, CL/F, and V/F was 135.6%, 55.5%, and 64.5%CV, respectively, as compared to 117%, 91.9%, and 89.6%CV for the base pharmacokinetic model (including no covariate effects).

The population mean values of the pharmacokinetic parameters were estimated as described in the following equations:

$$Ka_{ij} = 2.67 * A(1)_{ij} / (3.56 + A(1)_{ij}) + 0.237 * (1 + 0.679 * SEXF_j)$$

$$CL/F_{ij} = (4.51 * (WTKG_j / 87)^{1.12} * (1 + 1.03 * ANTIncg_{ij}))$$

$$V/F_{ij} = 168 * (WTKG_j / 87)^{0.205} + 1.08 * (TITER_{ij} - 125) \cdot (TTRG_{ij})$$

Where:

Ka_{ij} = typical value of Ka at the i^{th} sampling time for the j^{th} subject.

CL/F_{ij} = typical value of CL/F at the i^{th} sampling time for the j^{th} subject.

V/F_{ij} = typical value of V/F at the i^{th} sampling time for the j^{th} subject.

$A(1)_{ij}$ = amount remaining in the depot compartment at the i^{th} time for the j^{th} subject.

$SEXF_j$ = gender of the j^{th} subject (0= male and 1=female).

$WTKG_j$ = total body weight (kg) of the j^{th} subject.

$ANTIneg_{ij}$ = anti-exenatide status of the j^{th} subject at the i^{th} sampling time (0=antibody positive and 1=antibody negative),

$TITER_{ij}$ = the anti-exenatide antibody titer ratio at the time of the i^{th} sample for the j^{th} subject, and

$TTRG_{ij}$ = anti-exenatide titer ratio of the j^{th} subject at the i^{th} sampling time (0 if titer ratio > 125 and 1 if titer ratio ≤ 125).

It was predicted that CL/F increased approximately 3.7-fold as weight increased from 50 kg to 160 mg for both anti-exenatide antibody negative and positive subjects (4.9 to 18.1 L/hr and 2.4 to 8.9 L/hr, respectively). For antibody positive subjects, CL/F was approximately half the value for antibody negative subjects. As body weight increases from 50 to 160 kg, V/F increased 3.7 fold for antibody-negative subjects, and increases approximately 3-fold, 2-fold, and 1.3-fold for subjects with titer ratios of 5, 25, and >=125, respectively. The typical value of V/F increased by 5, 27, and 135 L for titer ratios of 5, 25, and >125, respectively **(Figure 1)**

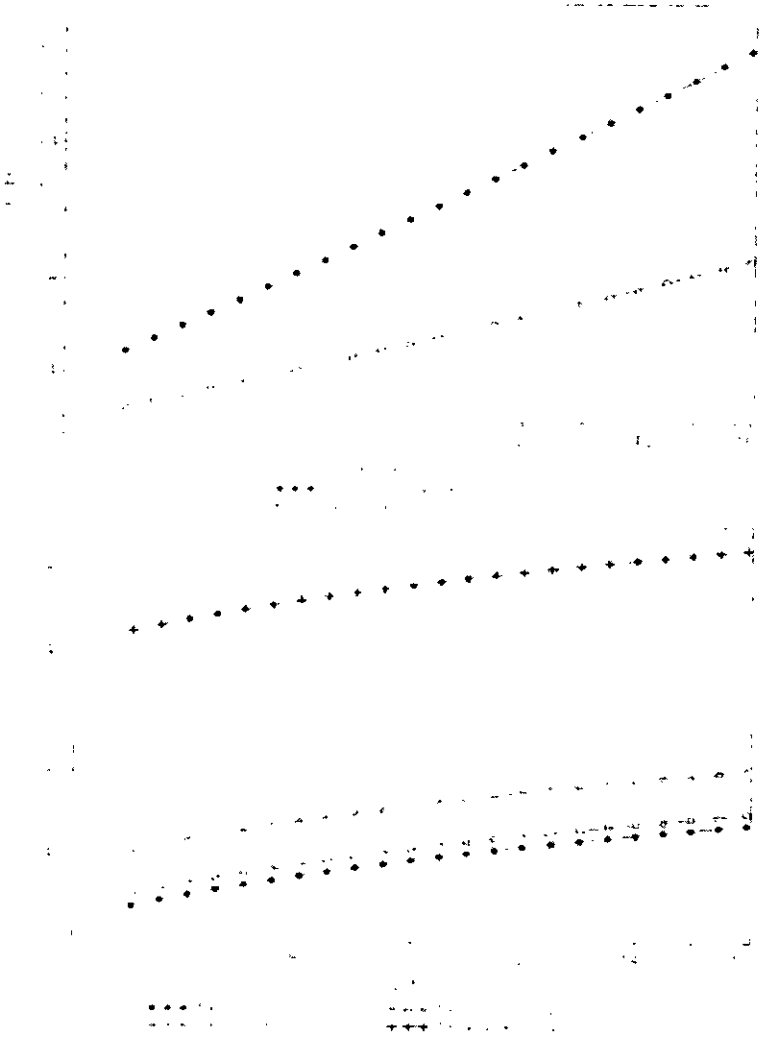


Figure 1. Population Mean Values of CL/F and V/F versus Weight for the Final PK Model

