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MEDICAL REVIEW

CLINICAL REVIEW

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Established Name Exenatide Injection
(Proposed) Trade Name Exenatide
Therapeutic Class Incretin-mimetics
Applicant Amylin Pharmaceuticals Inc.

Priority Designation Standard

Formulation
Dosing Regimen BID SQ Injection
Indication To improve glycemic control
whether used alone or as an
adjunctive therapy to
metformin and/or a
sulfonylurea

Intended Population Patients with Type 2 Diabetes

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1 EXECUTIVE SUMMARY

1.1 Recommendation on Regulatory Action

- A) This Reviewer recommends the approval of exenatide as an adjunctive therapy to metformin, a sulfonylurea, or a combination of metformin and a sulfonylurea when they fail to achieve adequate glycemic control.

- B) The one short-term controlled trial #2993-120 to support the use of exenatide as a monotherapy does not suffice as a proof of efficacy. This Reviewer recommends an action of “approvable” of exenatide as a monotherapy for the treatment of type 2 diabetes, pending evidence from at least one adequately controlled Phase III trial to support its use as a monotherapy in type 2 diabetes.

1.2 Recommendation on Postmarketing Actions

1.2.1 Risk Management Activity

The Risk Management Plan proposed by the Sponsor is acceptable to this reviewer.

Identified Risks

Exenatide treatment is associated with gastrointestinal side effects (nausea in 44%, vomiting in 13%, Diarrhea in 13% and dyspepsia in 6% of the treated subjects). Exenatide delays gastric emptying and may delay or decrease the absorption of concomitant drugs administered orally. When exenatide is used together with a sulfonylurea (SFU), it may increase the risk of SFU-induced hypoglycemia. Exenatide therapy is not associated with increased risk of hypoglycemia when used alone or in combination with only metformin. Forty-four percent of patients treated with exenatide develop anti-exenatide antibodies, but both the number of antibody-positive subjects and the titers of the antibodies in individual patients generally decrease as the length of exposure increases. Patients who developed anti-exenatide antibodies had similar rates and types of adverse events as those with no anti-exenatide antibodies. However, for the 14% of anti-exenatide-positive subjects (6% of the total exenatide-treated subjects) with higher antibody titers (1/625 to 1/15,625) still present at Week 30, glycemic responses were diminished for about half of the subjects while the rest had no apparent decrease in efficacy. Patients with diminished glycemic response to exenatide may therefore be patients with high anti-exenatide antibody titers.

Proposed Risk Management Activity

In addition to dealing with potential risks by using the appropriate language in the US Package Insert (USPI) and in the content of medical education instructional programs, a three-component risk management program will be established with:

- (1) Pharmacovigilance and signal detection to monitor and assess the post-launch safety profile of exenatide, with particular attention to adverse events where hypoglycemia is suspected, to certain disease states, and to concomitant medication use.
- (2) Clinical studies (currently ongoing), to evaluate whether there are long-term consequences related to the presence of anti-exenatide antibodies in treated patients.
- (3) An observational study of pregnancy, to monitor whether any safety issues emerge from exposure of pregnant women and developing fetuses to exenatide.

1.2.2 Required Phase 4 Commitments

All applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred. The sponsor requests a waiver for pediatric studies in patients' ages 0 to 11 years and a deferral of pediatric studies in patients' ages 12 to 16 years for exenatide to improve glycemic control in patients with type 2 diabetes mellitus.

This Reviewer agrees that a waiver is justified for pediatric studies in patients' ages 0 to 11 years for exenatide to improve glycemic control in patients with type 2 diabetes mellitus. Pediatric studies in patients' ages 12 to 16 years for exenatide to improve glycemic control in patients with type 2 diabetes mellitus who have not achieved adequate glycemic control on metformin, a sulfonylurea, or a combination of metformin and a sulfonylurea are being deferred under 21 CFR 314.55 until December 31, 2007. In the interim, the applicant should submit its pediatric drug development plans within 120 days from the date of drug approval.

1.2.3 Other Phase 4 Requests

A single dose human in vivo drug interaction study between exenatide and a combination oral contraceptive (e.g., ethinyl estradiol plus norethindrone) in which the effect of timing of the exenatide injection relative to administration of the oral contraceptive on the bioavailability of the components of the oral contraceptive is studied.

1.2.4 Recommended Trade Name

The Sponsor requests to assign the trade name BYETTA instead of BYETTA to Exenatide. The consult from the Division of Medication Errors and Technical Support (DMETS) does not recommend the use of the proprietary name BYETTA, because it may be confused for Diabeta tab, Viagra tab, Zyrtec tab, Zebeta tab. This is not deemed a concern sufficient to preclude use of the name BYETTA. BYETTA is an injectable drug;

all others are oral tablets. The patient should know if he or she was prescribed an injection or not, and furthermore if he or she had, training on self-injection would have been given. Thus, given the fact that BYETTA would be the only one to be administered by injection, there is a very low likelihood of such medication error, if it happens, not being caught and corrected. Therefore, this reviewer recommends the approval of the proprietary name BYETTA to Exenatide instead of Byetta.

1.3 Summary of Clinical Findings

The Drug

Exenatide (synthetic exendin-4, AC2993, LY2148568) is a subcutaneously (SC) administered 39 amino acid peptide amide proposed for the treatment of type 2 diabetes. Exenatide is the first in a class of antidiabetic drugs compounds called incretin mimetics, because it overlaps in structure and function with the human incretin hormone GLP-1. Incretins, including GLP-1, are gut peptides secreted in response to glucose load to stimulate insulin secretion and thus promote glucose uptake. Exenatide binds and activates the human GLP-1 receptor, thus increasing the synthesis and secretion of insulin in a glucose-dependent fashion. Exenatide was originally isolated from the salivary secretions of *Heloderma suspectum* (Gila monster), in which it circulates after meal initiation and may have endocrine functions. The amino acid sequence of exenatide is: 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-Ser-NH₂.

Exenatide is a new molecular entity. It is not structurally related to other antidiabetic drugs. While it stimulates insulin release in a glucose dependent fashion, it is not structurally related to insulin and there is no evidence to support its use as a substitute to insulin in clinical practice.

Exenatide is equipotent to GLP-1, as demonstrated by the production of cyclic adenosine monophosphate (cAMP) in human- and rat-based receptor systems. Significant receptor binding of exenatide is observed in the pancreas where it is focally distributed within the islets of Langerhans. Studies in the perfused rat pancreas showed that exenatide potentiates both first- and second-phase insulin secretion. Another study showed that exenatide suppresses glucagon independent of the presence of insulin and somatostatin in the medium, suggesting an additional direct effect of Exenatide at the level of the α -cell. Exenatide potently slows gastric emptying in the presence of glucose (is this glucose-dependent?) in a dose-related manner. Acute administration of exenatide dose dependently reduces food intake by up to 75% (in animals or man, or both).

Review Strategy

Clinical study reports were first reviewed, including the auditing of selected case report forms. The Author then reviewed the Integrated Summary of Efficacy, Integrated Summary of Safety and The Risk Management Plan. The administrative sections of the 5-module electronic submission were reviewed last.

1.3.1 Brief Overview of Clinical Program

Most of the data used in the review come from the extensive clinical development program conducted by the applicant or its designee. None of the used data is derived from foreign postmarketing data. Literature support is obtained from the references provided by the applicant or through classic literature search of the available FDA electronic literature resources. Information from existing INDs was utilized as well. Consultations were obtained from the Office of Drug Safety (ODS) and from the Division of Scientific Investigation (DSI). No advisory committee meeting was convened to discuss this application.

The clinical development program consisted of 27 studies in which 2252 subjects participated: 1857 of whom received exenatide (with 840 for 6 months and 272 for 12 months) and 805 received placebo. Subjects who received both Exenatide and a placebo are counted in both groups. The majority of the completed studies addressed the PK, PD, mechanism of action, special population and drug-drug interactions. The studies led to the selection of fixed unit dosing of 5 and 10 ug bid SC regimens for the long-term controlled trials. The efficacy and safety studies focused on subjects with type 2 diabetes not achieving optimal glycemic control using maximally effective doses of metformin alone, SFU alone, or the two in combination.

The body of clinical data presented in this submission demonstrates that exenatide offers significant improvement in glycemic control with an acceptable adverse event profile when used in type 2 diabetes patients using metformin, sulfonylurea, or combination oral agent therapy. Additional beneficial effects of treatment include improved control of body weight with no adverse effects on either lipids or blood pressure. The risks and side effects associated with exenatide treatment are comparatively few and include nausea (for roughly half of treated patients) that is more frequent at the initiation of therapy and an increased risk of hypoglycemia if the patient is also using a sulfonylurea.

The proposed indication for exenatide injection is to improve glycemic control in patients with type 2 diabetes mellitus, ~~with type 2 diabetes mellitus~~, metformin, a sulfonylurea, or a combination of metformin and a sulfonylurea.

1.3.2 Efficacy

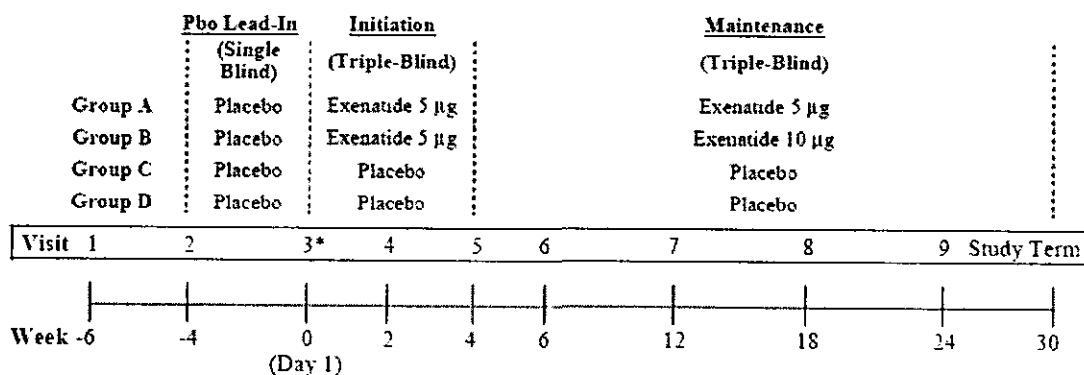
Exenatide as an Add-on Treatment

Three long-term (7-month), controlled trials, specifically designed to elucidate the safety and efficacy of exenatide when used in combination with metformin (2993-112), a

sulfonylurea (2993-113), or both (2993-115), account for the majority of the subjects in the exenatide clinical database. Subjects entering these studies were not adequately controlled with their OAD therapy alone in spite of being treated with maximally effective doses, but were on average not severely out of control (mean entry HbA_{1c} across the three studies was 8.4 ± 1.1%). Subjects deemed to be severely hyperglycemic (HbA_{1c} >11.0%) were excluded from these studies. The subjects were to continue using these OADs for the duration of the studies; in all 3 of these studies, it was recommended that subjects reduce their OAD therapy in response to hypoglycemia. Thus, in terms of ICH E10, these were add-on placebo-controlled studies. In each of the long-term, controlled trials, fixed unit dosing (exenatide 5 µg or 10 µg BID) was evaluated following a 4-week lead-in period of exenatide 5 µg BID.

The study subjects were males and females (surgically sterile, postmenopausal, or using appropriate contraceptive methods if of childbearing potential), age 16 to 75 years, and had an HbA_{1c} value of 7.1% to 11.0%, inclusive, for studies 112 and 113, or 7.5% to 11.0%, inclusive for study 115, and a BMI in the range of 27 kg/m² to 45 kg/m², inclusive, at screening. The studies excluded subjects who had ever received insulin as part of an outpatient diabetes treatment regimen, and those taking other oral antidiabetic agents within 3 months of screening (e.g., thiazolidinediones).

All three long-term studies lasted for 30 weeks. They commenced with a 4-week, single-blind placebo lead-in period. Subjects were then to be randomized to one of four treatment arms (A, B, C, or D) and were to begin a 4-week, double-blind treatment initiation period during which they were to receive either exenatide at 5 µg, BID (arms A and B), or the equivalent volume of placebo (arms C and D). Randomization to treatment was to be in the proportion 2:2:1:1 (A: B: C: D). Randomization was stratified according to screening HbA_{1c} values (<9% and ≥9%) to ensure a balanced distribution of subjects across the treatment arms. Following completion of the 4-week initiation phase, subjects were to continue receiving either placebo or exenatide at 5 µg, BID (arm A), or increase from 5 µg to 10 µg, BID (arm B), for the remaining 26-week, double blind, placebo-controlled maintenance period. The subjects assigned to placebo were to receive dose volumes equivalent to the 5 µg or 10 µg exenatide dose (arms C and D, respectively).



The metformin+SFU (study number) study stratified patients at baseline to 2 SFU management approaches (1:1). Patients randomized to a minimum recommended SFU dose were required to reduce the maximally effective SFU dose and allowed an upward adjustment based on fasting plasma glucose. Patients randomized to continue on the maximally effective SFU dose were allowed an SFU dose reduction based on hypoglycemia events.

The primary efficacy variable, HbA_{1c} change from baseline (Visit 3) to the last measurement was analyzed using analysis of variance method with treatment, center, screening HbA_{1c} stratum ($\leq 9\%$ or $> 9\%$) as fixed effects. Secondary efficacy variables included HbA_{1c} change from baseline to each of the intermediate visits, change in body weight from baseline, and the proportion of patients achieving HbA_{1c} target values by Week 30. The target values were HbA_{1c} $\leq 7\%$ and 8% , as well as HbA_{1c} reductions of $\geq 0.5\%$ and $\geq 1.0\%$.

A total of 1446 patients were randomized in the three long-term placebo-controlled trials. The subject population included both female (42%) and male (58%) subjects. A substantial proportion (18%) of subjects enrolled in the long-term, controlled trials were 65-years-old or greater, although relatively few (1.5%) of the subjects were aged 75 or older. Of the 1446 subjects, 991 (68.5%) were Caucasian, 224 (15.5%) were Hispanic, and 174 (12.0%) were Black. Mean HbA_{1c} values at baseline for the trials ranged from 8.2% to 8.7%. The study population was also relatively overweight (mean BMI 34 kg/m²), consistent with the characteristics of the type 2 diabetes population in general.

Table 1: Key Results of Exenatide in the long term controlled studies

Study	Metformin 112			SFU 113			Metformin +SFU 115		
	placebo	5 μ g	10 μ g	placebo	5 μ g	10 μ g	placebo	5 μ g	10 μ g
n	113	110	113	123	125	129	247	245	241
Baseline Mean HbA _{1c}	8.20	8.26	8.18	8.69	8.49	8.61	8.49	8.46	8.50
LSM Change HbA _{1c}	-0.00	-0.46	-0.86	0.06	-0.51	-0.91	0.12	-0.66	-0.88
Difference vs. Placebo		-0.46	-0.86		-0.57	-0.97		-0.78	-1.00
2-sided p-value		0.0016	<0.0001		0.0002	<0.0001		<0.0001	<0.0001
Baseline Body Weight (BW)(kg)	99.9	100.0	100.9	99.1	94.9	95.2	99.1	96.9	98.4
BW change at wk 30	-0.3	-1.6	-2.8	-0.6	-0.9	-1.6	-0.9	-1.6	-1.6
% HbA _{1c} $\leq 7\%$	13%	31.6%	46.4%	8.8%	32.6%	41.3%	9.2%	27.4%	33.5%
Hypoglycemia	6 (5%)	5 (5%)	6 (5%)	4 (3%)	18 (14%)	46 (36%)	31 (13%)	47 (19%)	67 (28%)
Nausea	26(23%)	40(36%)	51 (45%)	9 (7%)	49 (39%)	66 (51%)	50 (21%)	96 (39%)	117 (49%)
anti-exenatide antibody	3 (3%)	44(40%)	51(46%)	2 (2%)	46 (38%)	51 (41%)	13 (5%)	120 (49%)	107 (45%)

Exenatide, at dosage regimens of 5 and 10 μ g BID, administered SC as an adjunct to metformin and/or a sulfonylurea in subjects with type 2 diabetes, produced clinically and statistically significant reductions from Baseline in HbA_{1c} at Week 30 (Table 1). The magnitude of the reduction with the 10 μ g BID dose (0.9-1.0% relative to change in the placebo group) was consistent across the three studies, and thus not apparently affected by the type of background OAD therapy, and a strong dose relationship to outcome (HbA_{1c} lowering) was observed in each study. This magnitude and extent of the HbA_{1c}

response in the studied populations represents a meaningful clinical benefit of improved glycemic control.

In addition, a substantial proportion of exenatide-treated subjects (30% and 39% for the exenatide 5 µg and 10 µg groups, respectively) achieved an HbA_{1c} of ≤7% at Week 30. Similar patterns of response as those seen for changes in HbA_{1c} from Baseline to Week 30 were observed for the secondary endpoints of the study: fasting and postprandial plasma glucose and body weight. The observed loss in body weight in the study subjects reflects a potential ancillary benefit to overweight patients with type 2 diabetes. As noted, the observed weight loss was not necessarily dependent on nausea and other gastrointestinal side effects of treatment, as weight loss was also observed in those subjects who never experienced these adverse events and there was virtually no correlation between weight change and subjects' total days of nausea. Ability to prevent weight gain is helpful in the overall management of type 2 diabetes. Of note, postprandial triglyceride concentrations were reduced, there were also no adverse effects of exenatide treatment on lipid profiles, and blood pressure tended to be unchanged, or slightly reduced.

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Durability of Exenatide Treatment Effect

The effect of exenatide on HbA_{1c} was shown to be durable through 52 weeks of treatment in four uncontrolled trials (the open-label extensions to the long-term, controlled trials and Study 2993-117, a 52-week open-label trial). In these studies, Cohorts I and II refer to subjects treated with exenatide or placebo, respectively, during the 30-week, controlled trial preceding the open-label extension. Of the 1125 patients who completed the 7-month placebo-controlled trials, 86.8% elected to participate in open-label extension studies.

The mean change in HbA_{1c} at Week 30 achieved by subjects treated with exenatide 10 µg BID in the controlled studies was clearly maintained throughout the subsequent 22-week open-label period (Cohort I, 10 µg). Subjects originally treated with either placebo (Cohort II) or exenatide 5 µg (Cohort I, 5 µg) in the controlled studies achieved changes from baseline in HbA_{1c} by Week 52 comparable to those observed for subjects continuously treated with a 10-µg dose. The reductions from baseline HbA_{1c}, fasting plasma glucose, and body weight observed during the placebo-controlled trials of exenatide were maintained through 52 weeks during the extension studies.

Figure 1: Time Plot for Mean Change in HbA_{1c} From Original Baseline by Subject Cohort for Studies 2993-112/112E, 2993-113/113E and 2993-115/115E Combined (Population: Intent-to-Treat)

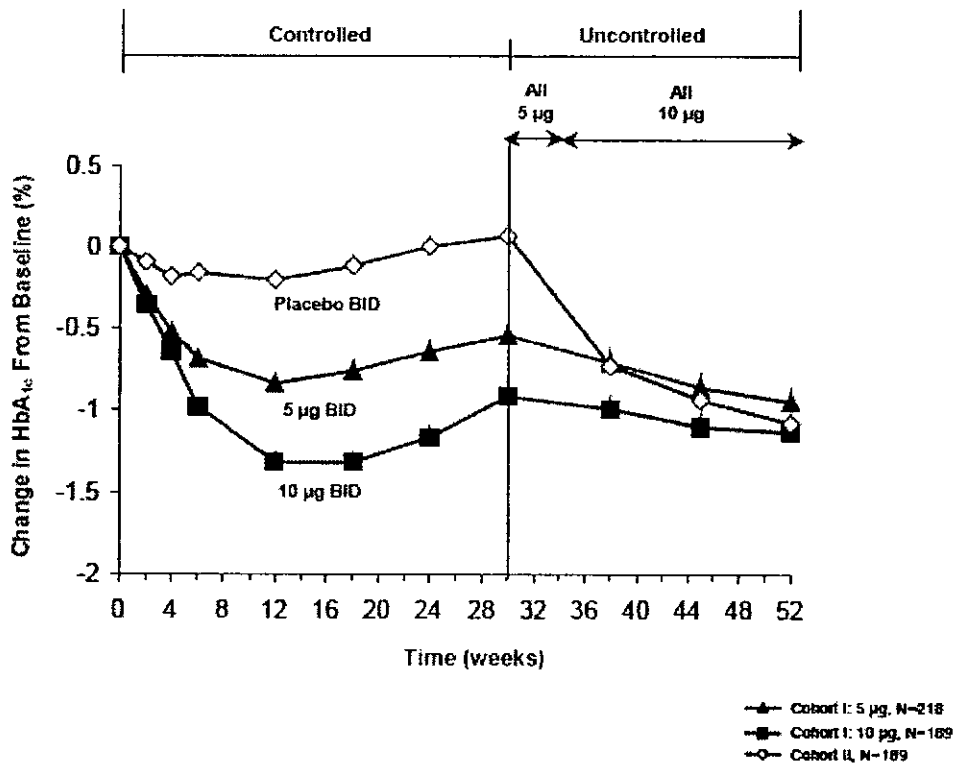
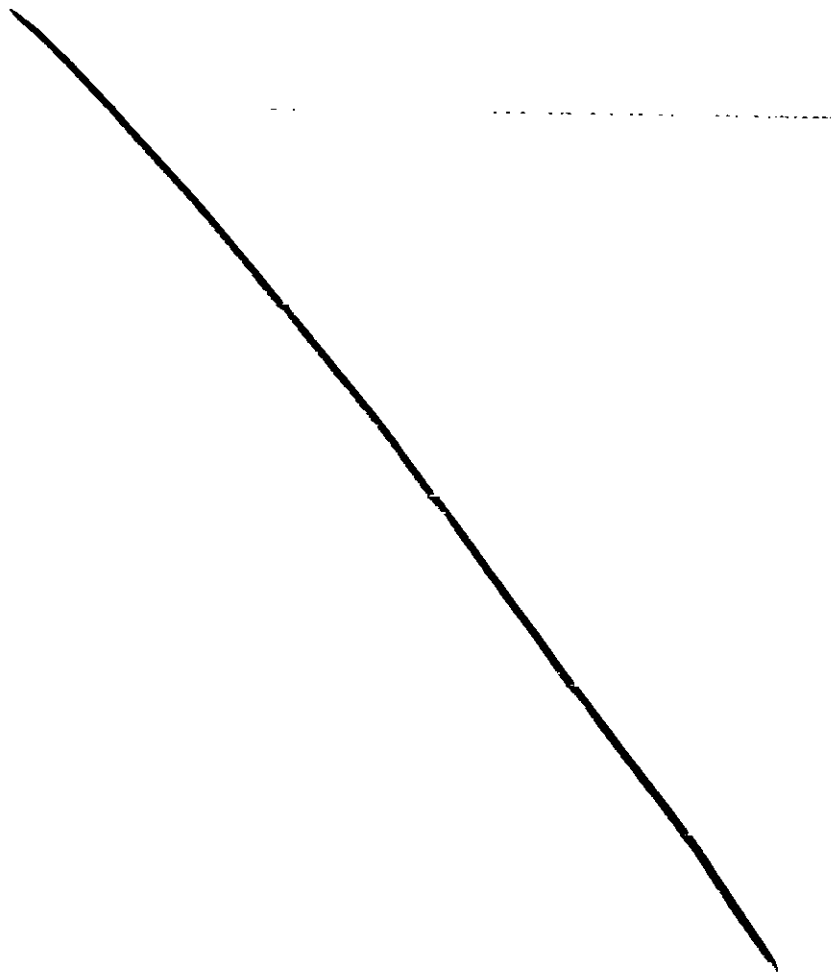
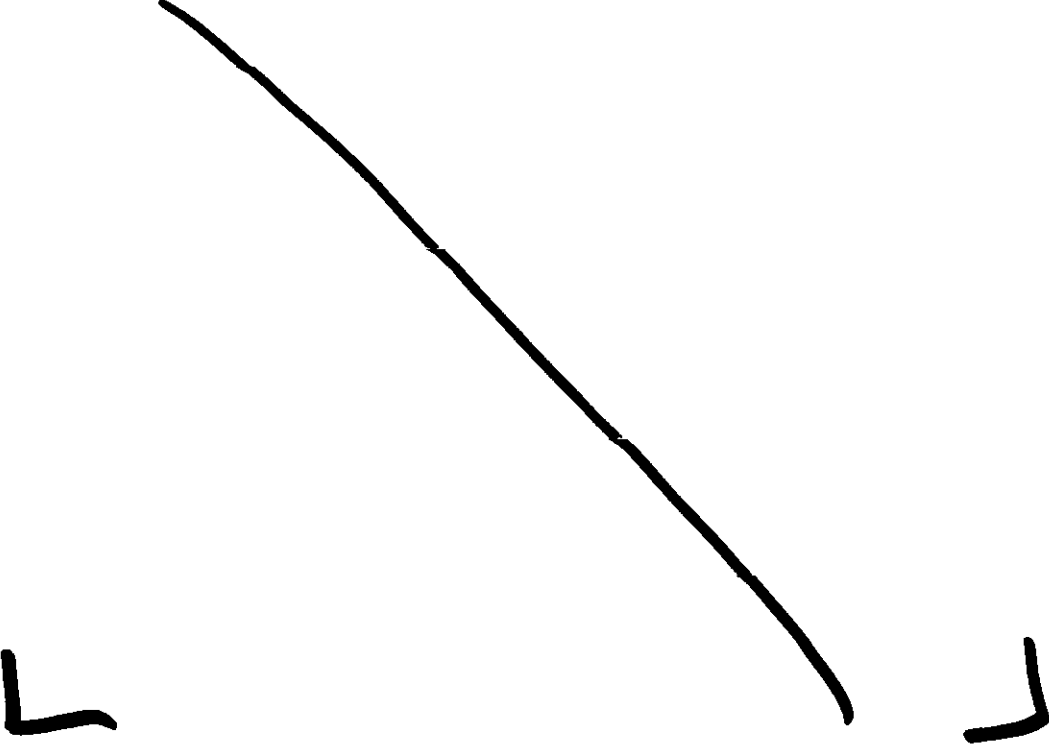


Table 2: One-Year Clinical Results of Exenatide 10 µg BID in Combination with Metformin, a Sulfonylurea or Both (Studies 2993-112/112E, 2993-113/113E, and 2993-115/115E Combined; Population: Study Completers [N = 163])

	HbA1c (%)	Fasting Plasma Glucose (mg/dL)	Body Weight (kg)
Baseline (mean)	8.4	175.4	99.2
Change at Week 30	-1.0	-14.0	-2.6
Change at Week 52	-1.1	-25.3	-3.6

Exenatide as a Monotherapy





In brief, the information submitted is not adequate to support the proper method of use of the drug as a monotherapy.

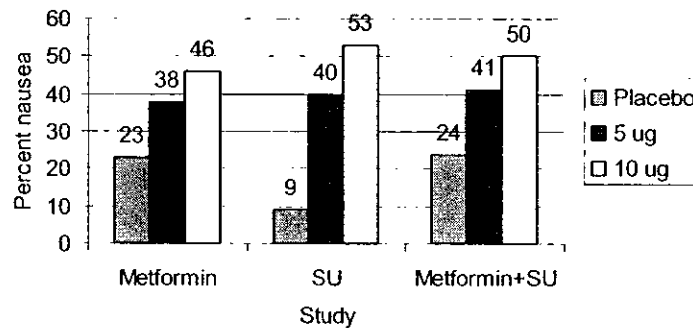
1.3.3 Safety

The clinical development program exposed male and female subjects in the target population to a range of doses of exenatide, including the dosage regimens of 5 µg BID and 10 µg BID that are recommended in labeling, with a mean duration of exposure of 22 weeks. A total of 1857 subjects, 1083 males and 774 females, were exposed to exenatide in the studies included in the Integrated Safety Database. Of these 1857 subjects, 840 were treated for 6 months and 272 for 12 months. Of the 1857 subjects exposed to exenatide, 443 (23.9%) received a maximum total daily dose of 10 µg (5 µg BID) and 996 (53.6%) received a maximum total daily dose of 20 µg (10 µg BID) at some time during the development program. A total of 167 subjects (9.0%) were exposed to total daily doses in excess of 20 µg.

General Adverse Events. The majority of subjects who participated in the exenatide long-term, controlled studies experienced at least one treatment-emergent adverse event

(91% and 82% for exenatide- and placebo-treated subjects, respectively). The adverse event profile varied depending on the background oral antidiabetic agent therapy, but adverse events were generally mild to moderate, and the frequency with which they were reported diminished with continued therapy. In the long-term, controlled studies, treatment-emergent adverse events with an incidence of at least 5%, and a greater incidence with exenatide- than placebo-treated subjects, were nausea (44% exenatide, 18% placebo), hypoglycemia (20% exenatide, 8% placebo), vomiting (13% exenatide, 4% placebo), diarrhea (13% exenatide, 6% placebo), feeling jittery (9% exenatide, 4% placebo), dizziness (9% exenatide, 6% placebo), headache (9% exenatide, 6% placebo), and dyspepsia (6% exenatide, 3% placebo). The data on occurrence of nausea for the three phase 3 studies of combination therapy are summarized in figure 2, below.

Figure 2 Percent of patients with nausea by treatment group and study



Withdrawals in the long-term, controlled studies due to any adverse event were 7% for exenatide-treated subjects and 3% for placebo-treated subjects.

The incidence of serious adverse events was comparable between exenatide subjects (4%) and placebo subjects (6%) in those same trials. Five deaths were reported in the clinical development program: two placebo subjects (one motor vehicle accident, one cardiac arrest) and three exenatide subjects (one motor vehicle [pedestrian] accident, one myocardial infarction, and one bladder cancer). None of the deaths was attributed by the investigator to the study drug.

Hypoglycemia. When the pooled data from the long-term, controlled studies were broken down to the individual study level, the elevated incidence of hypoglycemia relative to the placebo comparator occurred only in patients receiving exenatide in combination with a sulfonylurea. In Studies 2993-113 (concomitant sulfonylurea) and 2993-115 (concomitant sulfonylurea and metformin), hypoglycemia was observed in 25% (versus 3% in placebo) and 24% (versus 13% in placebo) of the patients, respectively, whereas in Study 2993-112 (concomitant metformin), hypoglycemia was observed in both the exenatide plus metformin and the placebo plus metformin groups at equal frequency (5%). Therefore, patients receiving exenatide in combination with a

sulfonylurea may be at increased risk of hypoglycemia, but those receiving exenatide in combination with metformin appear not to be. This is consistent with the known risks of sulfonylureas, which act by inducing non-glucose-dependent secretion of insulin by the beta cell, and obviously consistent (in the case of the metformin combination finding) with the mechanism of action of exenatide to promote glucose-dependent insulin secretion. The vast majority of hypoglycemia events were mild or moderate. Of 189 subjects who experienced hypoglycemia in the long-term, controlled studies, only in one subject (and in one instance of hypoglycemia) was the hypoglycemia rated severe (requiring the assistance of another person) and, in this case, the hypoglycemia was resolved with an oral snack.

Figure 3 Percent of patients with hyperglycemia

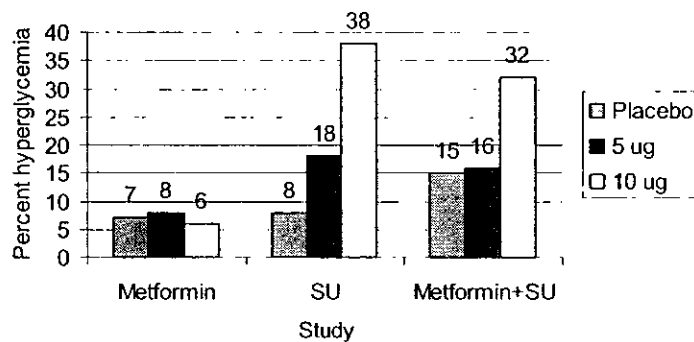


Table 3 Analysis of hypoglycemia

Study	Placebo	5 µg	10 µg	p-value
Metformin	8/113 (7%)	9/110 (8%)	7/113 (6%)	0.80
SFU	10/123 (8%)	23/125 (18%)	49/129 (38%)	<0.0001
Metformin+SFU	37/247 (15%)	63/245 (26%)	77/241 (32%)	<0.0001

To address the management of hypoglycemia, subjects in Study 2993-115 were stratified at randomization into subgroups that either used the maximally effective dose of their sulfonylurea or reduced to the minimum recommended dose prior to beginning exenatide treatment. The latter subgroup experienced treatment-emergent, mild or moderate hypoglycemic events at approximately one third of the rate observed for those who remained on the maximally effective sulfonylurea dose, although, as expected, the patients taking lower SFU doses experienced less glucose lowering. Reduction in the dose of the sulfonylurea may therefore reduce the risk of hypoglycemia associated with its use with exenatide.