Comments: According to Dr. Jim Wei (primary Clinical Pharmacology Reviewer), the sponsor did not conduct any study to evaluate the effect of exenatide antibody in human plasma on the measurement of

exenatide in the assay development. Therefore, the antibody effect on clearance and volume of distribution discovered in this population pharmacokinetic analysis might be attributed to the measurement error caused by the presence of antibody and/or altered elimination and distribution characteristics by antibody. Therefore, a definite conclusion on the effect of antibody on PK parameter can not be drawn before an in vitro study of evaluating the antibody effect on the measurement of exenatide in plasma is conducted. However, the evaluation of the effects of other covariates on pharmacokinetic parameter is still valid because the model considered the antibody effect. The clearance was evaluated by splitting the data into two groups, antibody negative and antibody positive.

Appendix:

Noncompartmental Meta-Analyses: Noncompartmenal pharmacokinetic parameters of a single dose exenatide in type 2 diabetic patients derived from six Phase 1 and Phase 2 studies (Studies 2993-102, -103 (day 1), -104 (Part 2), -107 (Day 1), -110, and -118(SC treatment arm)) were combined to form a combined, single-dose meta-analyses database (TY2P12SD). Multiple parameter estimates from the same individual were considered discrete data in the analyses. Studies 2993-102, -103, -110, and -118 involved pharmacokinetic sampling for longer duration (≥ 10 hour post dose) compared with the other two studies 2993-104 and 2993-107 (5 to 6 hour post dose) and were deemed to yield more reliable estimates of clearance and volume of distribution. Therefore, the clearance and volume of distribution were not calculated for those patients participating in Studies 2993-104 and 2993-107. Demographic values at admission were used for the meta-analyses. Covariate analyses were conducted on the pharmacokinetic parameters CL/F and V/F. For the evaluation of age, gender, racial origin, and obesity (BMI ≥ 30 kg/m^2), a linear mixed effects model was fitted to calculate least squares means and their variability using SAS, where subject was a random effect, and the log-transformed dose, weight, Cockcroft-Gault creatinine clearance (CGCL) were fixed effect. All the covariates were included together as fixed effects to evaluate the effect of each covariate when other covariate effects were adjusted. For the evaluation of the relationship between CL/F and CGCL, data from study H8O-EW-GWAB were also combined with the Combined, Single -dose dataset. For each covariate, the ratios of geometric means and the corresponding 95% confidence intervals between categories were calculated (**Table**).

Table. Effects of Gender, Age, Race, Obesity, and Cockcroft-Gault Creatinine Clearance on Single Dose Noncompartmental Pharmacokinetic Parameters of Exenatide Obtained from Studies 2993-102, -103, -110, -118, and Study H8O-EW-GWAB

	PK parameter		No of subject	LS-GM	Comparison	Ratio (95% CI)	p-value
Gender[1]	Cl/F (L/hr)	Male	50	9.53	Male/female	1.15 (0.97, 1.37)	0.1107
		Female	17	8.28			
	Vz/F (L)	Male	50	30.04	Male/female	1.26 (0.99, 1.61)	0.0576
		Female	17	23.80			
Age[1]	Cl/F (L/hr)	< 65 yrs	59	8.98	<65 />=65	1.12 (0.97, 1.29)	0.1221
		>=65 yrs	8	8.04			
	Vz/F (L)	<65 yrs	59	26.53	<65/>=65	0.92 (0.76, 1.12)	0.3898
		>=65 yrs	8	28.88			
Race[1]	Cl/F (L/hr)	Caucasian	24	7.98	Caucasian/Black	0.78 (0.64, 0.94)	**0.0123**
		Hispanic	31	8.56	Caucasian/Hispanic	0.93 (0.79, 1.10)	0.3976
		Black	12	10.26	Hispanic/Black	0.83 (0.68, 1.02)	0.0810
	Vz/F (L)	Caucasian	24	21.73	Caucasian/Black	0.63 (0.48, 0.83)	**0.0012**
		Hispanic	31	25.62	Caucasian/Hispanic	0.85 (0.67, 1.07)	0.1564
		Black	12	34.34	Hispanic/Black	0.75 (0.56, 0.99)	0.0410
Obesity[1]	CL/F (L/hr)	BMI>=30 kg/m^2	37	9.80	>=30 /<30	1.22 (1.00, 1.47)	**0.0449**
		BMI<30 kg/m^2	30	8.05			

	Vz/F (L)	BMI>=30 kg/m^2	37	29.17	>=30 / <30	1.19 (0.91, 1.55)	0.1924
		BMI<30 kg/m^2	30	24.51			
CGCL[2] (mL/min)	CL/F (L/hr)	Normal (>80)	71	8.14			
		Mild (>50, ≤80)	12	7.11	mild/ normal	0.87 (0.69, 1.11)	0.2581
		Moderate (>30, ≤50)	6	5.19	Moderate/ normal	0.64 (0.46, 0.89)	**0.0083**
		ESRD (≤30)	8	1.33	ESRD/ normal	0.16 (0.12, 0.22)	**<0.0001**

1. Model: ln(PK) = ln(DOSE) AGE WEIGHT CGCL GENCAT (gender category) OBESECAT (obese category) RACECAT (race category)
2. Model: ln(PK)= ln(DOSE) wegith CGCLCAT (CGCL category)

Results showed that clearance and volume of distribution were approximately 15% and 26% higher, respectively, in males (50 patients) compared with females (17 patients). However, the differences in both clearance and volume of distribution were not statistically significant.