Anti-Exenatide Antibodies. Forty-four percent of subjects in the long-term, controlled trials developed anti-exenatide antibodies, with the majority (86% of the anti-exenatide-positive subjects) exhibiting titers of 1/5 to 1/125 by Week 30 of treatment. For this lower titer group, the level of glycemic control (HbA_{1c}) was generally comparable to that

observed in those without antibody titers. For the 14% of anti-exenatide-positive subjects with higher antibody titers (1/625 to 1/15,625) still present at Week 30, glycemic responses were diminished for about half of the subjects while the rest had no apparent decrease in efficacy. A comparison of adverse event profiles for subjects with any level of anti-exenatide antibody titer versus those who never exhibited an antibody response did not reveal evidence of adverse events apparently related to the presence of antibodies per se, nor were there any acute allergic reactions. There were no events that might be related to an IgE response. Examination of antibody-positive specimens from a long-term (52-week), uncontrolled study (2993-117) revealed no significant treatment-emergent cross-reactivity with structurally similar endogenous peptides (glucagon, GLP-1).

An examination of efficacy in the 30-week studies based on both titer and dose reveals that in the 5- μ g group subjects who were antibody negative had a reduction in HbA_{1c} of -0.55% at week 30, and those with low titers had a similar reduction (-0.53%). In contrast, those subjects with higher antibody titers had an overall increase in HbA_{1c} (0.16%). Similar results were seen for the 10- μ g group; subjects who were antibody negative had a reduction in HbA_{1c} of -0.89%, and those with low titers had a similar reduction (-0.79%). However, those subjects with higher antibody titers had an overall increase in HbA_{1c} (0.11%). When both doses were pooled, subjects who were antibody negative had a reduction in HbA_{1c} of -0.72%, and those with low titers had a nearly identical reduction (-0.67%). Those subjects with higher antibody titers had an overall increase in HbA_{1c} (0.14%).

When a similar analysis of HbA_{1c} response based on antibody titer was done for subjects in the 52-week long-term uncontrolled studies, a similar pattern of reduced efficacy was observed for those subjects with titers \geq 1/625. Subjects who were antibody negative had a reduction in HbA_{1c} of -1.17%, and those with low titers had a similar reduction (-0.97%). Those subjects with higher antibody titers had no mean change in HbA_{1c} (0.01%)

Pregnancy. Four pregnancies were reported during the clinical study of exenatide. All subjects were receiving exenatide treatment at the time of conception, and two of the subjects were using an oral contraceptive. All stopped exenatide treatment soon after the

determination of pregnancy was made, and exposure of the fetus to exenatide ranged from 16 to 48 days. The pregnancies to date have been uneventful, with two women giving birth to healthy babies, one having a planned abortion not related to exenatide use, and one still awaiting delivery. While exenatide is unlikely to cause any direct, untoward fetal effects given its very low potential to cross the placental barrier, at this time the clinical information itself is inadequate to permit conclusions of safety to the fetus.

Other General Safety Measures.

There was no indication from the long-term, controlled trials of any adverse effect of exenatide on clinical laboratory measures, vital signs, electrocardiograms, or circulating cortisol concentrations.

1.3.4 Dosing Regimen and Administration

The proposed dosing recommendation is: “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. When exenatide is added to a regimen of metformin, a sulfonylurea, or both, the current dose of metformin or sulfonylurea can be continued upon initiation of exenatide therapy. It is unlikely that the dose of metformin will require adjustment due to hypoglycemia when used with exenatide. Patients treated with a sulfonylurea and exenatide have a higher risk of hypoglycemia. To reduce the risk of hypoglycemia associated with the use of a sulfonylurea, a reduction in the dose of sulfonylurea may be considered.”

Support for Proposed Dosing

Single-dose pharmacokinetic/pharmacodynamic studies (2993-102, 2993-104) showed little incremental benefit in postprandial glucose reduction at doses greater than 0.1 µg/kg, with doses exceeding 0.2 µg/kg resulting in increased gastrointestinal side effects. Simulations based on population pharmacokinetic/pharmacodynamic modeling of data from Studies 2993-102 through 2993-105 supported transition from weight-normalized dosing to a fixed-dosing paradigm. A dose of 10 µg was predicted to optimally balance maximal glucose reduction and acceptable gastrointestinal tolerability; a 5-µg dose was predicted to further reduce the probability of gastrointestinal adverse events while still eliciting an acceptable reduction in glucose concentrations for the majority of subjects. One 28-day controlled study (2993-116) demonstrated that doses in the range 2.5 to 10.0 µg BID elicited dose-related reductions in HbA_{1c}. In addition, data from another 28-day controlled study (2993-107) suggest no substantial difference in HbA_{1c} response between BID dosing and TID dosing (with the third dose given at bedtime). Data from a third 28-day controlled trial (2993-120) confirm that 10 µg BID is an effective dose in subjects with type 2 diabetes not using other antidiabetic agents. Another key finding from this

study is that once-daily (QD) morning dosing with exenatide is less efficacious (10 µg QD) or less efficacious and not well tolerated (20 µg QD), compared with 10 µg BID dosing regimens. These pharmacodynamic and efficacy outcome findings, together with the exenatide exposure dose-proportionality, strongly supported the choice of 5 and 10 µg BID in the long-term, controlled trials, in which dose-related effects on both fasting and postprandial plasma glucose and HbA_{1c} were also observed.

A dose-timing study (H8O-EW-GWAJ) showed that administration of exenatide at various times ranging from 1 hour before to 1 hour after meals resulted in significant reductions in postprandial glucose exposure. However, treatments administered 30 or 60 minutes after a meal were associated with transient, low circulating glucose concentrations and higher excursions in peak postprandial glucose concentrations. As premeal treatments exhibited a better postprandial glycemic control and were not associated with specific safety issues, dosing of exenatide is recommended to occur at any time within 60 minutes prior to a meal, but not after a meal.

A forced dose-titration study (2993-108) demonstrated that gradually increasing the exenatide dose to achieve a therapeutic target dose mitigates gastrointestinal side effects as compared to direct administration of the final target dose to an otherwise drug-naïve individual. Thus, escalation of the exenatide dose to 10 µg following an initial dosing period with 5 µg was expected to reduce the frequency and severity of gastrointestinal side effects; this expectation was borne out in the results of the long-term, controlled trials. The designs of some of the clinical pharmacology trials precluded the use of dose-escalation as that would have confounded the results. Therefore, the incidence of events such as nausea was higher than it might have been if dose-escalation had been employed.

1.3.5 Drug-Drug Interactions

As exenatide is a peptide primarily cleared via renal mechanisms, it is not expected to cause metabolism-based interactions with concomitantly administered oral medications. However, because exenatide slows gastric emptying, it is likely to alter the rate of intestinal absorption of concomitant oral drugs, when administered within a certain timeframe relative to the exenatide dose. Study 2993-121 used acetaminophen, an established marker of gastric emptying, to determine the time relative to exenatide dosing when the effect would be most prominent. The results of the study indicate that the most pronounced effect on the rate of concomitant medication absorption would occur if administered 1 to 2 hours after exenatide dosing. Interaction studies were also conducted with lisinopril, lovastatin, and digoxin. As anticipated from the results of the acetaminophen marker evaluations, exenatide administered concomitantly at the maximum intended therapeutic dose of 10 µg with oral lovastatin (H8O-EW-GWAG), lisinopril (H8O-EW-GWAE), or digoxin (H8O-FW-GWAF), produced changes in their pharmacokinetic profile (lower C_{max} and delayed T_{max}) that were consistent with slowing of gastric emptying in the presence of exenatide. In Study H8O-EW-GWAG, a reduction in the lovastatin AUC was also observed. There were, however, no adverse clinical correlates observed in the long-term, controlled trials among the substantial numbers of

subjects using HMG-CoA Reductase Inhibitors or ACE Inhibitors. In each case, concomitant administration of exenatide was generally well-tolerated with the most frequent adverse events being mild to moderate gastrointestinal side effects that appeared to dissipate over the course of the study. Based on these data, the timing of exenatide dosing should be a consideration in patients receiving oral medications that require rapid gastrointestinal absorption.

1.3.6 Special Populations

Efficacy in subgroups of the intent-to-treat population based on demographic (gender, age, and race) and the primary endpoint, i.e., change in HbA_{1c} for data pooled from the three long-term, controlled studies is summarized here.

For the change in HbA_{1c} values from Baseline to Week 30, there were no apparent gender differences in the response of type 2 diabetes subjects to exenatide. There also were no clear trends indicating age-related differences in the response of type 2 diabetes subjects to exenatide.

There was an apparent difference in the response of type 2 diabetes subjects to exenatide based on race, with Black subjects being less responsive to both 5 µg and 10 µg BID exenatide treatment than either Caucasian or Hispanic subjects. In addition, Hispanic subjects appeared to be equally responsive to the 5 µg and 10 µg BID dosage regimens, in contrast to the observed dose-response in other two race subgroups. The former finding is consistent with the observation that Black subjects seem to have a slightly greater exenatide clearance than those in other ethnic subgroups. This could at least in part account for the somewhat blunted efficacy response as observed in the long-term, controlled trials. However, there is substantial overlap in clinical response both across ethnicities and within each race group, indicating that no dose-adjustment based on race is warranted. The reason for an absence of a dose-response among Hispanic subjects is unknown and was driven entirely by the results of Study 2993-115, but also does not point to the need for specific dose adjustments simply based on race. Dose-adjustments for all subjects should instead be based on individual subject glycemic outcome and tolerability to exenatide treatment.

Statistically significant reductions from Baseline to Week 30 in HbA_{1c} were observed in both the 5 µg BID and 10 µg BID exenatide treatment groups for each predefined baseline HbA_{1c} strata subgroups (<9% and ≥9%). As expected, the magnitude of the treatment effect was somewhat greater for the subgroup with higher baseline HbA_{1c} concentrations compared with the subgroup with lower baseline HbA_{1c} concentrations. These findings are consistent with the larger reductions in HbA_{1c} for patients with higher pretreatment HbA_{1c} observed with many OADs.

Statistically significant reductions from Baseline to Week 30 in HbA_{1c} were observed in both the 5 µg BID and 10 µg BID exenatide treatment groups for each baseline BMI strata subgroup (<30 kg/m² versus ≥30 kg/m²). The magnitude of the treatment effect was greater for the subgroup with lower baseline BMI compared with the subgroup with

higher baseline BMI. Similar trends were observed for the treatment effect sizes in each treatment group. Nevertheless, as for the other subgroups examined, there is substantial overlap in clinical response across BMI strata subgroups, indicating that no dose-adjustment based on BMI is warranted.

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2 INTRODUCTION AND BACKGROUND

Type 2 diabetes accounts for approximately 90% of individuals with diabetes, has a usual onset after age 35 years, and is associated with obesity in >80% of those afflicted. Type 2 diabetes has a complex pathophysiology characterized by abnormalities in insulin secretion, excess hepatic glucose production, and insulin resistance in peripheral target tissues. Type 2 diabetes is associated with high rates of morbidity and mortality, often associated with microvascular and macrovascular complications secondary to chronic hyperglycemia and dysmetabolic conditions. The hallmark of the disease is hyperglycemia resulting from impaired carbohydrate metabolism. In addition, metabolism of proteins and lipids is altered. These multiple metabolic abnormalities arise primarily from deficient insulin activity due to either decreased insulin secretion secondary to beta-cell failure, compromised insulin action in peripheral target tissues (insulin resistance), or a combination of the two abnormalities.

While in healthy humans an oral glucose load elicits a much higher insulin response than an intravenous glucose administration leading to similar rises in glycemia ("isoglycemic" intravenous glucose infusions), this "incretin effect" is reduced or absent in patients with Type 2 diabetes. The incretin effect is based predominantly on the secretion of two known gut hormones with insulinotropic properties, glucagon-like peptide 1 (GLP-1), and glucose-dependent insulinotropic polypeptide (GIP, also referred to as gastric inhibitory polypeptide). The pathophysiological basis for the deficiency in incretin stimulation in Type 2 diabetes is a slightly reduced secretion of GLP-1 and a reduced insulinotropic activity of especially GIP, relative to healthy subjects. While the insulinotropic effect of GLP-1 is relatively well preserved (although somewhat reduced if compared to healthy subjects, GIP is almost inactive as an insulinotropic agent in patients with Type 2 diabetes, especially when administered continuously. In healthy humans, however, it probably is the most important physiological incretin hormone. The reduced overall incretin effect, most likely due to an inability of the diabetic endocrine pancreas to respond to GIP, is the basis to use GLP-1 (with its at least partially preserved insulinotropic activity) as a replacement therapy in order to reintroduce incretin stimulation.

2.1 Product Information

Exenatide (Byetta, AC2993, LY2148568) is the USAN-approved generic name for exendin-4, a 39-amino acid peptide amide (elemental composition, $C_{184}H_{282}N_{50}O_{60}S$; molecular weight, 4186.6 Daltons). The amino acid sequence for exenatide is 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. The amino acid sequence of exenatide overlaps partially with that of the human incretin hormone GLP-1, a recently identified gut peptide which has major glucoregulatory effects that could benefit patients with type 2 diabetes*. Exenatide was

originally isolated from the salivary secretions of *Heloderma suspectum* (Gila monster), in which it circulates after meal initiation and may have endocrine functions. 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 by mechanisms involving cyclic AMP and/or other intracellular signaling pathways. Exenatide increases beta-cell responsiveness to glucose and leads to insulin release in the presence of elevated glucose concentrations. When administered in vivo; exenatide mimics certain antihyperglycemic actions of GLP-1. When administered to humans, exenatide mimics certain glucoregulatory effects of GLP-1, and hence is described as an incretin mimetic.

Pharmacologic Class

Exenatide is proposed as the first incretin mimetic to treat diabetes. As described above, endogenous incretins, such as glucagon-like peptide-1 (GLP-1), enhance insulin secretion following their release from the gut into the circulation in response to food intake. Incretin mimetic agents have multiple antihyperglycemic actions that mimic the effects of GLP-1 and which cannot be duplicated with current therapeutic regimens. Exenatide differs in chemical structure and pharmacologic actions from insulin, sulfonylureas (including D-phenylalanine derivatives and meglitinides), biguanides, thiazolidinediones, and alpha-glucosidase inhibitors. As an incretin mimetic, exenatide improves glycemic control in people with type 2 diabetes mellitus. It enhances glucose-dependent insulin secretion, improves beta-cell function, suppresses inappropriately elevated glucagon secretion, and slows gastric emptying.

Targeted Indication

The proposed indication for exenatide is: "To improve glycemic control in patients with type 2 diabetes mellitus either alone or as an adjunctive therapy to metformin, a sulfonylurea, or a combination of metformin and a sulfonylurea." Evidence to support the claim of adjunctive therapy comes from three 30-week, long term adequately controlled trials and their open label extension to 52 weeks and from one uncontrolled 52 week trial in patients with type 2 diabetes. Evidence to support the monotherapy claim is extracted from the results of two 4 week Phase II, trials in patients with type 2 diabetes. Exenatide has not been studied in type 1 diabetes.

Dosing Recommendation

The proposed dosing recommendation of Exenatide is to 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, but not 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.

When exenatide is added to a regimen of metformin, a sulfonylurea, or both, the current dose of metformin or sulfonylurea can be continued upon initiation of exenatide therapy. It is unlikely that the dose of metformin will require adjustment due to hypoglycemia when used with exenatide. Patients treated with a sulfonylurea and exenatide have a higher risk of hypoglycemia. To reduce the risk of hypoglycemia associated with the use of a sulfonylurea, a reduction in the dose of sulfonylurea may be considered.

Dosage Form

Exenatide is supplied for subcutaneous (SC) injection as a sterile, preserved isotonic solution in a glass cartridge assembled in a pen-injector (pen). Each milliliter (mL) contains synthetic exenatide, 2.2 mg metacresol as an antimicrobial preservative, mannitol as a tonicity-adjusting agent, and glacial acetic acid and sodium acetate trihydrate in water for injection as a buffering solution at pH 4.5. Two prefilled pens are available to deliver unit doses of 5 micrograms (mcg) or 10 mcg. Each prefilled pen will deliver 60 doses to cover 30 days when administered twice daily administration.

2.2 Currently Available Treatment for Indications

Type 2 diabetes is treated by diet and exercise, oral antidiabetic agents, and eventually by insulin itself. Tailoring the treatment to the individual patient is important because oral antidiabetic drugs are heterogeneous. The available OAD classes are secretagogues (including sulfonylureas, D-phenylalanine derivatives, and meglitinides), biguanides, thiazolidinediones, and alpha-glucosidase inhibitors.

These main mechanisms of OADs are

To stimulate insulin secretion (sulfonylureas and rapid-acting non-sulfonylurea secretagogues),

To reduce hepatic glucose production (biguanides),

To delay digestion and absorption of intestinal carbohydrate (alpha-glucosidase inhibitors)

To improve insulin action (thiazolidinediones)

In pregnancy or severe hepatic or renal impairment, insulin may be the treatment of choice. Insulin is also required for metabolic decompensation, that is, incipient or actual diabetic ketoacidosis, or non-ketotic hyperosmolar hyperglycaemia. Certain comorbidities, for example presentation with myocardial infarction during other acute intercurrent illness, may make insulin the best option.

Finally, pramlintide (Symlin), a synthetic peptide analogue of human amylin, has been approved as an adjunct to insulin in patients with diabetes.

2.3 Availability of Proposed Active Ingredient in the United States

Exenatide is not currently marketed in the U.S.

2.4 Important Issues with Pharmacologically Related Products

No available therapy alone or in combination has to date led to fully satisfactory glycemic and metabolic control for sustained periods. The need for supplemental therapies reflects the progressive nature of the disease due to the inevitable decline in beta-cell function. As a result, interest in new therapies for type 2 diabetes, particularly those with a potential to favorably alter the underlying beta-cell dysfunction in a sustained fashion, remains keen. The desired beneficial effects of treatment include reductions in circulating glucose concentrations (both fasting and postprandial), improvement of lipid profiles, improved control of body weight and food intake, as well as a favorable impact upon the microvascular and macrovascular complications of diabetes.

Exenatide improves glycemic control by reducing fasting and postprandial glucose concentrations in patients with type 2 diabetes. It enhances glucose-dependent insulin secretion, improves beta-cell function, suppresses inappropriately elevated glucagon secretion, and slows gastric emptying. Exenatide differs in chemical structure and pharmacologic actions from insulin, sulfonylureas (including D-phenylalanine derivatives and meglitinides), biguanides, thiazolidinediones, and alpha-glucosidase inhibitors.

Exenatide presents a novel, multifaceted new therapy that has unique actions relative to those of existing therapies. Sulfonylureas are insulin secretagogues, and unlike exenatide, they stimulate insulin secretion irrespective of the prevailing glucose concentration and also do not generally mitigate the significant secretion of unprocessed proinsulin associated with type 2 diabetes. Metformin restrains hepatic glucose production; exenatide has the complementary property of reducing hyperglucagonemia. Exenatide has not demonstrated a direct effect on insulin sensitivity in humans, a beneficial effect of the thiazolidinediones (TZDs).

2.5 Presubmission Regulatory Activity

Amylin submitted IND 57,725 to evaluate exenatide as a potential treatment for type 2 diabetes on January 12, 1999.

Upon successful completion of a Phase 1 dose-rising tolerability study and five Phase 2 studies, Amylin requested an EOP2 meeting. In this meeting (10 October 2001), the FDA provided feedback regarding the overall development program, including specific suggestions for modifying the proposed Phase 3 study designs. In addition, the Agency recommended conducting an additional dose-ranging study to confirm appropriateness of

5 and 10 µg BID dosing regimens; which resulted in the design and conduct of Study 2993-116.

Following the EOP2 meeting with the Agency, three Phase 3, long-term, controlled studies were designed. Protocols 2993-112 (metformin only) and 2993-113 (sulfonylurea only) were submitted to the FDA for Special Protocol Assessment. A teleconference was conducted on 08 January 2002 regarding the Special Protocol Assessment of these two protocols. It was agreed that the feedback received for Studies 2993-112 and -113 would apply equally to Study 2993-115 (metformin and sulfonylurea), due to the similarities in design.

Assessment of anti-exenatide antibody formation and its potential impact on clinical outcomes (both safety and efficacy) in completed long-term, controlled and ongoing long-term, uncontrolled studies were discussed in a teleconference with the FDA on 03 September 2003. Agreement was reached on a plan for characterization and reporting of the treatment emergent anti-exenatide antibodies in the long-term studies, as well as how safety would be evaluated in subjects who developed antibodies. Consistent with agreements in that teleconference a separate report is included in Module 5, Section 5.3.5.3.4, where the presence of anti-exenatide antibodies, their titers, and their impact on both safety and efficacy have been thoroughly analyzed and presented. Additionally, as previously agreed, samples from the long-term, uncontrolled study (2993-117) were evaluated for cross-reactivity to glucagon and GLP-1 and these results are summarized in the antibody report. At the Agency's request, Amylin considered the utility of measuring IgE in exenatide-treated subjects. Discussions with external experts concluded that the measurement of IgE had minimal clinical benefit unless indicated for characterization of suspected systemic allergic reactions. As neither the adverse event profiles nor changes in percent eosinophils within subjects indicate potential systemic allergic reactions, IgE antibody measurements were not performed.

On February 02, 2004, a pre-NDA meeting was held and led to the following agreements:

- Amylin received Agency agreement on the content and format of the exenatide NDA.
- The Agency agreed that there were no outstanding items that would prevent filing.
- Amylin was informed by the FDA electronic submissions group that the table of contents and the electronic format of the eCTD were acceptable.
- A pediatric deferral was requested by Amylin and subsequently granted by the Agency.

- An agreement was reached whereby Amylin would submit CM&C stability updates during the NDA review.

Amylin and the Agency discussed the inclusion of a monotherapy indication. The Agency recommended that Amylin provide all relevant information in a separate section of the NDA, which would address both the justification for and the durability of exenatide as monotherapy. Although the enclosed draft package insert includes monotherapy as part of the indication, it is understood that if the Agency decides that the available data does not provide adequate support for a monotherapy claim, the indication would be revised accordingly.

- ExenatideTM, the proposed proprietary (trade) name for exenatide, was submitted as Serial 175, dated 03 October 2003, to the Division of Metabolic and Endocrine Drug Products. Amylin subsequently received a letter, dated 23 December 2003, indicating that the Agency tentatively had no objections to the proposed trade name.
- The United States Adopted Names Council assigned the established name, exenatide, to the product in 2002. The WHO Nomenclature Committee has recently approved exenatide as a recommended International Nonproprietary Name (rINN). Due to the timing of when documents were approved for inclusion in the NDA and when Amylin was made aware of the change to rINN status, some documents in the NDA may still refer to exenatide as a proposed INN.

2.6 Other Relevant Background Information

Exenatide has been shown to reduce fasting and postprandial plasma glucose concentrations in nonclinical studies and clinical studies through multiple mechanisms of action and independent of background antihyperglycemic therapies. These mechanisms of exenatide action include:

1. effects on the beta cell
 - a. enhancement of glucose-dependent insulin secretion
 - b. restoration of first-phase insulin secretion
 - c. enhanced insulin synthesis and processing and increased beta-cell mass
2. glucose-dependent suppression of inappropriately elevated glucagon secretion
3. slowing the rate of gastric emptying, resulting in slowed absorption of meal-derived glucose

These mechanisms work in concert to reduce fasting and postprandial glucose concentrations by modulation of both glucose appearance (slowing of gastric emptying, suppression of glucagon secretion) and glucose disposal (beta-cell effects). Clinical studies have demonstrated that enhancement of insulin secretion and suppression of glucagon secretion are evident during hyperglycemic and euglycemic conditions but not under hypoglycemic conditions. Nonclinical studies also indicate that the effect of exenatide to slow gastric emptying, which in turn slows the rate of glucose entry into the circulation, is reversed during hypoglycemia. These glucose-dependent actions of

exenatide lead to improvements in glucose control while minimizing the risk of hypoglycemia. In addition, reductions in food intake have been well documented in nonclinical studies and reported in a study of healthy volunteers. This effect on food intake may explain, at least in part, the reductions in body weight observed in long-term studies in subjects with type 2 diabetes.

3 SIGNIFICANT FINDINGS FROM OTHER REVIEW DISCIPLINES

3.1 CMC (and Product Microbiology, if Applicable)

Please refer to CMC and Microbiology reviews.

3.2 Relevant Animal Pharmacology/Toxicology

BRIEF OVERVIEW OF NONCLINICAL FINDINGS

Exenatide is a DPP IV (dipeptidylpeptidase IV) resistant synthetic peptide that extends its duration of action relative to mammalian GLP-1 (7-36) amide. Many, but not all activities of Exenatide appear to be mediated by binding and subsequent activation of the GLP-1 receptor. Exenatide acts through binding to the GLP-1 receptor to reduce plasma glucose and lower HbA_{1c}. Long term reductions of HbA_{1c} are seen in diabetic rats. Exenatide decreases fasting glucose concentrations in rat and mouse models of type 2 diabetes and in monkey. Glycemic control occurs in conjunction with the reduction in the rate of plasma glucose (from increased glucose-dependent insulin secretion, improved insulin sensitivity and increased pancreatic β -cell mass) via glucose-dependent reduction in gastric emptying, reduced food consumption, and suppression of inappropriately elevated glucagon. By limiting the rate at which nutrients enter the GI tract, exenatide attenuates postprandial glucose elevations. Chronic administration of exenatide to normal glycemic mice rats and monkeys at systemic exposure multiples of 400X, 100X and 450X respectively the clinical dose of 20 μ g/day did not produce signs of hypoglycemia or related neurological signs or pathology. The effects of reduced food consumption and decreased body weight were noted in the 2-year rat (not mouse) carcinogenicity study where this contributed to the increased survival compared to the heavier control rats. Gravid mice and rabbits were particularly sensitive to the decreased food consumption and subsequent weight loss with exenatide in the reproductive toxicity evaluations.

Exenatide exposures increase with dose (linear kinetics except for pregnant rabbits) but do not show dose limiting accumulation. Metabolism occurs by proteolytic cleavage into progressively smaller peptides to amino acids predominately in the renal tubules.

Elimination occurs by renal excretion. Less than 3% of the administered dose crosses the placenta in rats, mice, rabbits (0-0.025) and ex vivo human placenta (0.008-0.017). Exenatide is minimally secreted (2.5%) into milk from mice. Developmental effects observed include delayed fetal/neonatal growth, peri- and neonatal mortality in the absence of maternal toxicity and at higher doses adverse maternal food consumption and body weight. The pregnant rabbit is very sensitive to exenatide toxicity as a function of the greater than dose proportional exposure following repeated SC dosing. Water consumption is dramatically reduced in these animals and it is possible that decreased renal clearance of exenatide (and metabolism) may be contributors to this elevated exposure.

The drug substance and product were tested by BID SC injection in mice, rats and monkeys chronically. Injection site changes consisted of those changes expected from repeated SC injection (inflammation, hemorrhage, fibrosis, epithelial hyperplasia minimal to slight). To compare lots of exenatide drug substance with impurities across three different manufacturers; 28-day toxicity studies in mice were performed. Genetic toxicity studies (Ames, chromosomal aberration) with these lots were also unremarkable. Heat inactivated exenatide was tested in a 28-day mouse toxicity using representative batches from all three manufacturing sources to assess degradant toxicity. No difference in target organ toxicity was observed with the different batches. However, some detectable anti-exenatide antibodies were observed.

Exenatide is a synthetic peptide of the lizard (Gila Monster) proexendin gene therefore; its antigenicity in rodents and monkeys is not unexpected. Anti-exendin antibodies at titers $\geq 1:125$ in monkey resulted in altered pharmacokinetics but were not considered neutralizing based on the observed pharmacologic activity (reduced body weight). The sponsor has suggested that the alteration in pharmacokinetics reflects decreased renal filtration due to antibody binding which results in decreased renal clearance the primary metabolic/excretory pathway of exenatide. Anti-exenatide antibodies were observed as early as one month dosing in monkey.

Toxicity studies using drug lots from different manufacturing sources ([redacted]) were tested in 28 day mouse studies with no difference in toxicologic profile. However 2/20 mice given the [redacted] drug lot showed very low anti-exenatide antibodies (titer 1:25). Heat degraded exenatide from these three manufacturers also demonstrated no differences compared to the untreated exenatide. Only 1 mouse showed any positive anti-exenatide titers (1:5) albeit very low. Interestingly it appears that the [redacted] manufactured drug substance lots are the only ones showing a positive antibody response and these are also the drug lots used for the subchronic and chronic toxicity studies some of which show positive antibody titers.

Species	Rat	Mouse	Monkey
Body Weight	↓	↑ F (3 Mo) - (6 Mo)	↓
Food consumption	↓	↑	↓
Parotid Salivary gland basophilia	+	+	Mononuclear infiltrate +
Pancreas islet cell	lymphocytic infiltration +	-	+

hyperplasia			
Anti-exenatide antibody	-	-	+
Titer \geq 1:25	+ (titer 1:5) 1-2/8 MD, HD		
Injection site inflammation	+	+	+

The significance of the parotid salivary gland basophilia in rodents and mononuclear infiltration in monkey is unclear. Historically this is a tissue not routinely sampled in toxicology studies. Basophils are related to mast cells and have phagocytic activity. Pancreatic islet cell hypercellularity is noted in monkeys. Exenatide including the natural form exendin-4 from lizard and GLP-1 and its analogues have been shown to increase β -cell mass in vitro and in vivo. However this does not appear to be a preneoplastic lesion based on the lack of tumorigenicity observed in the carcinogenicity evaluation.

Exenatide did not show a mutagenic or clastogenic potential with or without metabolic activation in *in vitro* Ames or chromosomal aberration assay in CHO cells or *in vivo* in the mouse micronucleus assay.

Lifetime carcinogenicity evaluations in rats and mice demonstrate increased thyroid C-cell adenomas in female rats at exposures 130X the clinical dose of 20 μ g/day. Mice did not demonstrate a tumorigenic potential.

Exenatide treatment during organogenesis results in impaired fetal/neonatal growth and skeletal effects at exposures 3X MRHD.

PHARMACOLOGIC ACTIVITY

Byetta™ (exenatide) is an incretin mimetic that mimics several glucoregulatory actions of the endogenous incretin, GLP-1 both in vitro and in vivo including decreased fasting and postprandial glucose. The actions of exenatide are partially mediated through binding to the human pancreatic GLP-1 receptor, leading to the glucose-dependent enhancement of both synthesis and secretion of insulin from pancreatic beta cells via a cyclic AMP-dependent mechanism and β -cell proliferation. Actions of exenatide noted in vivo include sustained improvement in beta-cell function. 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. Decreased glycosylated HbA_{1c} is observed.

NONCLINICAL SAFETY ISSUES RELEVANT TO CLINICAL USE

Injection site inflammatory, hemorrhagic, fibrotic, exudative and degenerative changes were observed across species. Parotid gland basophilia of unclear relevance was observed in the rat (5X MRHD) and mouse (10X MRHD). In monkeys, there was a treatment-related increase in percentage of animals that tested positive for anti-exenatide antibodies suggesting that the drug may be antigenic to monkey. 5% of control animals tested positive for anti-AC2993 antibodies compared to 38%, 25% and 50% for the 0.6, 6.7 or 75 μ g/kg BID groups respectively. The positive finding in some control animals (which may be due to contamination or background error) undermines the accuracy of this study.

However, NOAEL for anti-exenatide antibodies is < 0.6 µg/kg BID (< 6X MRHD). Teratologic finding that occurred at maternal NOAEL (3 µg/kg/d BID = 3X MRHD) in mice during organogenesis were cleft palate with/without holes and delayed ossification of ribs and skull (interfrontal) bone. In pregnant rabbits irregular skeletal ossifications were also seen with treatment during organogenesis. In pregnant mice treated from organogenesis through weaning, neonatal death was observed post-partum days 2 to 4.

4 DATA SOURCES, REVIEW STRATEGY, AND DATA INTEGRITY

4.1 Sources of Clinical Data

Most of the data used in the review come from the extensive clinical trials program conducted by the applicant or its designee. None of the used data is derived from trials conducted by a third party or from foreign postmarketing data. Literature support was obtained from the references provided by the applicant or through classic literature search of the available FDA electronic resources. Information from existing INDs was utilized as well. Consultations were obtained from the Office of Drug Safety (ODS) and from the Division of Scientific Investigation (DSI). None of the information was obtained from an advisory committee because an AC meeting was not warranted.