The influence of age on clearance and volume of distribution was evaluated using two categories: <65 years of age (59 patients) and ≥ 65 years (8 patients). There was no statistically significant difference in clearance or volume of distribution between the two age groups.

The influence of race was evaluated for Caucasians (24 patients), Hispanics (31 patients), and Blacks (12 patients). Caucasian patients showed least square (LS) mean estimates of clearance and volume of distribution that were approximately 22% and 37% lower, respectively, than those of Black patients. There was no significant different in clearance or volume of distribution between Hispanics and Caucasians. Hispanics had 17% and 25% lower in clearance and volume of distribution, respectively, compared to Black. However, the difference in clearance was not statistically significant.

The influence of obesity (defined as BMI ≥ 30 kg/m^2) on clearance and volume of distribution was evaluated in 37 obese patients and 30 non-obese patients. Statistical analyses showed that obese patients exhibited approximately 22% higher clearance and 19% higher volume of distribution than non-obese patients did. These differences were statistically significant for clearance but not for volume of distribution.

The influence of renal impairment (CGCL) on clearance was evaluated in 71 patients with normal renal function, 12 mild impaired patients, 6 moderate impaired patients, and 8 patients with end-stage renal disease (ESRD). Statistical analyses implied that mild impaired patients had comparable clearance as patients with normal renal function. However, for patients with moderate renal impairment and patients with ESRD, mean exenatide clearance was decreased by approximately 36% and 84%, respectively, compared with patients with normal renal function

Summary of Clinical Pharmacology and Biopharmaceutics Findings (Population Pharmacokinetic-Pharmacodynamic Analysis) prepared by Dr. Sang Chung

Exposure-response (E-R) relationship of exenatide was characterized using a population pharmacokinetics and pharmacokinetics analysis (PPKPD). The parameter for the exenatide exposure was area under the plasma concentration-time curve after subcutaneous injection (AUC_{exe}), and the response parameter was the postprandial glucose area under the curve (AUC_{glc}). A sigmoid-inhibitory E_{max} model was used to describe the E-R relationship.

The E-R analysis had the following major contribution to the issues related to CPB:

- Dosing regimens for Phase III studies (PPKPD Study 1) - justification on dosing transition from body weight adjusted dose (i.e., 0.01μg/kg to 0.4μg/kg in the Phase II studies) to fixed dose regimens for the Phase III studies (i.e., 5μg or 10μg BID),
- Identification of significant covariates on the pharmacodynamics of exenatide (PPKPD Study 2).

The PPKPD Study 1 for the justification on dosing transition was primarily composed of two parts:

1) Characterization of PPKPD using data from four Phase II studies (Study 2993-102 to 105)

Total of 195 PK-PD data from 50 patients were included in the study and dosing range was from 0.01μg/kg to 0.4μg/kg. An inhibitory E_{max} model was employed for the PK-PD modeling, and it was concluded that there was no covariate as a statistically significant predictor of AUC_{50} (exenatide exposure corresponding to 50% of maximal response).

2) Selection of fixed dosage regimens based on PPKPD results and simulations of the exenatide exposure

Optimal target window of exenatide AUC was chosen as between 600 pg h/ml and 950 pg h/ml based on acceptable glycemic benefits in efficacy (i.e., at least 30% reduction in AUC_{glc}) and gastrointestinal adverse events in safety (e.g., nausea and vomiting). The exenatide exposure up to 5 hours postdose ($AUC_{exe,0-5}$) were simulated using the Bayesian parameter estimates in the final PK model with doses of 0.1, 0.15, 0.175, and 0.2 μg/kg (Simulation Study 1). Total doses ranging from 5μg to 16μg with median value of 9μg showed exenatide exposure within the target window according to the results of Simulation Study 1. Doses of 5, 9, 10, and 12μg were selected to simulate the exenatide exposure range ($AUC_{exe,0-5}$) under fixed dosage regimens (Simulation Study 2). Fixed dosing of 5μg or 10μg BID was proposed under the conclusion that two doses would have a favorable balance of glucose reduction and incidence of adverse events based on the results of Simulation Study 2. The results were presented at the End-of-Phase 2 (EOP2) meeting between the sponsor and the Agency.

To identify significant covariates for the postprandial glucose exposure, PPKPD analysis (PPKPD Study 2) was conduced using 540 PK-PD data from 183 patients. Exenatide exposure up to 3 hours postdose ($AUC_{exe,0-3}$) and corresponding postprandial glucose exposure ($AUC_{glc,0-3}$) were the PK and PD parameters. In the PPKPD Study 2, PK-PD data were from two Phase 2 studies (Study 2993-107 and 2993-110) and four Phase 3 studies (Study 2993-112, 113, 115, and 118) in addition to data for the PPKPD Study 1. A sigmoid-inhibitory E_{max} model was employed for the PPKPD analysis, and the influence of covariates on E_{max} and AUC_{50} (exenatide exposure corresponding to 50% of maximal response) was evaluated to identify significant covariates. Baseline $AUC_{glc,0-3}$ and antibody status were identified as significant covariates on E_{max} and AUC_{50}. However, it was concluded that there was no clinical significance of the covariate effect and thus no dose adjustment. The inter-subject variability of AUC_{50} for the final model was about 62.5% as CV.

Review comments were identified as follows:

- Model for the PK-PD relationship: a sigmoid-inhibitory E_{max} model
  The E_{max} was assumed to be a constant fraction of baseline glucose AUC (e.g., E_{max} = a * (baseline glucose AUC)) in the final model of the PPKPD Study 1 and 2. Although the assumption might be

acceptable in a theoretical consideration, it appears to be overly simplified (Figure 1). For example, drug effect can be proportional or inversely proportional to the baseline glucose AUC as illustrated in Figure 2. Therefore, it is recommended to estimate E_{max} and AUC_{50} of exenatide in the study conditions, not based on an assumption.

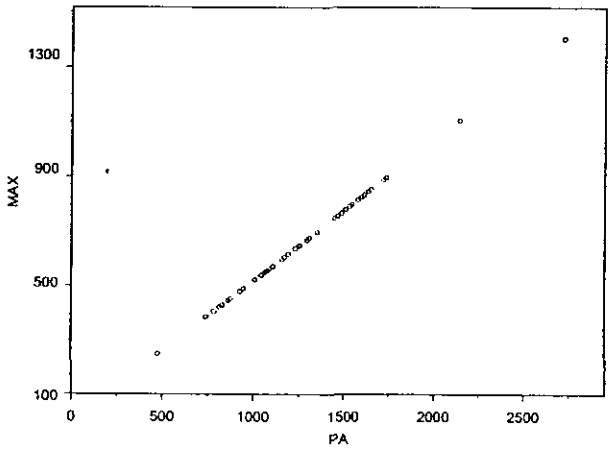


Figure 1 **Relationship between baseline glucose AUC_{0-5} (PA) and estimate of E_{max} (MAX) for the final model (PPKPD Study 1); E_{max} = 0.5146 *(baseline glucose AUC) - 0.0002**

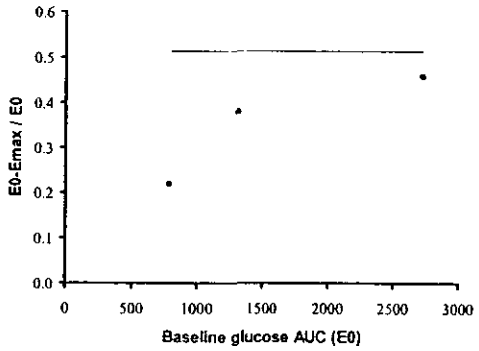


Figure 2 **Relationship between baseline glucose AUC and apparent E_{max} (closed circle for the apparent E_{max} from 3 patients, and line for the proposed E_{max} as a constant fraction in the modeling)**

There was underlined assumption to be tested in the selection of E_{max} model, and that was PK-PD was assumed to be in the apparent plateau. However, apparent E_{max} was observed only in 6% of patients according to the exploratory analysis (i.e., 3 patients out of total 50 patients; Figure 3). Therefore, it should be cautious in the interpretation and application of the E_{max} modeling results.

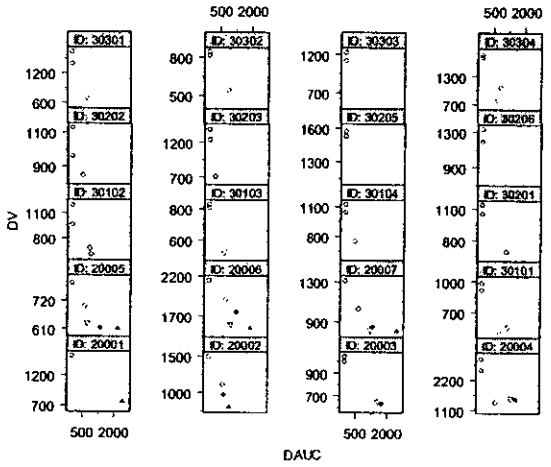


Figure 3 **Individual relationship between exenatide AUC_{0-5} and glucose AUC_{0-5} (20 patients out of total 50 patients as examples) (3 patients showed apparent E_{max}; patient ID 2004, 20005, and 20007)**

- Parameters for PK and PD
  Exenatide AUCs up to 3 hours (i.e., $AUC_{exe,0-3}$ and $AUC_{glc,0-3}$) were used for the PPKPD Study 2. According to the explanation by the sponsor, the AUC truncation was necessary to use data from Phase III studies, where limited sampling was unavoidable. However, the systematic AUC truncation brought a drawback for the PK-PD relationship. The representative profiles of concentration-time are shown in Figure 4, and exenatide exposure appeared to be truncated in the area of maximum concentration, which was expected based on t_{max} of 2.1 hr and $t_{1/2}$ of 2.4 hr. It indicated that E-R could be systematically biased.