4.2 Tables of Clinical Studies

A total of 2252 unique subjects participated in 27 studies. Across all study groups, 1857 subjects received exenatide and 805 subjects received placebo. Some subjects were treated with both exenatide and placebo and are counted in both groups. The exenatide clinical development program consisted of the following 27 completed studies under IND 57,725

Table 4: Composition of the Clinical Development Program

Clinical Pharmacology Studies

- Bioavailability/Bioequivalence (BA/BE)
 - 2993-118 (Injection Site PK)
- Human PK-Healthy Subject PK and Initial Tolerability
 - 2993-101 (Rising Single-dose PK/Tolerability)
- Human PK-Intrinsic Factor
 - H8O-EW-GWAB (Renal Impairment, Exenatide PK)

Human Pharmacokinetics (PK)

- 2993-121 (Dose-timing Effect on Acetaminophen PK)
- H8O-EW-GWAE (Lisinopril Drug-drug Interaction)
- H8O-FW-GWAF (Digoxin Drug-drug Interaction)
- H8O-EW-GWAG (Lovastatin Drug-drug Interaction)

Human Pharmacodynamics (PD)

2993-106 (Insulin Sensitivity)

2993-111 (Counter-regulation During Euglycemia and Insulin-induced Hypoglycemia)

PK/PD

2993-102 (Dose-finding, PK/PD)

2993-103 (Multiday Twice-daily Preprandial Dosing, PK/PD)

2993-104 (Dose-finding, PK/PD)

2993-105 (Dosing Frequency PK/PD)

2993-109 (Subcutaneous Infusion PK/PD)

2993-110 (Fasting PK/PD)

2993-122 (First- and Second-phase Insulin Secretion)

H8O-EW-GWAJ (Dose-timing PD)

Efficacy and Safety Studies

Short-term, Controlled Studies^a

2993-107 (28-day Dose-regimen, Metformin and/or a Sulfonylurea, Efficacy, PK/PD, Safety)

2993-116 (28-day Dose-ranging, Metformin or Diet and Exercise, Efficacy, PD, Safety)

Long-term, Controlled Studies

2993-112 (30-week, Double-blind, Efficacy and Safety in Metformin-using Subjects With Type 2 Diabetes)

2993-113 (30-week, Double-blind, Efficacy and Safety in Sulfonylurea-using Subjects With Type 2 Diabetes)

2993-115 (30-week, Double-blind, Efficacy and Safety in Metformin- and Sulfonylurea-using Subjects With Type 2 Diabetes)

Long-term, Uncontrolled Studies^b

2993-112E (22-week Open-label Extension, Safety and Efficacy)

2993-113E (22-week Open-label Extension, Safety and Efficacy)

2993-115E (22-week Open-label Extension, Safety and Efficacy)

2993-117 (52-week Open-label, Safety and Efficacy)

Other Studies Placebo-controlled Dose-escalation Study

2993-108 (Dose-escalation to Mitigate Gastrointestinal Side Effects)

The clinical pharmacology program includes studies on pharmacokinetics, pharmacodynamics, special populations, mechanism of action, and drug-drug interactions. Potential interactions with metformin and sulfonylureas were investigated using data from the three long-term, controlled studies (2993-112, 2993-113, and 2993-115). Pediatric studies were deferred, with Agency concurrence at the pre-NDA meeting

(02 February 2004), until after approval of the NDA (FDA minutes dated 27 February 2004). Simulations based on pharmacokinetic/pharmacodynamic modeling of Clinical Studies 2993-102, 2993-103, 2993-104, and 2993-105 provided guidance on the appropriate doses likely to maximize effect while limiting gastrointestinal side effects. These pharmacokinetic/ pharmacodynamic analyses and data from Study 2993-107 contributed to the selection of the dosing regimens (5 and 10 µg BID) for the long-term, controlled studies. Appropriateness of these doses was confirmed by the dose-response study (2993-116) and the long-term, controlled trials. Study 2993-111 was designed to assess the effects of exenatide on counter-regulatory hormones during hypoglycemia, while Study 2993-122 investigated the effect of exenatide on first- and second-phase insulin response. Study 2993-118 evaluated the relative bioavailability of exenatide injected subcutaneously into the abdomen, arm, or thigh.

The efficacy and safety studies focused on subjects with type 2 diabetes that were not achieving optimal glycemic control using OADs, either alone or in combination. Most of the subjects were using metformin, a sulfonylurea, or a combination of both. This group of studies was further subdivided into short-term, controlled studies; long-term, controlled studies; and long-term, uncontrolled studies. The inclusion of subjects using TZDs was intentionally limited throughout the development program to date, pending establishment of a more complete safety profile for exenatide.

The two short-term (28-day), controlled studies of exenatide in subjects using OADs are Studies 2993-107 and 2993-116. Study 2993-107 was a randomized, double-blind, placebo-controlled, parallel-group, add-on, multicenter study to assess glucose control and evaluate safety in subjects who were to receive one of three regimens (twice daily [BID] or three times daily [TID]) of exenatide (0.08 µg/kg) injected SC in addition to their current therapy of metformin, sulfonylurea, or a combination of both. Data from this study indicated that exenatide at these dose regimens led to clinically and statistically significant reductions in both fructosamine and HbA_{1c} values. The regimen (BID vs TID) did not appear to differentially affect clinical outcome, although the study was insufficiently powered to adequately assess this conclusion.

Study 2993-116 was a randomized, double-blind, placebo-controlled, parallel-group, add-on, multicenter study evaluating the dose-response of glucose control and safety of exenatide in subjects with type 2 diabetes, treated with diet modification and exercise or metformin. Exenatide was injected SC BID before meals in the morning and evening for 28 days. The data indicate a statistically significant and monotonic dose-dependent (2.5 to 10.0 µg BID) reduction in HbA_{1c} in subjects treated with metformin or with diet and exercise alone.

Three long-term (7-month), controlled trials (2993-112, 2993-113, 2993-115), specifically designed to elucidate the safety and efficacy of exenatide when used in

combination with metformin, a sulfonylurea, or both, account for the majority of the subjects in the exenatide clinical database. Subjects entering these studies were not adequately controlled with their OAD therapy alone in spite of being treated with maximally effective doses, but were on average not severely out of control (mean entry HbA_{1c} across the three studies was 8.4 ± 1.1%). Subjects deemed to be severely hyperglycemic (HbA_{1c} >11.0%) were excluded from these studies. The studies enrolled subjects treated with either metformin (2993-112), a sulfonylurea (2993-113), or the combination (2993-115); and subjects were to continue using these OADs for the duration of the studies; in all 3 of these studies, it was recommended that subjects reduce their OAD therapy in response to hypoglycemia. Thus, in terms of ICH E10, these were add-on placebo-controlled studies. In each of the long-term, controlled trials, fixed unit dosing (exenatide 5 µg or 10 µg BID) was evaluated following a 4-week lead-in period of exenatide 5 µg BID. The improvement in glycemic control observed in all three studies was comparable across the variety of underlying diabetes therapies studied.

In addition to the ability to reactively reduce the sulfonylurea dose in response to hypoglycemia (in both Studies 2993-113 and 2993-115), a key aspect of Study 2993-115 was to evaluate the effect of using a maximally effective (MaxED) sulfonylurea dose versus a minimally recommended (MinRD) sulfonylurea dose at initiation of exenatide treatment on both efficacy and the occurrence of hypoglycemia when exenatide treatment was added to the existing OAD treatment regimen. In Studies 2993-113 and 2993-115, subjects were required to reduce their SFU dose to the protocol-defined maximally effective dose (MaxED) at Week -4 if they exceeded MaxED at study entry. Standardization at study entry was done so that efficacy of SFU agents would be maintained; positioning all subjects at the maximum effective dose rather than the maximum recommended dose was done so that any reduction in SFU dose due to hypoglycemic events would result in a meaningful reduction in the risk of additional events. In Study 2993-115, subjects randomized to receive the MinRD sulfonylurea dose were to titrate their sulfonylurea dose upwards based on self-monitored blood glucose measurements.

Table 5: Main Safety and Efficacy Studies

Study Identifier	Objective(s) of the Study	Study Design	Test Product(s): Dosage Regimen; Route of Administration	Key Outcomes
Number and type of Subjects		Duration of Treatment		
2993-107 109 (97 completed) Type 2 diabetes mellitus treated with diet and a SFU and/or metformin	Assess effect of SC exenatide on glucose control when injected BID or TID; assess serum fructosamine, plasma glucose, safety and tolerability. Assess exenatide PK, fasting	Randomized, double-blind, placebo controlled 28 days (preceded by 2 week single-blind placebo lead-in period)	Injectable formulation: exenatide 0.08 µg/kg. Four regimens: -exenatide BID before breakfast and dinner, -exenatide BID before breakfast and bedtime, -exenatide TID	One month of exenatide treatment significantly reduced fructosamine concentrations and HbA _{1c} in subjects with type 2 diabetes who had not previously achieved optimal glucose control with SFU and/or metformin. Exenatide eliminated the abnormal rise in postprandial plasma glucose concentrations and sustained this effect throughout 28 days of dosing. Peak exenatide concentrations occurred 90 to 120 minutes post dose.

	glucose, fasting and postprandial circulating lipids, body weight, HbA _{1c} .		before breakfast, dinner, and bedtime, or -placebo TID before breakfast, dinner, and bedtime; SC	Bedtime dosing, in BID or TID regimens, did not substantially affect fasting glucose concentrations. Small, acute, and transient increase in cortisol occurred after dosing with exenatide on Day 1 compared with placebo. No rise in mean post dose cortisol occurred in any treatment arm on Day 28.
2993-116 156 Type 2 diabetes mellitus, treated with metformin or diet and exercise	Assess effect of a range of doses of SC exenatide injected BID for 28 days on glucose control as measured by HbA _{1c} , and to assess the safety and tolerability of these regimens; Assess effect of a range of doses of exenatide on concentrations of fasting plasma glucose and serum fructosamine.	Randomized, 4-week double blind, placebo – controlled. Randomization stratified according to treatment dose, HbA _{1c} values (< 7.5% and ≥7.5%), and method of diabetes management. 28 days (preceded by 2 week single-blind placebo lead-in period)	Injectable formulation: exenatide 2.5 µg BID, 5.0 µg BID, 7.5 µg BID, 10.0 µg BID, or placebo, BID; SC	Exenatide administered for 28 days at each dose had a clinically and statistically significant effect on HbA _{1c} , and all doses reduced fasting plasma glucose. A similar HbA _{1c} response was apparent when exenatide was added to metformin therapy or diet and exercise alone. The majority of TEAEs were GI in nature and were mild or moderate in intensity. No severe hypoglycemia occurred.

2993-120

<p>Efficacy and Safety, Long-term, Controlled Studies 2993-112</p> <p>336 (270 evaluable)</p> <p>Type 2 diabetes mellitus + ≥ 1500 mg/day metformin</p>	<p>Assess effects of SC exenatide injected BID before the morning and evening meals on glucose control as measured by HbA_{1c}.</p> <p>Assess safety and tolerability. Assess fasting glucose, lipids, insulin, proinsulin, and body weight; anti-exenatide antibody response. Assess exenatide PK and postprandial glucose in a subset of subjects.</p>	<p>Randomized, double-blind, placebo controlled. Randomization stratified according to screening HbA_{1c} values ($< 9\%$ and $\geq 9\%$).</p> <p>30 week 4-week single-blind placebo lead-in, 4-week double-blind initiation, and 26-week maintenance period.</p>	<p>Injectable formulation, SC, BID before meals: 4-week initiation phase, placebo; 4-week double-blind initiation period, exenatide at 5 μg, BID or the equivalent volume of placebo; 26-week, maintenance period, either placebo or exenatide at 5 μg, BID, or increase from 5 μg to 10 μg, BID. Placebo subjects: SC dose volumes equivalent to the 5 μg or 10 μg exenatide dose.</p>	<p>Long-term use of exenatide in subjects with type 2 diabetes was associated with:</p> <ul style="list-style-type: none"> <input type="checkbox"/> significantly reduced HbA_{1c} and fasting and postprandial glucose concentrations among subjects who had failed to achieve glycemic control with metformin. <input type="checkbox"/> sustained reduction in body weight over the course of the study. <input type="checkbox"/> improved beta-cell function as evidenced by the HOMA-B analysis. <input type="checkbox"/> reduced fasting proinsulin to insulin ratio for the exenatide 10 μg group compared with placebo. <input type="checkbox"/> no clinically significant changes in fasting lipid concentrations. <input type="checkbox"/> no reports of severe hypoglycemic events.
<p>2993-113</p> <p>377 (255 evaluable)</p> <p>Type 2 diabetes mellitus + at least a maximally effective dose of a SFU SFU adjustment in response to hypoglycemia</p>	<p>Assess effects of SC exenatide injected BID before the morning and evening meals on glucose control as measured by HbA_{1c}.</p> <p>Assess safety and tolerability. Assess fasting glucose, lipids, insulin, proinsulin, and body weight; anti-exenatide antibody response. Assess exenatide PK and postprandial glucose in a subset of subjects.</p>	<p>Randomized, double-blind, placebo controlled. Randomization stratified according to screening HbA_{1c} values ($< 9\%$ and $\geq 9\%$).</p> <p>30 week 4-week single-blind placebo lead-in; Treatment: 4-week double-blind initiation, and 26-week maintenance period</p>	<p>Injectable formulation, SC, BID before meals: 4-week initiation phase, placebo; 4-week double-blind initiation period, exenatide at 5 μg, BID or the equivalent volume of placebo; 26-week, maintenance period, either placebo or exenatide at 5 μg, BID, or increase from 5 μg to 10 μg, BID. Placebo subjects: SC dose volumes equivalent to the 5 μg or 10 μg exenatide dose.</p>	<p>Long-term use of exenatide in subjects with type 2 diabetes was associated with:</p> <ul style="list-style-type: none"> <input type="checkbox"/> significantly reduced HbA_{1c} and fasting glucose concentrations in subjects who had failed to achieve glycemic control with a SFU. <input type="checkbox"/> improved beta-cell function as indicated by the HOMA-B analysis. <input type="checkbox"/> significantly decreased fasting proinsulin to insulin ratio over 30 weeks for subjects treated with exenatide 10 μg versus placebo. <input type="checkbox"/> no clinically significant changes in fasting lipid concentrations. <input type="checkbox"/> no reports of severe hypoglycemic events.
<p>2993-115</p> <p>733</p>	<p>Assess effects of SC exenatide injected BID before the</p>	<p>Randomized, double-blind, placebo controlled. Randomization</p>	<p>Injectable formulation, SC, BID before meals:</p>	<p>Long-term use of exenatide in subjects with type 2 diabetes was associated with:</p> <ul style="list-style-type: none"> <input type="checkbox"/> significantly reduced HbA_{1c} and fasting plasma glucose

<p>(577 evaluable)</p> <p>Type 2 diabetes mellitus + metformin and SFU</p> <p>adjustment in response to hypoglycemia and fasting glucose concentrations</p>	<p>morning and evening meals on glucose control as measured by HbA_{1c}.</p> <p>Assess safety and tolerability. Assess fasting glucose, lipids, insulin, proinsulin, and body weight; anti-exenatide antibody response. Assess exenatide PK and postprandial glucose in a subset of subjects</p>	<p>stratified according to screening HbA_{1c} values (<9% and ≥9%).</p> <p>Subjects also randomly assigned to one of two SFU management groups (minimum recommended dose [MinRD] or maximally effective dose [MaxED]).</p> <p>30 week 4-week single-blind placebo lead-in; Treatment: 4-week double-blind initiation, and 26-week maintenance period</p>	<p>4-week initiation phase, placebo; 4-week double-blind initiation period, exenatide at 5 µg, BID, or the equivalent volume of placebo; 26-week, maintenance period, either placebo or exenatide at 5 µg, BID, or increase from 5 µg to 10 µg, BID.</p> <p>Placebo subjects: SC dose volumes equivalent to the 5 µg or 10 µg exenatide dose.</p>	<p>concentrations in subjects who had failed to achieve glycemic control with metformin and a SFU.</p> <p>□a reduction in body weight was observed over the course of the study.</p> <p>□no clinically significant changes in fasting lipid concentrations.</p> <p>□significantly suppressed postprandial plasma glucose for each exenatide treatment compared with placebo.</p> <p>□a lower incidence of hypoglycemia for the MinRD group than for the MaxED group; however, the reduction in the risk of hypoglycemia was associated with some loss of benefit in terms of HbA_{1c} reduction. Peak concentrations of plasma exenatide were achieved at 90 to 120 min post dose in both exenatide groups. Similar plasma exenatide PK profiles were observed at Week 4 and Week 30.</p>
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The clinical program also included long-term, uncontrolled studies that were open-label extensions (2993-112E, 2993-113E, 2993-115E) of the three long-term, controlled studies, and a long-term, open-label trial (2993-117). For purposes of reporting in this application, these four studies are treated, in part, as though they were completed studies and in part as ongoing studies, since subjects continued in the participation in the studies. The approach to reporting these data was agreed to by the Agency at the pre-NDA meeting. Specifically, interim data for subjects in Studies 2993-112E, 2993-113E, 2993-115E, and 2993-117 who completed a total of 52 weeks of treatment by 15 October 2003 (the data cutoff date), or who withdrew prior to that date but would have achieved 52 weeks of treatment had they remained in the study, were summarized in final clinical study reports (CSRs) and categorized as completed long-term, uncontrolled studies. This interim “study completion” category was prospectively defined in the respective clinical study protocols, with more details provided in the corresponding statistical analysis plans. Limited safety information (exposure, deaths and other serious adverse events [SAEs], and withdrawals due to adverse events) collected for subjects who did not have an opportunity to complete 52 weeks of treatment as of the data cutoff date and are therefore not in the interim data set, as well as data beyond 52 weeks for the interim study completers, are included in the Ongoing Studies sections of this Integrated Summary of Safety and the Summary of Clinical Safety Data.

One study is included in the Other Studies grouping: a forced dose-escalation study

(2993-108) designed to assess whether gradual dose-escalation of exenatide can mitigate the gastrointestinal side effects associated with introducing exenatide.

The number of subjects exposed to at least one dose of exenatide within the aforementioned completed studies (including the subjects in the long-term, uncontrolled studies who met the "study completion" criteria) is 1857, with 840 subjects and 272 subjects having been exposed to exenatide for 6 months and for 12 months, respectively, as of the 15 October 2003 data cut-off. These values for subject exposure exceed the requirements of the ICH E1 guideline on the "Extent of Population Exposure."

Additional Studies

In addition to the open-label extension studies and Study 2993-117, the following studies were also ongoing as of 15 October 2003: a long-term, open-label study conducted in the US (2993-119), a 28-day placebo-controlled study in subjects with type 2 diabetes treated with diet and exercise alone (2993-120), and an active-comparator study versus insulin glargine (in subjects treated with metformin, a sulfonylurea, or both agents) conducted in the US, Europe, and other countries worldwide (H8O-MC-GWAA). Study H8O-MC-GWAA and other active comparator studies in the clinical development program are being conducted to support European registration. Of these ongoing studies, Study 2993-120 has since been completed.

Limited data on subject exposure to exenatide are also available from the studies listed below.

For completeness, limited safety information from these studies is included in Module 2, Section 2.7.4 and in the ISS in Module 5, Section 5.3.5.3.1.

ALK23-001 (Conducted in the United Kingdom)

A total of seven studies either started after the 15 October 2003 data cutoff or are currently planned for initiation during the coming year. While all of these studies will provide further insight into the use of exenatide, none of them is considered necessary for filing and approval in the US with the labeling proposed in the current application. The studies include:



4.3 Review Strategy

Clinical study reports were first reviewed, including the auditing of selected case report forms. The Author then reviewed the Integrated Summary of Efficacy, Integrated Summary of Safety and The Risk Management Plan. The administrative sections of the 5-module electronic submission were reviewed last.

This review is authored by the clinical reviewer with input from the biometrics reviewer. The clinical reviewer is responsible for the synthesis and overall conclusion of the review. The input from the biometrics reviewer is mostly contained in the Special Population Section of the efficacy review. The clinical pharmacology discipline review is a stand-alone entity separate from this review. The efficacy review was divided by indication. The efficacy review of the first indication, as an adjunctive therapy to metformin, sulfonylurea, or both, focused on the three 30 week, add-on, placebo controlled trials #2993-112, 2993-113 and 2993-115. The efficacy review of the second indication, as a monotherapy, focused on the 4 week placebo-controlled trial #2993-120. The safety review on the other hand focused on the pooled data from all subjects who participated in the 27 completed studies and was not divided by indication.

4.4 Data Quality and Integrity

This reviewer requested a routine audit of the sites that enrolled the highest number of participants in the main clinical trials #2993-112, 2993-113 and 2993-115. The DSI audited all sites and concluded that the data from all of them is acceptable. When data integrity was in question, *vide infra*, both the sponsor and the Agency recommended the exclusion of such data. The sponsor terminated all the patients and excluded data from investigator Nath of New York (Site 87) due to concerns of GCPs (Good Clinical Practices). A total of 68 patients were excluded: 6 in metformin alone study, 3 in SFU alone study and 49 in metformin+SFU study.

This reviewer finds that there is consistent substantiation of a dose-related effect of exenatide to improve glycemic control in multiple adequate and well-controlled studies, as discussed in the following sections. Due to the robustness of the

development program, the results cannot be attributed to bias, chance, site-specific trends, or aberrant results.

Table 6: A list of the audited clinical sites that enrolled the highest number of participants in Studies 2993-112, 2993-113 and 2993-115

Site	Investigator	Address	Protocol	Study Title	N (% of total)
Site 088	Waldo Harvey	Illinois Center for Clinical Trials 737 N. La Salle, 3rd Floor Chicago, IL 60610	2993-115	A phase 3, randomized, double-blind, parallel-group, long-term, placebo-controlled, multicenter study to examine the effect on glucose control (HbA1c) of exenatide given twice daily in subjects with type 2 diabetes mellitus treated with metformin and a sulfonylurea	32 (4.4%)
Site 009	Sam Miller	S.A.M. Clinical Research Center 7711 Louis Pasteur Drive, # 300 San Antonio, TX 78229	2993-115	A phase 3, randomized, double-blind, parallel-group, long-term, placebo-controlled, multicenter study to examine the effect on glucose control (HbA1c) of exenatide given twice daily in subjects with type 2 diabetes mellitus treated with metformin and a sulfonylurea	30 (4.1%)
Site 055	Walter Gaman	North Texas Clinical Research 1110 Cottonwood Lane, # 200 Irving, TX 75038	2993-113	A phase 3, randomized, double-blind, parallel-group, long-term, placebo-controlled, multicenter study to examine the effect on glucose control (HbA1c) of exenatide given twice daily in subjects with type 2 diabetes mellitus treated with sulfonylurea alone	26 (6.9%)
Site 108	Eric Klein	West Olympia Internal Medicine 406 Yauger Way SW, Suite A Olympia, WA 98502	2993-112	A phase 3, randomized, double-blind, parallel-group, long-term, placebo-controlled, multicenter study to examine the effect on glucose control (HbA1c) of exenatide given twice daily in subjects with type 2 diabetes mellitus treated with metformin alone	17 (5.1%)

Reasons for the Exclusion of Long-Term, Controlled Study Subjects at Site 087

During a visit to Study Site 087 (Principal Investigator: Chithranjan Nath, MD; Beth Israel Medical Center; Yonkers, NY) by an Amylin employee in early 2003, concerns were raised that the study site's documentation procedures were not in compliance with Amylin's Standard Operating Procedures (SOPs) and desired Good Clinical Practices, and an observation that adverse events were possibly under-reported. Thus, a "for-cause" audit was requested. A third party conducted the audit in May 2003 and noted similar findings. Based on these findings, a decision was made to withdraw all subjects from

Site 087 across all three studies and transfer them to an alternate site if they wished to continue participating in the study. The FDA was formally notified of the audit findings on 15 July 2003 (IND Serial 161). This decision affected a total of 68 subjects (6 in 2993-112, 13 in 2993-113, and 49 in 2993-115).

Amylin's monitoring representatives conducted a rigorous audit of all source documents and case report forms (CRFs) for all subjects from Site 087. These data are provided in a separate set of by-subject listings in the respective CSR appendices, and were not summarized or analyzed except for the sensitivity analyses of the primary efficacy endpoint requested by the FDA (see below).

Each of the long-term, controlled study CSRs contains a sensitivity analysis summarizing the change in HbA_{1c} from Baseline to Week 30 including data for the subjects from Site 087, consistent with the recommendation made in a facsimile communication from the Agency dated 04 November 2003. These analyses were performed in order to confirm that exclusion of the subjects from the intent-to-treat population had no effect on the outcome of the primary efficacy analysis, as data for these subjects were excluded from the primary summaries and analyses. The magnitude of change in HbA_{1c} from Baseline to Week 30 for all subjects, including those at Site 087, was similar to that observed for the protocol defined intent-to-treat population across all three studies.

4.5 Compliance with Good Clinical Practices

With the exception of investigations performed by one investigator, Dr. Nath, as described above, the Sponsor certifies that all clinical trials were conducted in adherence to the principles of Good Clinical Practices (GCPs), including direction set forth in relevant regulatory guidance (e.g., ICH E6) and in keeping with study subject protections as outlined in the Declaration of Helsinki (1964), up to and including the South Africa revision (1996). Some specific key study conduct and data analysis aspects are summarized below.

Precautions to Maintain Study Blind in Long-Term, Controlled Trials

Hypothetically, knowledge of key glucose control measures (HbA_{1c}, fasting and postprandial glucose concentrations) could unmask the identity of the subject treatment assignment. In order to minimize this possibility and lessen potential bias in data review and cleanup, subjects and investigators were to remain blinded to these values during the course of the study (the exception to this was self-monitored glucose values recorded by the study subjects). During blinded data review by Amylin personnel for the purposes of data cleaning and reconciliation prior to database lock, HbA_{1c} and plasma glucose values were assigned "dummy" identification codes to prevent correlation with other patient outcomes. Similarly, unblinded exenatide plasma concentration data and anti-exenatide

antibody data were not made available to subjects, investigators, or Amylin personnel directly involved in the conduct, monitoring, data management, or analysis of study results until after database lock and unblinding. “Dummy” identification codes were also used for these data during blinded data reviews. Unblinding occurred only after the databases had been finalized and locked.

Dose of Oral Antidiabetic Agent in an Add-on Study Design Setting

In Studies 2993-112 and -113, subjects were required to have been treated with the maximally effective dose of the appropriate OADs (at least 1500 mg/day metformin in Study 2993-112 and sulfonylurea doses as defined in the literature in Study 2993-113) for 3 months prior to screening. This approach was recommended by the US Food and Drug Administration (FDA) at the End-of-Phase 2 (EOP2) Meeting (10 October 2001) and implemented in the protocols after review via the Special Protocol Assessment process (IND Serial 54 [22 October 2001], 56 [26 October 2001], and 58 [09 November 2001]). A subsequent teleconference (08 January 2002) provided clarity and consensus on specific details. In Study 2993-112 approximately 59% of the subjects received ≥ 2000 mg/day of metformin, and 99% received ≥ 1500 mg/day. The median (mean) metformin dose was 2000 mg/day (1857 mg/day). Similarly, maximally effective sulfonylurea doses were used in Study 2993-113, although the sulfonylurea dose could be reduced in response to hypoglycemia. This approach in the long-term clinical trials allowed for a true assessment of the efficacy and safety of exenatide over the background of “maximally effective doses” of OADs.

In Study 2993-115, subjects were to be using maximally effective doses of metformin and a sulfonylurea prior to entry into the study. Approximately 76% of the subjects received ≥ 2000 mg/day of metformin, and 99% received ≥ 1500 mg/day. The median (mean) metformin dose was 2000 mg/day (1966 mg/day). They were then to be randomized in a stratified manner according to whether they continued using the maximally effective dose of the sulfonylurea or had their sulfonylurea dose reduced to the minimally recommended dose. The rationale for this design was to assess whether the anticipated sulfonylurea-induced hypoglycemia could be proactively mitigated by initial reduction in the sulfonylurea dose (minimally recommended dose stratum) and whether reactive reduction in sulfonylurea dose in response to hypoglycemia could mitigate the occurrence of further hypoglycemia (maximally effective dose stratum). Assessment of changes in HbA_{1c} in these two subgroups provided valuable information on the impact of these approaches to risk minimization on glycemic control.

Provision for Early Withdrawal of Subjects Due to Loss of Glucose Control

In order to avoid undue risk to subjects in the long-term, controlled trials, prospective rules were defined in the study protocols to force early withdrawal in the face of overt loss of glucose control, so that these subjects could seek other effective therapy. Such loss of control could be envisioned for some subjects due to either being assigned to placebo and not allowing a second or third antidiabetic therapy to be added, or for subjects assigned to active treatment who did not respond to exenatide. As agreed to during the Special Protocol Assessment teleconference (08 January 2002; FDA minutes dated 07 February 2002), subjects who had either a 1.5% increase from Baseline in HbA_{1c} or an HbA_{1c} value $\geq 11.5\%$ at protocol-specified time points were to complete early termination procedures and be withdrawn from the study. Similarly, a subject could have been withdrawn if fasting plasma glucose values of >240 mg/dL or finger-stick fasting blood glucose values of >260 mg/dL were observed at protocol-specified time points during study conduct. In the latter case, it was expected that the investigator would ascertain that the increase in self-monitored glucose concentration was not secondary to a readily identified intercurrent illness or pharmacological treatment. The ascertainment of these values that could trigger early withdrawal from the study was done in a manner consistent with the blinded approach described earlier.

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Definition of Missing Data Imputation Methods for Long-Term, Controlled Trials

Upon review of the statistical analysis plans for the long-term, controlled trials, the FDA suggested (communications dated 07 July 2003 and 04 November 2003) an alternative imputation method for analyses based on the intent-to-treat population. As defined in the analysis plan for the primary efficacy endpoint, missing values were always imputed as the last observation, except when the last observation was a baseline value or when the only post-baseline value was an unscheduled measurement performed more than 7 days after the last dose and the measurement was the only post-baseline value. The alternative imputation method requested by the FDA carries forward the unscheduled measurement to impute missing values, even when the unscheduled measurement was the only post-baseline value and was performed more than 7 days after the last dose. This alternative method includes a small number of additional data points in the analysis of the primary endpoint at Week 30. Across the three studies, the results are nearly identical to those of the primary analysis described in the statistical analysis plan. The CSRs for the long-term, controlled trials include as the main analysis the imputation method as defined in the statistical analysis plans, with the alternative imputation method for the primary efficacy endpoint provided in the appendices.

Use of Foreign Clinical Data

The bulk of the clinical data comprising this submission is from studies conducted in the US. This includes the three long-term, controlled trials and their corresponding long-term, uncontrolled trials (2993-112/112E, 2993-113/113E, 2993-115/115E) that form the principal basis for assessments of safety and efficacy. Long-term, uncontrolled Study 2993-117 was conducted in Hungary, and has been mainly used to assess long-term safety, including some specific anti-exenatide antibody characterization. Clinical pharmacology studies were conducted in the US, as well as in a variety of other countries; this is not expected to impact the interpretation of the clinical pharmacology data. All clinical studies, including those conducted outside of the US, were in compliance with GCPs.

4.6 Financial Disclosures

For each investigator/subinvestigator named below that disclosed a financial interest in accordance with 21 CFR §54.2, Amylin Pharmaceuticals, Inc. (Amylin) took efforts to minimize any potential bias. All of the named investigators or sub-investigators participated in large multicenter studies. During routine monitoring visits, no indications or findings of misconduct were found. None of the named individuals were the sole party listed on the Form FDA 1572. Each investigator or sub-investigator, study, and disclosable interest are identified below:

- [REDACTED]
1. [REDACTED] (principal investigator): In [REDACTED], he entered into two consulting agreements with Amylin for \$1000 and \$20,000, respectively. In [REDACTED] he entered into another consulting agreement for \$10,000 plus travel.
 2. [REDACTED] (principal investigator): Owns 3000 shares of Amylin stock.
 3. [REDACTED] (subinvestigator): Owns 3750 shares of Amylin stock, purchased in [REDACTED] he has since increased the amount of shares to 4500.

- [REDACTED]
1. [REDACTED] (principal investigator): In [REDACTED] he entered into two consulting agreements with Amylin for \$1000 and \$20,000, respectively. In [REDACTED] he entered into another consulting agreement for \$10,000 plus travel.
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 3. [REDACTED] (subinvestigator): Owns 3750 shares of Amylin stock, purchased in [REDACTED] he has since increased the amount of shares to 4500.

- [REDACTED]
1. [REDACTED] (principal investigator): In [REDACTED] he entered into two consulting agreements with Amylin for \$1000 and \$20,000, respectively. In [REDACTED] he entered into another consulting agreement for \$10,000 plus travel.
 2. [REDACTED] (principal investigator): Owns 3000 shares of Amylin stock.

- [REDACTED]
1. [REDACTED] (subinvestigator): Owns 3750 shares of Amylin stock,

purchased in [REDACTED] he has since increased the amount of shares to 4500.

- [REDACTED]
1. [REDACTED] (subinvestigator): Owned 2975 shares of Amylin stock that was purchased in [REDACTED], she transferred a total of 1025 shares to charitable organizations during the last 2 years.
 2. [REDACTED] (principal investigator): Owns 15,000 shares of Amylin stock purchased in [REDACTED].

5 CLINICAL PHARMACOLOGY

5.1 Pharmacokinetics

Exenatide reaches peak concentrations in approximately 2 hours. Exenatide absorption did not vary over time during 30 weeks of BID injection, and anatomical SC injection site did not influence exenatide pharmacokinetics. An evaluation of results across studies shows that exenatide concentrations greater than 50 pg/mL are associated with reductions in plasma glucose concentrations. Exenatide exposure (C_{max} and AUC) was shown to be dose-proportional and linear with doses up to ~40 µg. Exenatide is eliminated rapidly (half-life of approximately 2 hours) primarily through renal clearance.

Population pharmacokinetic analyses were conducted on data from 10 clinical studies (including a subset of subjects from the three long-term, controlled studies) in order to characterize exenatide pharmacokinetics and exenatide exposure-response relationships. These analyses also evaluated the potential influence of various covariates of clinical interest including anti-exenatide antibodies and body mass. The population pharmacokinetic database included subjects encompassing a wide range of demographic (age, gender, race) and clinical laboratory values.

Exenatide pharmacokinetics were described by a one-compartment model and were shown to be influenced to some extent by gender, body weight, and the presence of anti-exenatide antibodies. No other study subject factors or laboratory values were deemed to have a statistically significant effect on exenatide clearance.