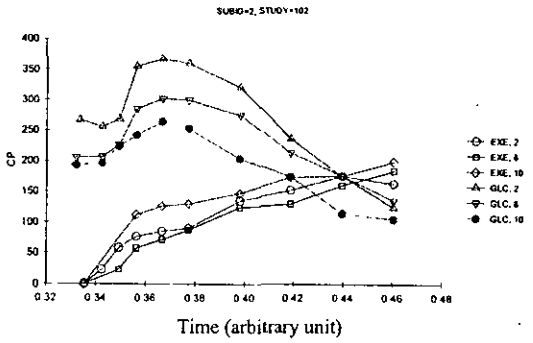


Figure 4 **Representative concentration-time profiles for plasma exenatide (EXE) and glucose (GLC) in the PPKPD Study 2**

In addition, all the AUCs were calculated using the trapezoidal rule. It indicated that the AUC did not differentiate anti-hyperglycemic effect (efficacy) and hypoglycemic effect (safety) because of the averaged nature on fluctuation above and below baseline (Figure 4).

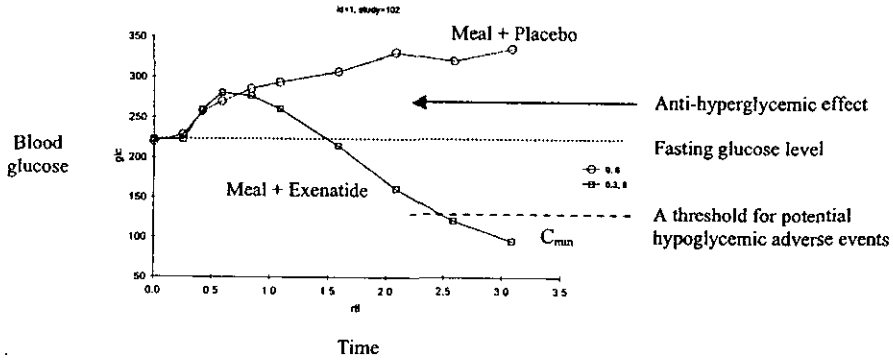


Figure 4 **Postprandial glucose excursion and possible effects of exenatide on it in a patient**

In these regards, it is recommended considering a predictor for hypoglycemic adverse events using AUC below a threshold in conjunction with minimum glucose concentration (C_{min}).

A sparse sampling for population analysis is intended to reduce number of sampling, not to limit sampling period. Therefore, it is recommended considering a prospectively study design in the future PPKPD study using a sparse sampling principle in the number of sampling, not to systematically limit sampling period.

- Postprandial glucose excursion as a PD marker

The postprandial glucose excursion (PGE as AUC_{glc}) was the primary PD marker for the PPKPD analysis, and the PGE data were obtained after single doses, or different times after multiple doses. Without having a quantitative characterization on kinetics of exenatide on PGE, the sponsor's PGE data contained confounding factor of variability by time. Therefore, it is recommended considering characterization of kinetics of exenatide on PGE to demonstrate a clinically meaningful PK-PD analysis using exenatide exposure and glucose AUC.

2. Summary of PPKPD Study 1

Data

Exenatide AUC and glucose AUC up to 5 hours postdose were calculated using trapezoidal rule. Plasma glucose concentrations were measured following a Sustacal® breakfast except Study 105, where a standardized solid breakfast was provided. Samples for glucose were collected following a single doses, after multiple doses (i.e., five days of BID dosing, or two days of QID dosing), or infusion (i.e., two days of continuous infusion).

Statistical Methods

Data preparation and PK-PD analysis were primarily conducted using SAS® and NONMEM®. The change in the minimum objective function value was used to define statistical significance in the hierarchical

model selection. The goodness-of-fit was assessed by the examination of weighted residuals, percent standard error (SE/estimate ×100), and changes in the estimates of inter-subjects, and residual variability for the specific model. The general procedure to develop the PK-PD modeling was followed diagnostic plots, structural models development, univariate analysis of covariates, evaluation of statistical error models, backward elimination of covariates, and the final model establishment.

Structural PK-PD Model

$$AUC_{glc,0-5} = E_0 - \left[\frac{E_{max} \times AUC_{exe,0-5}}{AUC_{50} + AUC_{exe,0-5}}\right]$$

where,

E_0 = measured baseline glucose AUC when administered placebo (mg h/dL)
E_{max} = the maximum reduction in glucose ACU_{0-5} from placebo (mg h/dL)
AUC_{50} = the exenatide AUC at which 50% of the maximum reduction in glucose AUC occurs
An exponential error model and an additive error model were incorporated for inter-subject variability and residual variability of AUC50, respectively.

Results

The relationship between exenatide exposure ($AUC_{exe,0-5}$) and glucose response ($AUC_{glc,0-5}$) was described by an sigmoid-inhibitor E_{max} model, and results were summarized in the following figures and tables.

Figure 5 **Goodness-of-fit plots for the structural PK-PD model; measured glucose AUC vs. predicted values (left panel), and predicted values vs. weighted residuals (right panel).**

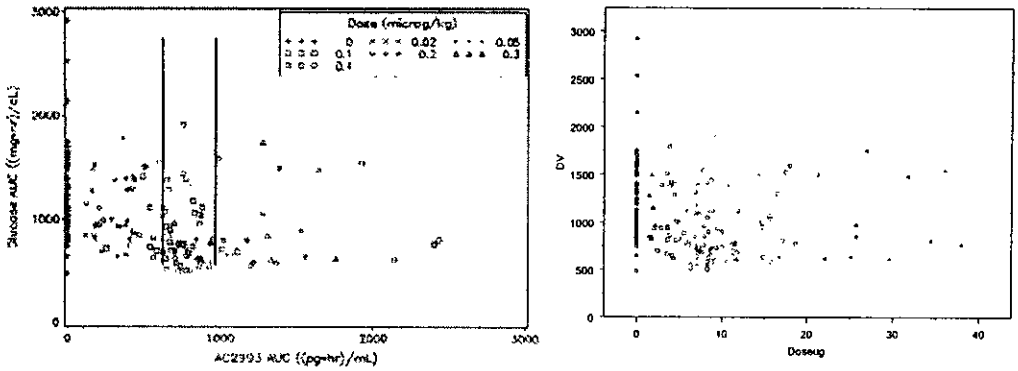


Figure 6 **Glucose AUC vs. exenatide AUC with the optimal window (left panel), and glucose AUC vs. total doses (right panel)**

Table 1 **Summary statistics for the PK-PD model building results**

Model	MOFV	DF	Change in MOFV
Inhibitor E_{max}	2095.24		
Inhibitory sigmoid-E_{max}	2093.676	1	-1.568
Inhibitory E_{max}, E_{max} linear function of baseline glucose AUC	Minimization not successful	1	
Inhibitory E_{max}, E_{max} proportional to baseline glucose AUC	2065.006	0	-30.238

Table 2 **Estimates and SE for the structural model***

Parameter	Population mean		Inter-subjects variability (%CV)	
	Final estimate	%SEM	Final estimate	% SEM
AUC_{50} (pg h/ml)	444	29.3	29.3	29.3
E_{max} (fraction of baseline glucose AUC)	0.515	6.6		
Residual variability (SD)	100.0	19.6		

*: $$AUC_{glc,0-5} = E_0 \times \left[1 - \frac{E_{max} \times AUC_{exe,0-5}}{AUC_{50} + AUC_{exe,0-5}}\right]$$

Influence of covariates on AUC_{50} were evaluated were evaluated. Weight and creatinine clearance were identified as statistically significant covariate based on univariate analysis between Bayesian estimates of AUC50 and covariates (e.g., age, HbA1c, placebo AUC, breakfast, insulin, weight, and CrCL). However, both covariates were not retained in the final model because step-wise backward elimination of the covariates from the full multivariable model did not show statistical significance (p>0.006)

Simulation Study

Selection of the target window

Dose limiting adverse events (nausea and vomiting) were greater in the 0.2, 0.3, and 0.4 µg/kg dosing. Therefore, exenatide exposure was decided to be less than that after 0.2 µg/kg dose. The upper window was chosen as 950 pg h/ml because it was shown to be a representative exposure dataof lower 25% after 0.2µg/kg dosing and upper 75% after 0.1µg/kg dosing.

Based on the PK/PD modeling, postprandial glucose AUC was reduced about 30% with exenatide AUC of 596 pg h/ml.

Based on the above information, the target window was selected as 600-950 pg h/ml.

To predict exenatide AUC range, exenatide AUCs were simulated using the Bayesian parameter estimates from the final model with 4 doses (0.1, 0.15, 0.175, and 0.2 µg/kg). Among 50 subjects, 46 subjects had at least one in the target range, and the average total dose ranged from 5 to 16 µg with a median of 9 µg.

Based on the above results, exenatide exposure was simulated for the fixed doses of 8, 9, 10, 11, and 12µg for the population of 50 subjects. Results of 9 and 10µg doses showed the highest percentage of subjects within the target window (i.e., 60 and 56%, respectively).

Clinical trial simulation (CTS) was conducted using 4 doses; two doses from the above results, and two other doses (5 and 12µg) as alternatives. For each doses, ten trials were simulated using 100 subjects. The results were summarized in the following table.

With the 10µg dose, exenatide exposure was predicted to be less than the upper limit window in 77% of the subjects, and about 75% of the subjects showed more than 20% glucose AUC reduction. In addition, 5µg dose showed that about 61% of the subjects were at least 20% glucose AUC reduction yet most subjects were below the upper limit of exenatide exposure window. Therefore, two doses were selected as the fixed dose regimen for the Phase III studies.

Table 4 **Distribution of exenatide AUC and % glucose AUC reduction from placebo**

Dose (µg)	Exenatide AUC			Glucose AUC		
	% of subjects <600	% of subjects 600-950	% of subjects > 950	% of subjects <20% reduction	% of subjects 20-40% reduction	% of subjects >40% reduction
5	91.7	8.2	0.1	39	47.5	13.5
9	19.8	65.7	14.5	24.5	55.9	19.8
10	13	63.9	23.1	23.4	54.8	21.8
12	6.6	42.2	51.2	20.1	55.5	24.4