- Gender exhibited a statistically significant influence on the absorption rate constant. Thus females were predicted, on average, to approach peak concentrations 0.5 hours earlier than males.
- Exenatide clearance and volume of distribution were predicted to increase as body weight was increased.
- In the presence of anti-exenatide antibodies, mean exenatide clearance was predicted to be reduced to half the value observed in antibody-negative subjects, possibly because the larger antibody-exenatide complex hinders glomerular filtration.

For any individual, the steady-state profile would be dictated by the net effect of these covariates (gender, body weight, antibody titer). Bayesian distribution- predicted individual concentration profiles stratified by gender, antibody status, and body weight showed a high degree of overlap. As such, the population pharmacokinetic database was fairly diverse and representative of the target population. Thus, findings from the pharmacokinetic evaluations do not warrant dosage-adjustments based on gender, antibody status, or body weight.

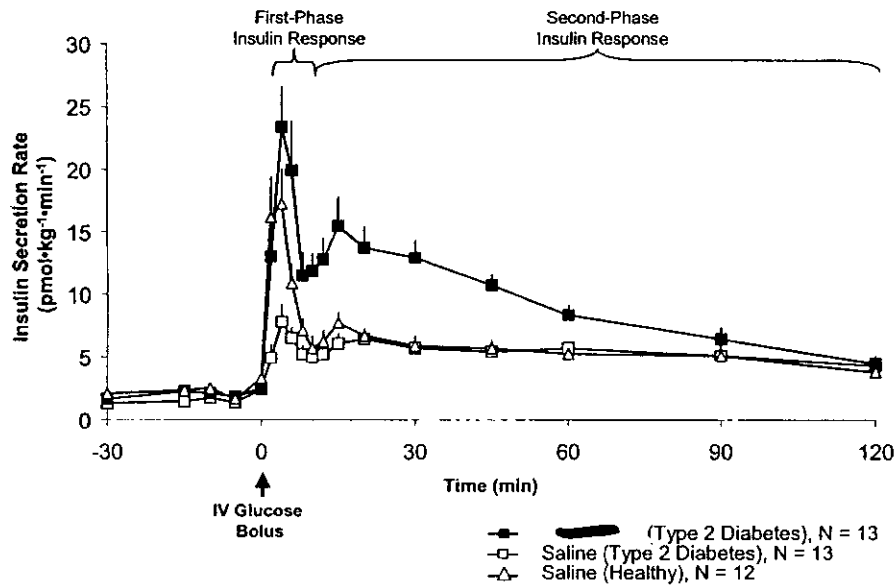
5.2 Pharmacodynamics

Maximal glucose response was shown to be directly proportional to baseline glucose exposure. For a given baseline glucose exposure, maximum mean postprandial glucose reduction was 34% smaller in subjects with antibody titers >1/125 (26% reduction) versus antibody-negative subjects.

Mean changes in HbA_{1c} response when stratified by anti-exenatide antibody status were 34% smaller for anti-exenatide antibody-positive subjects compared with antibody-negative subjects.

First-phase insulin response: In healthy individuals, robust insulin secretion occurs during the first 10 minutes following intravenous (IV) glucose administration. This secretion, known as the “first-phase insulin response,” is characteristically absent in patients with type 2 diabetes. The loss of the first-phase insulin response is an early beta-cell defect in type 2 diabetes, indicating beta-cell dysfunction. Continuous infusion of Exenatide at therapeutic plasma concentrations restored first-phase insulin response to an IV bolus of glucose in patients with type 2 diabetes, who are known to be insulin resistant (Figure 1). Both first-phase insulin secretion and second-phase insulin secretion were significantly increased in patients with type 2 diabetes treated with Exenatide compared with saline ($p < 0.001$ for both).

Figure 4: Mean (+SEM) Insulin Secretion Rate During Infusion of Exenatide or Saline in Patients With Type 2 Diabetes and During Infusion of Saline in Healthy Subjects



Beta-cell function: In animal models of type 2 diabetes, exenatide treatment increased beta-cell mass in proportion to insulin demand by differentiating noninsulin producing pancreatic islet precursor cells into beta cells and/or by promoting replication of existing beta cells. Furthermore, clinical studies with Exenatide have demonstrated improvements in beta-cell function, using indicators such as the homeostasis model assessment for beta-cell function (HOMA-B) and the proinsulin to insulin ratio.

Glucagon secretion: In patients with type 2 diabetes, Exenatide suppresses inappropriately elevated glucagon secretion (hyperglucagonemia) during periods of hyperglycemia. Lower glucagon concentrations lead to decreased hepatic glucose output and decreased insulin demand. However, Exenatide does not impair the normal glucagon response to hypoglycemia.

Gastric emptying: Exenatide slows gastric emptying, thereby reducing the rate at which meal-derived glucose appears in the circulation.

Food intake: In both animals and humans, administration of exenatide has been shown to reduce food intake.

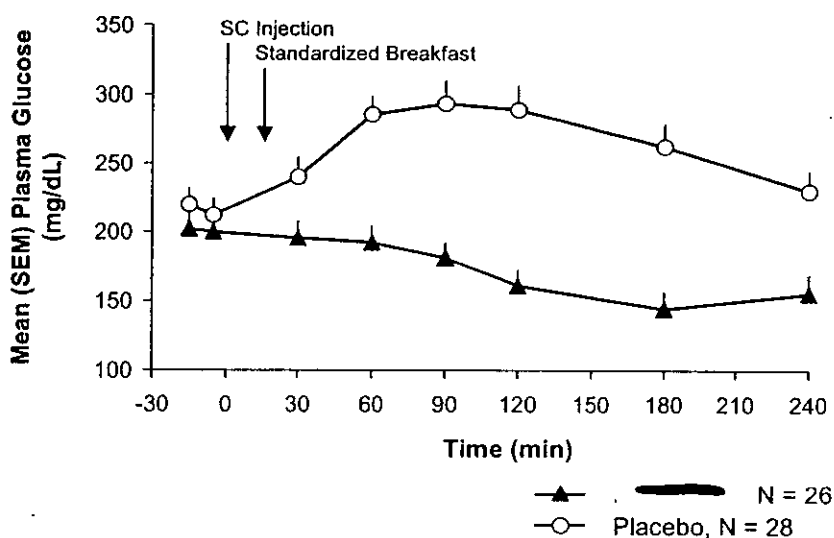
5.3 Exposure-Response Relationships

Improved glycemic control is achieved through the immediate and sustained effects of Exenatide on both postprandial and fasting glucose concentrations.

5.3.1 Postprandial Glucose

The first dose of Exenatide in patients with type 2 diabetes eliminated the abnormal rise in postprandial plasma glucose concentrations (Figure 2).

Figure 5: Mean (+SEM) Postprandial Plasma Glucose Concentrations on Day 1 of Exenatide Treatment in Patients With Type 2 Diabetes Treated With Metformin, a



Sulfonylurea, or Both (N = 54)

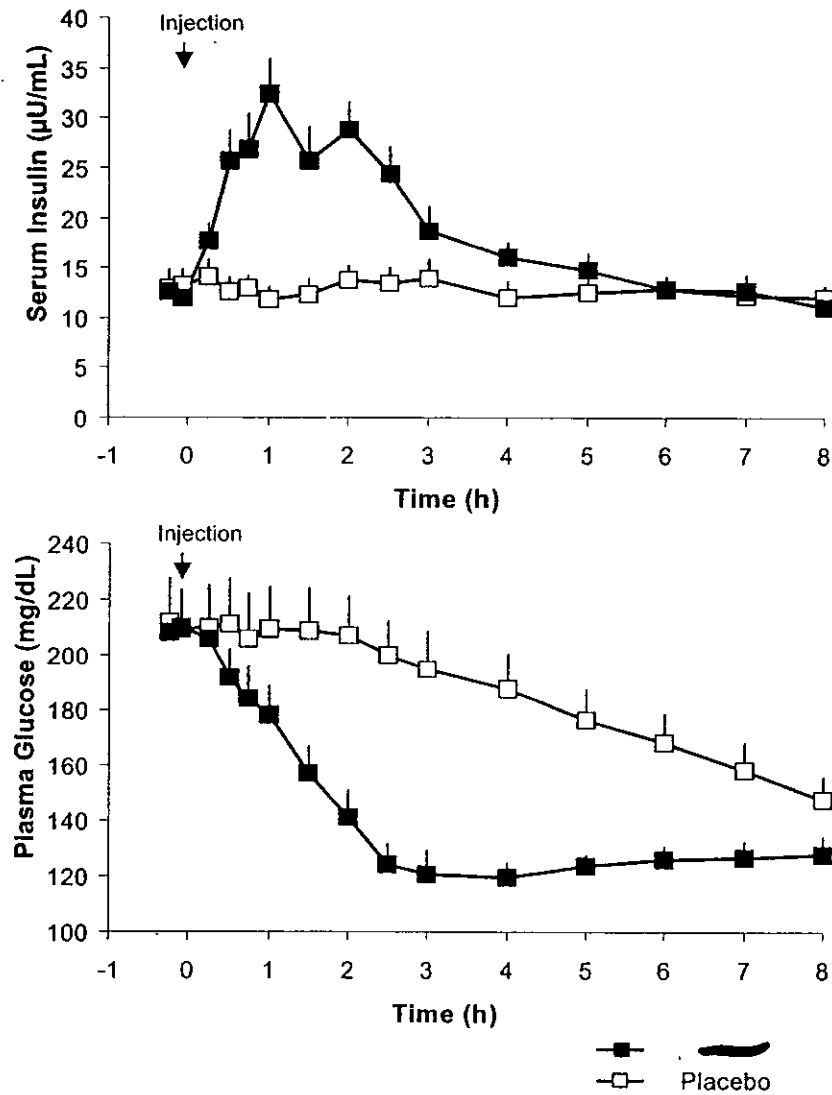
^a Mean dose (7.8 mcg based on body weight) was administered by subcutaneous (SC) injection.

Sustained, statistically significant reductions in postprandial plasma glucose concentrations were observed in long-term controlled trials in patients treated with Exenatide 10 mcg BID compared with those treated with placebo BID (see CLINICAL STUDIES, Fasting and Postprandial Glucose).

5.3.2 Fasting Glucose

In a single-dose crossover study in patients with type 2 diabetes, an immediate insulin release followed injection of Exenatide. Plasma glucose concentrations were significantly reduced with Exenatide compared with placebo (Figure 3). The enhancement of glucose-dependent insulin secretion by Exenatide subsided as fasting plasma glucose concentrations decreased and approached normal.

Figure 6: Mean (+SEM) Serum Insulin and Plasma Glucose Concentrations Following a One-Time Injection of Exenatide or Placebo in Fasting Patients With Type 2 Diabetes (N = 12)



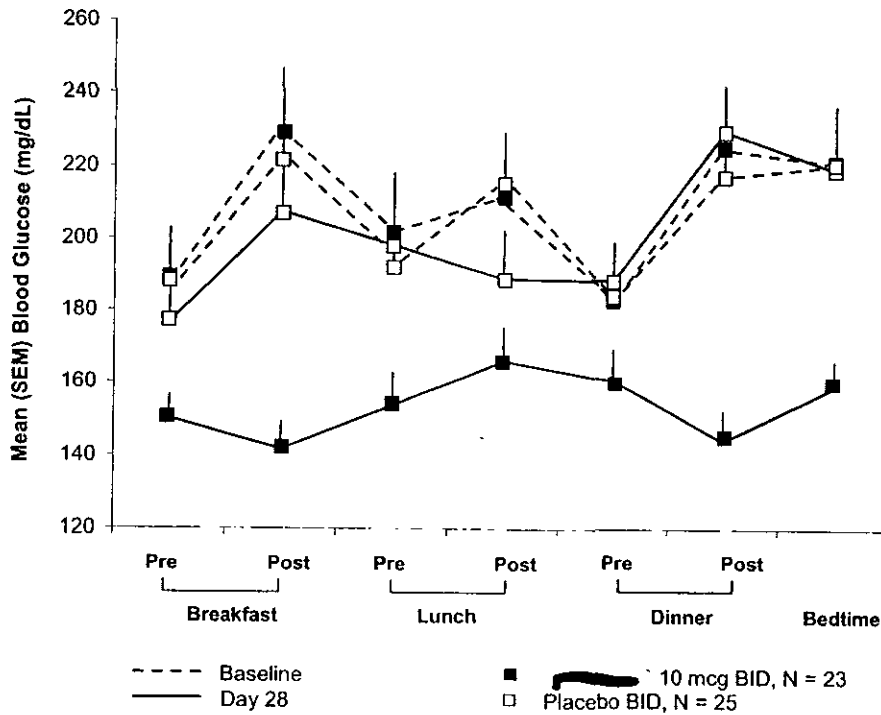
^a Exenatide administration was based on body weight at baseline; mean dose was 9.1 mcg.

In long-term controlled trials, Exenatide administered BID resulted in a sustained reduction in fasting plasma glucose concentrations, demonstrating a glucose-lowering effect that continues beyond the immediate postprandial period (see CLINICAL STUDIES, Fasting and Postprandial Glucose).

5.3.3 Glucose Profile

In a 28-day study in patients with type 2 diabetes, Exenatide administered BID reduced patient-reported fasting and postprandial glucose concentrations compared with placebo (Figure 4).

Figure 7: Mean (+SEM) Seven-Point Blood Glucose Concentrations With Exenatide or Placebo Administration for 28 Days (N = 48)



^a Twice daily (BID) before the morning and evening meals.

Exenatide did not alter the counter-regulatory hormone responses to insulin-induced hypoglycemia in a randomized, double-blind, controlled study in healthy subjects. Further analysis of the exposure-response relationship showed that mean exenatide exposure following preprandial doses of 5 and 10 μg exceeded the AUC_{50} (exenatide exposure associated with 50% of maximal response) and both approached the asymptotic portion of the exposure-response curve. Doses exceeding 10 μg were unlikely to provide an incremental benefit in terms of glucose reduction. Doses intermediate between 5 and 10 μg would likely not be clinically separable. Thus, these retrospective analyses confirmed the appropriateness of the selected

therapeutic doses of 5 and 10 µg, and were further reinforced by pharmacodynamic results from the dose-ranging Study 2993-116.

Consistent with the prominent contribution of the kidneys to exenatide clearance, single-dose data from clinical pharmacology trials, together with a study designed to assess exenatide pharmacokinetics in various stages of renal impairment (H8O-EW-GWAB) showed that individual exenatide clearance estimates decreased with reduced creatinine clearance. Clinically relevant reductions in exenatide clearance, accompanied by an increased intensity of gastrointestinal side effects such as nausea and vomiting, were observed for subjects with creatinine clearance values less than 30 mL/min. This finding leads to the recommendation that exenatide should not be used in patients with severe renal impairment (creatinine clearance ≤ 30 mL/min) or end-stage renal disease.

6 INTEGRATED REVIEW OF EFFICACY

6.1 Indication

As an add-on therapy to subjects with type 2 diabetes inadequately controlled to metformin and/or sulfonylurea

6.1.1 Methods

For purposes of confirming the effectiveness and demonstrating the safety of exenatide, the clinical development program focused primarily on a population with type 2 diabetes not achieving optimal glycemic control using OADs, either alone or in combination. Most of the subjects were using metformin, a sulfonylurea, or the combination of both. The clinical development program also included subjects using diet and exercise modification therapy alone and a limited number of subjects using TZDs.

The majority of the data in the NDA database comprise three long-term (7-month) controlled Phase 3 trials, referred to as the AMIGO (AC2993: Management for Improving Glycemic Outcomes) studies. The design and analyses of these trials benefited from FDA review and input into the protocols and statistical analysis plans. Studies 2993-112, 2993-113, and 2993-115 were Phase 3, randomized, triple-blind, add-on, placebo-controlled, parallel-group, multicenter studies designed to examine the effectiveness and safety of exenatide SC administered two times a day (BID, before meals in the morning and evening) for 30 weeks in subjects with type 2 diabetes mellitus. The design and analyses of these trials benefited from FDA review and input into the protocols and statistical analysis plans.

A total of 1446 patients were randomized in the three long-term placebo-controlled trials. The subject population included both female (42%) and male (58%) subjects. A substantial proportion (18%) of subjects enrolled in the long-term, controlled trials were 65-years-old or greater, although relatively few (1.5%) of the subjects were aged 75 or older. Of the 1446 subjects, 991 (68.5%) were Caucasian, 224 (15.5%) were Hispanic, and 174 (12.0%) were Black. Mean HbA_{1c} values at baseline for the trials ranged from 8.2% to 8.7%. The study population was also relatively overweight (mean BMI 34 kg/m²), consistent with the characteristics of the type 2 diabetes population in general.