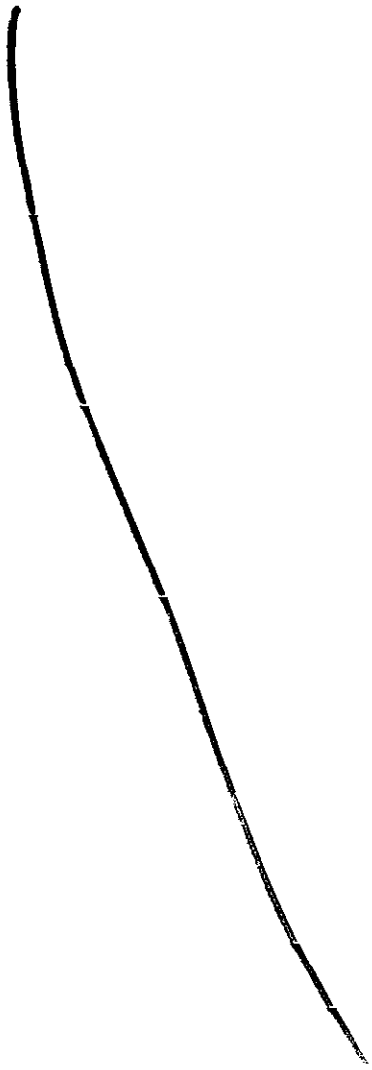
1 Page(s) Withheld

✓ § 552(b)(4) Trade Secret / Confidential

_____ § 552(b)(5) Deliberative Process

_____ § 552(b)(5) Draft Labeling

Withheld Track Number: Clin Pharm/Bio- 2



3. Summary of PPKPD Study 2

Data and Statistical Methods

Total of 540 pairs of exenatide AUC-glucose AUC from 183 patients were included in the study. Exenatide AUC and glucose AUC up to 3 hours postdose were calculated using trapezoidal rule. A sigmoid inhibitory E_{max} model was employed to characterize PPKPD.

Data preparation and PK-PD analysis were primarily conducted using NONMEM®. The change in the minimum objective function value was used to define statistical significance in the hierarchical model selection. The goodness-of-fit was assessed by the examination of weighted residuals, percent standard error (SE/estimate ×100), and changes in the estimates of inter-subjects, and residual variability for the specific model. The general procedure to develop the PK-PD modeling was followed diagnostic plots, structural models development, univariate analysis of covariates, evaluation of statistical error models, backward elimination of covariates, and the final model establishment.

The influence of anti-exenatide antibody status, demographic factors, CrCL, dosing regimen, average hourly dose rate, breakfast type, baseline HbA1c, method of diabetes control prior to treatment, and concomitant medication use on PK/PD were evaluated using forward selection (α=0.05) followed by backward elimination (α=0.001).

Final PK-PD Model

$$AUC_{glc,0-3,ij} = E_{0,j} - \left[\frac{E_{\max,j} \times AUC_{exe,0-3,ij}^{\ S}}{AUC_{50,j}^{\ S} + AUC_{exe,0-3,ij}^{\ S}} \right]$$

$$AUC_{50,j} = 169 * (1+1.25*DRI_{ij})$$

$$E_{max_J} = (0.258*BLGAUC_j)*(1+0.329*NANTI_{ij})$$

where,

E_0 = measured baseline glucose AUC when administered placebo (mg h/dL)

E_{max} = the maximum reduction in glucose ACU_{0-5} from placebo (mg h/dL)

AUC_{50} = the exenatide AUC at which 50% of the maximum reduction in glucose AUC occurs

S = 2.42

DRI = 1 if the ith pair in the jth subject followed multiple doses of exenatide for 2-5 days and 0 otherwise.

BLGAUCj = placebo glucose AUC in the jth subject

NANTIij = 1 if the ith AUC pair in the jth subject was collected in the absence of anti-exenatide antibody and 0 otherwise.

An exponential error model and an additive error model were incorporated for inter-subject variability and residual variability of AUC50, respectively.

Results

The final model retained three covariates; baseline glucose AUC and antibody presence for E_{max}, and the effect of dosing regimen (i.e., 2-5 days vs. 4 weeks or greater) on AUC_{50}. The sponsor concluded that the effect of dosing regimen (2-5 days vs. single dose or dosed > 5 days) was not clinically significant covariate because numbers of observation at the 2-5 days were fairly few and confounded by other study design factors. In addition, E_{max} difference is small between antibody positive (26%) and antibody negative (34%) patients with large intersubject variability. Therefore, there was no dose adjustment for antibody, and no routine measurement of antibody was proposed based on no clinically significant safety concerns.

Estimates of the final model were summarized in the following table and data were shown in the following figure.

Table 6 Estimates and SE for the final structural model

Parameter	Final Parameter Estimate		Magnitude of Interindividual Variability	
	Population Mean	%SEM	Estimate[1]	%SEM
AUC_{50} DREG = 1,2,5, 6[2]	169	12.5	62.45	20.4
S	2.42	19.1		
EMAX slope – BLGAUC	0.258	15.2	114.02	19.7
EMAX shift – NANTI	0.329	66.3		
AUC_{50} shift DREG=3, 4[2]	1.25	52.4		
RV (SD)	10.25	16.6		

MVOF=5421.127

[1] The IIV of AUC_{50} is expressed as %CV and the IIV of Emax is expressed as a standard deviation.

[2] DREG = 1 – Single doses with a 48 hour washout,
DREG = 2 – Single doses with a 24 hour washout.
DREG = 3 – Multiple doses for 2 days.
DREG = 4 Multiple doses for 5 days.
DREG = 5, 6 - Multiple doses > 4 weeks.

Parameter[1]	Subgroup[2]	Population n	Subgroup n	Mean	SD	Minimum	25th %-tile	Median	75th %-tile	Maximum
% Emax	A-	183	127	36.853	10.834		31.9	37	42.8	
% Emax	A+	183	56	28.991	15.003		22.1	29.65	38.5	
AUC_{50}	1 day, > 5 day	183	150	174.448	60.878		140.01	162.97	196.97	
AUC_{50}	MD 2-5 days	183	33	370.621	202.411		260.51	318.43	422.14	

[1] If a subject became antibody + during a study, the associated %EMAX value was used when computing the summary statistics.
If a subject received a maximum of 2-5 days of dosing, the associated AUC_{50} value was used when computing the summary statistics.

[2] A-/A+ denotes anti-exenatide antibody negative or positive.
MD represents subjects who received a maximum of 2-5 days of dosing and 1 day, > 5 day represents subjects who received single doses or more than 5 days of dosing.

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_____ § 552(b)(5) Deliberative Process

_____ § 552(b)(5) Draft Labeling

Withheld Track Number: Clin Pharm/Bio- 3

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/s/

Xiao-xiong Wei
4/12/05 10:46:44 AM
BIOPHARMACEUTICS

Individual study review

Hae-Young Ahn
4/12/05 11:57:50 AM
BIOPHARMACEUTICS

Office of Clinical Pharmacology and Biopharmaceutics
New Drug Application Filing and Review Form

General Information About the Submission

NDA Number	**21-773**	**Brand Name**	[redacted]
OCPB Division (I, II, III)	**DPE II**	**Generic Name**	**Exenatide**
Medical Division	**HFD-510**	**Drug Class**	**New class of anti-diabetic**
OCPB Reviewer	**Xiaoxiong (Jim) Wei**	**Indication(s)**	**Type 2 Diabetes Mellitus**
OCPB Team Leader	**Hae-Young Ahn**	**Dosage Form**	**0.25 mg/mL solution**
		Dosing Regimen	**5 - 10µg BID**
Date of Submission	**06-30-04**	**Route of Administration**	**S.C.**
Estimated Due Date of OCPB Review	**03-10-05**	**Sponsor**	**Amylin**
PDUFA Due Date	**04-30-05**	**Priority Classification**	**S1**
Division Due Date	**04-08-05**		

Clin. Pharm. and Biopharm. Information

	"X" if included at filing	Number of studies submitted	Number of studies reviewed	Critical Comments If any
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data, etc.	X			
Tabular Listing of All Human Studies	X			
HPK Summary	X			
Labeling	X			
Reference Bioanalytical and Analytical Methods	X			
I. Clinical Pharmacology				
Mass balance:				
Isozyme characterization:				
Blood/plasma ratio:				
Plasma protein binding:	X	1		
Pharmacokinetics (e.g., Phase I) -				
Healthy Volunteers-				
single dose:	X	2		
multiple dose:				
Patients-				
single dose:	X	2		
multiple dose:	X	11		
Dose proportionality -				
fasting / non-fasting single dose:	X			
fasting / non-fasting multiple dose:				
Drug-drug interaction studies -				
In-vivo effects on primary drug:				
In-vivo effects of primary drug:	X	4		
In-vitro:	X	2		
Subpopulation studies -				
ethnicity:				
gender:				
pediatrics:				
geriatrics:				

renal impairment:	X	1		
hepatic impairment:				
PD:				
Phase 2:				
Phase 3:				
PK/PD:				
Phase 1 and/or 2, proof of concept:	X	2		
Phase 3 clinical trial:				
Population Analyses -				
Data rich:	X	1		
Data sparse:	X			
II. Biopharmaceutics				
Absolute bioavailability:	X	(1)		
Relative bioavailability -	[redacted]	[redacted]		
solution as reference:				
alternate formulation as reference:				
Bioequivalence studies -				
traditional design; single / multi dose:				
replicate design; single / multi dose:				
Food-drug interaction studies:				
Dissolution:				
(IVIVC):				
Bio-wavier request based on BCS				
BCS class				
III. Other CPB Studies				
Genotype/phenotype studies:				
Chronopharmacokinetics				
Pediatric development plan				
Literature References				
Total Number of Studies		26		

Filability and QBR comments		
	"X" if yes	**Comments**
Application filable ?	**YES**	
Comments sent to firm ?	**NO**	

Briefing in Content:

[redacted] (Exenatide) is the first drug in a new drug class as an incretin mimetic to improve glycemic control in people with type 2 diabetes mellitus. Exenatide is a 39-amino acid peptide amide. Exenatide is rapidly absorbed with Tmax of 2.1 hrs following SC administration. Exenatide is predominantly eliminated through the kidney. The mean exenatide clearance is reduced to 0.9 L/h (compared with 9.1 L/h in healthy subjects) in patients with end-stage renal disease receiving dialysis.

The commercial formulation was used in pivotal clinical trials. PK and PD data were evaluated using population methods to characterize the exposure-response relationship. Total ten PK, PK/PD and clinical efficacy studies were used for population modeling.

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/s/

Xiao-xiong Wei
8/24/04 08:00:27 AM
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Hae-Young Ahn
8/24/04 09:58:08 AM
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