6.1.2 General Discussion of Endpoints

The primary endpoint in each study was mean change from baseline HbA_{1c} at 30 weeks. The primary efficacy measure (the effect of exenatide on glucose control) in all 3 studies was the change in HbA_{1c} from baseline (Day 1) to study termination (Week 30). Secondary efficacy measures included the change in HbA_{1c} from baseline to each of the intermediate visits; the proportion of subjects achieving HbA_{1c} values $\leq 7.0\%$ and $\leq 8.0\%$ and those achieving HbA_{1c} reductions of $\geq 0.5\%$ and $\geq 1.0\%$ at Week 30; change from baseline in postprandial glucose concentrations, fasting plasma glucose (FPG) concentrations, and change in body weight from baseline to each of the intermediate visits and to study termination (Week 30). Additionally, improvements in beta-cell function were documented using indicators such as the homeostasis model assessment for beta-cell function (HOMA-B) and the fasting proinsulin to insulin ratio. The HOMA-B assessments are derived from mathematical modeling of fasting insulin and glucose concentrations² while the fasting proinsulin to insulin ratio is reported to reflect beta-cell efficiency.³

6.1.3 Study Design

After a 4-week placebo lead-in period, patients were randomly assigned to receive EXENATIDE 5 mcg BID, EXENATIDE 10 mcg BID, or placebo BID before the morning and evening meals, in addition to their existing oral antidiabetic agent. All patients assigned to EXENATIDE began a treatment initiation period with 5 mcg BID for 4 weeks. After 4 weeks, those patients either continued to receive EXENATIDE 5 mcg BID or had their dose increased to 10 mcg BID. Patients assigned to placebo received placebo BID throughout the study. The specific design of the three pivotal studies is summarized as follows:

2993-112

There were 336 intent-to-treat subjects (270 evaluable, based on completing 30 weeks and compliance with dosing) with type 2 diabetes treated with a maximum effective dose of

metformin (≥ 1500 mg/day). Subjects were randomized to one of four treatment arms and began a 4-week, triple-blind treatment initiation period during which they received either exenatide at 5 μ g BID, or the equivalent volume of placebo. Randomization was stratified according to screening HbA1c values ($<9\%$ and $\geq 9\%$). Following completion of the 4-week initiation phase, subjects continued receiving either placebo or exenatide at 5 μ g, BID, or increased from 5 μ g to 10 μ g, BID, for the remaining 26-week, maintenance period. Subjects assigned to placebo received dose volumes equivalent to the 5 μ g or 10 μ g exenatide dose. Measures included HbA1c, plasma glucose, plasma exenatide, lipids, insulin, proinsulin, beta-cell function, insulin sensitivity, body weight, standard safety parameters, and anti-exenatide antibodies.

2993-113

There were 377 intent-to-treat subjects (255 evaluable, based on completing 30 weeks and dosing compliance) with type 2 diabetes treated with the maximally effective dose of a sulfonylurea. Subjects were randomly assigned to one of four treatment groups and received either exenatide 5 μ g or the equivalent volume of placebo, BID, during a 4-week, triple-blind treatment initiation period. Randomization was stratified according to screening HbA1c ($<9\%$ and $\geq 9\%$). Following completion of the initiation period, subjects continued to receive either placebo or exenatide 5 μ g, BID, or increased their dose from 5 μ g to 10 μ g for the remaining 26-week maintenance period. Subjects assigned to placebo received dose volumes equivalent to exenatide 5 μ g or 10 μ g doses. Measures included HbA1c, plasma glucose, lipids, insulin, proinsulin, body weight, standard safety parameters, and anti-exenatide antibodies.

2993-115

There were 733 intent-to-treat subjects (577 evaluable, based on completing 30 weeks and dosing compliance) with type 2 diabetes treated with maximally effective doses of metformin and a sulfonylurea at baseline. Subjects were randomly assigned to exenatide 5 μ g BID, exenatide 10 μ g BID, or equivalent volumes of placebo BID, and were further randomized to one of two sulfonylurea management groups, which directed subjects to adjust their SFU dose to the minimum recommended dose [MinRD] or to remain at the maximally effective dose [MaxED]. Randomization was stratified according to screening HbA1c values ($<9\%$ and $\geq 9\%$). During the 4-week triple-blind treatment initiation period, subjects assigned to exenatide 5 μ g or 10 μ g received 5 μ g, BID and subjects assigned to placebo received an equivalent volume of placebo. During the 26-week triple-blind maintenance period, subjects received their assigned treatment (exenatide 5 μ g BID, exenatide 10 μ g BID, or placebo BID). Subjects assigned to the MinRD SFU management group were to have an upward adjustment in their SFU dose based on predefined fasting blood glucose criteria at specific visits during the study as defined in the study protocol. Measures included HbA1c, plasma glucose, lipids, body weight, insulin, proinsulin, standard safety parameters, and anti-exenatide antibodies.

Subject Disposition

A total of 1447 subjects were randomized into the three long-term, controlled studies; 336 in Study 2993-112, 377 in Study 2993-113, and 734 in Study 2993-115. Of the 1447 subjects

randomized, 77.7% completed: 81.0% in Study 2993-112, 69.0% in Study 2993-113 and 80.8% in Study 2993-115. One subject in Study 2993-115 who was initially randomized to the exenatide 10- μ g BID treatment group withdrew consent due to illness prior to receiving randomized treatment. This subject is included in the randomized population but excluded from the ITT population. Therefore, the randomized population and the ITT population for the three long-term, controlled studies differ by this one subject. Except as noted below for the Kaplan-Meier plots, which are based on the ITT Population, the numbers and percentages in this subsection on Subject Disposition are based on the randomized population.

Table 7: Subject Disposition by Treatment: Descriptive Statistics for Studies 2993-112, 2993-113, and 2993-115 Combined Population: Randomized

Disposition	Placebo	5 ug dose	10 ug dose	all subjects
	N=483 n (%) [2]	N=480 n (%) [2]	N=484 n (%) [2]	N=1447 n (%) [2]
Completed	351(72.7)	391(81.5)	383(79.1)	1125(77.7)
Withdrawn	132(27.3)	89(18.5)	101(20.9)	322(22.3)
Reason for Withdrawal				
Withdrawal of consent	44(9.1)	25(5.2)	25(5.2)	94(6.5)
Adverse Event	16(3.3)	27(5.6)	43(8.9)	86(5.9)
Investigator Decision	9(1.9)	2(0.4)	2(0.4)	13(0.9)
Protocol Violation	11(2.3)	5(1.0)	7(1.4)	23(1.6)
Lost to Follow-up	16(3.3)	14(2.9)	15(3.1)	45(3.1)
Administrative	1(0.2)	1(0.2)	0(0.0)	2(0.1)
Loss of Glucose Control	35(7.2)	15(3.1)	9(1.9)	59(4.1)
Other	0(0.0)	0(0.0)	0(0.0)	0(0.0)

In order to avoid undue risk to subjects in the long-term, controlled trials, prospective rules were defined in the study protocols to suggest early withdrawal in the face of overt loss of glucose control, so that these subjects could seek other effective therapy. Such loss of control could be envisioned for some subjects due to either being assigned to placebo and not allowing a second or third antidiabetic therapy to be added, or for subjects assigned to active treatment who did not respond to exenatide. Thus, subjects who had either a 1.5% increase from baseline in HbA_{1c} or an HbA_{1c} value \geq 11.5% at protocol-specified time points were to complete early termination procedures and be withdrawn from the study. Similarly, a subject could have been withdrawn if a fasting plasma glucose value >240 mg/dL was measured by the central laboratory at two consecutive visits to the clinic at protocol-specified time points or if a subject consistently recorded finger-stick fasting blood glucose concentrations >260 mg/dL for at least 2 weeks during study conduct. In the latter case, it was expected that the investigator would ascertain that the increase in self-monitored glucose concentrations was not secondary to a readily identified intercurrent illness or pharmacological treatment that could be discontinued. In Studies 2993-112 and 2993-113 the criteria were applied throughout the protocol while in Study 2993-115 subjects were not recommended to withdraw due to loss of glucose control until Visit 8 (Week 18) to allow sufficient time for upward titration of the sulfonylurea dose in the MinRD treatment groups (see Section 2.7.3.3.2). Subjects meeting the criteria described here and withdrawing from the study for this reason have a disposition outcome of “loss of glucose control”.

The three most common reasons for withdrawal were withdrawal of consent (6.5%), adverse event (5.9%) and loss of glucose control (4.1%). A corresponding Kaplan-Meier plot of the dropout data over time for subjects who discontinued due to loss of glucose control for the ITT population in the three long-term controlled studies combined

Demographic and Baseline Characteristics

Within each study and for the three studies combined, the treatment groups were well balanced in terms of demographic and baseline characteristics. In each treatment group in each study, there were more males than females, with the total population in the three long-term, controlled studies combined consisting of 843 (58.3%) males and 603 (41.7%) females. The overall mean age of the population was 54.7 years, with mean age across treatment groups ranging from 54.5 to 55.0 years. The majority of subjects, 1184 of 1446 (81.9%), were <65 years old. However, there was reasonable representation of older subjects: 262 age ≥65 years and of these, 22 age ≥75 years. The majority of subjects (991; 68.5%) were Caucasian; 224 (15.5%) subjects were Hispanic; and 174 (12%) were Black.

Table 8: Demographic and Baseline Characteristics by Treatment: Descriptive Statistics for Studies 2993-112, 2993-113, and 2993-115 Combined Population: ITT

Parameter	Placebo (N=483)	5 µg (N=480)	10 µg (N=483)	All Subjects (N=1446)
Gender - n(%)				
Male	282(58.4)	276(57.5)	285(59.0)	843(58.3)
Female	201(41.6)	204(42.5)	198(41.0)	603(41.7)
Age (yr)				
n	483	480	483	1446
Mean (SD)	55.0(10)	54.6(10)	54.5(11)	54.7(10)
Age < 65 yr				
n	389	404	391	1184
Mean (SD)	51.5(7.9)	51.9(8.4)	51.1(8.4)	51.5(8.3)
≥ 65 yr				
n	94	76	92	262
Mean (SD)	69.5(3.5)	69.1(3.0)	69.3(3.3)	69.3(3.3)
≥ 75 yr				
n	11	4	7	22
Mean (SD)	75.9(0.9)	75.0(0.0)	75.7(1.1)	75.7(0.9)
Race - n(%)				
Caucasian	333(68.9)	331(69.0)	327(67.7)	991(68.5)

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 {NDA 21,773}
 {Byetta (Exenatide)}

Black	57(11.8)	58(12.1)	59(12.2)	174(12.0)
Asian	7(1.4)	13(2.7)	13(2.7)	33(2.3)
Native American	2(0.4)	2(0.4)	2(0.4)	6(0.4)
Hispanic	77(15.9)	70(14.6)	77(15.9)	224(15.5)
Other	7(1.4)	6(1.3)	5(1.0)	18(1.2)
Weight (kg)	483	480	483	1446
Mean (SD)	99.3(19)	97.1(20)	98.1(20)	98.2(20)
Height (cm)				
n	483	480	483	1446
Mean (SD)	171(10)	170(10)	170(10)	170(10)
BMI (km/m ²)				
n	483	480	483	1446
Mean (SD)	34.1(5.4)	33.4(5.8)	33.7(5.9)	33.7(5.7)
HbA _{1c} (%)				
n	483	480	483	1446
Mean (SD)	8.5(1.1)	8.4(1.1)	8.5(1.1)	8.4(1.1)
HbA _{1c} subgroup				
<9 %				
n	332	334	341	1007
Mean (SD)	7.9(0.6)	7.8(0.6)	7.9(0.6)	7.9(0.6)
>= 9 %				
n	151	146	142	439
Mean (SD)	9.8(0.6)	9.8(0.6)	9.9(0.7)	9.8(0.6)
Fasting Plasma Glucose (mg/dL)				
n	483	480	483	1446
Mean (SD)	181(50)	180(48)	176(46)	179(48)
Duration of Diabetes (yr)				
n	483	480	483	1446
Mean (SD)	7.8(6.0)	7.5(5.8)	7.3(6.3)	7.5(6.0)

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Within each study, and for the three long-term, controlled studies combined, the treatment groups in the ITT population were particularly well-balanced with respect to baseline HbA_{1c}, body weight, BMI, and duration of diabetes. Despite the use of maximally effective doses of metformin and/or SFU, the HbA_{1c} values of these subjects were still suboptimal with an overall mean baseline HbA_{1c} of 8.4%, with mean HbA_{1c} ranging from 8.2% to 8.7% across treatment groups and studies. HbA_{1c} at baseline was <9% in 1007 (70%) subjects and ≥9% in 439 (30%) subjects. Mean weight for all subjects was 98.2 kg (range 94.9 to 101 kg across treatment groups and studies). 29% had a BMI <30 kg/m² and 71% had a BMI ≥30 kg/m². The 5-μg BID and 10-μg BID groups of Study 2993-113 had a baseline mean weight that was approximately 4 kg lower than that of the placebo arm of this study as well as the majority of the treatment groups in

Studies 2993-112 and 2993-115. Mean BMI was 33.7 kg/m² (range 32.7 to 34.4 across treatment groups and studies); 424 subjects (29 controlled studies differed in the subjects' mean duration of diabetes as might be expected based on the concomitant OAD therapies required for entry into the individual studies. Subjects had diabetes for the longest amount of time prior to study participation in Study 2993-115 (8.7 - 9.4 years); followed by Study 2993-113 (5.7 - 6.6 years) and Study 2993-112 (4.9 - 6.6 years), reflecting typical treatment practice relative to progression of type 2 diabetes.

Thus, for the ITT population, the demographic and baseline characteristics in the individual studies were similar to those seen in the combined analysis. Overall, there were no clinically meaningful differences in demographic or baseline characteristics among treatment groups within any study or for the three long-term studies combined.

The demographic and baseline characteristics for the combined studies were similar to those for each of the long-term, controlled studies, with the exception of duration of diabetes, which when averaged across studies had a mean of 7.5 years.

In Studies 2993-112 and 2993-115, where subjects were required to be on a maximum effective regimen of metformin at study entry (≥ 1500 mg daily dose), the mean (SD) baseline metformin daily dose was 1857 mg (314 mg) and 1966 mg (320 mg), respectively. The median baseline metformin daily dose in each study was 2000 mg. Of subjects in Study 2993-112, 41% were using doses of metformin below 2000 mg/day and 59% subjects were using doses greater than or equal to 2000 mg/day. In Study 2993-115, 24% of subjects were using doses of metformin below 2000 mg/day and 76% of subjects were using doses ≥ 2000 mg/day.

Similarly, maximally effective sulfonylurea doses were required at study entry in Studies 2993-113 and 2993-115, although the sulfonylurea dose could be reduced in response to hypoglycemia. Among subjects in these studies, greater than 96% of the population met the inclusion criteria at enrollment that required subjects to be taking at least the maximum effective dose (MaxED) of a SFU, as defined in the protocols and here in Table 9.

Table 9: Dosage of Sulfonylurea Drugs

Sulfonylurea Agent	Maximum Effective Dose (mg/day) ^{5,6,7}	Maximum Recommended Dose (mg/day) ^{5,6,7}
Glimepiride (Amaryl)	4	8
Glipizide (Glucotrol)	20	40
Glipizide (Glucotrol XL)	10	20
Glyburide (Micronase, Diabeta)	10	20
Micronized Glyburide (Glynase)	6	12
Chlorpropamide (Diabinese)	350	750
Tolazamide (Tolinase)	500	1000
Tolbutamide (Orinase)	1500	3000

In these trials, subjects who were taking greater than the maximum effective dose of an SFU were required to decrease their dose to the MaxED at study enrollment to ensure that any subsequent SFU decreases due to hypoglycemia would result in a substantial reduction in the SFU effect, thereby diminishing the risk of subsequent hypoglycemia events. This protocol-mandated dose reduction of a sulfonylurea at study entry from doses above the maximum effective dose to the protocol-defined MaxED did not result in increases in mean HbA_{1c} prior to randomization.

This approach in the long-term clinical trials allowed for a true assessment of the efficacy and safety of exenatide over the background of “maximally effective doses” of the OADs most frequently used in the clinical management of patients with type 2 diabetes.

Further details on the demographic and baseline characteristics for subjects in the long-term controlled studies can be found in ISE Section 4.1.3, located in Module 5.

6.1.4 Efficacy Findings

Efficacy data were summarized for both the ITT and evaluable populations. The ITT population consisted of all subjects who received at least one injection of randomized medication after Visit 3. The evaluable population consisted of all ITT subjects who received at least 80% of injections and completed treatment through Week 30; those who missed injections on 7 consecutive days during the last 2 months of the study were excluded. All inferential statistical tests were conducted at the significance level of 0.05 (2-sided). Data from subjects assigned to volume-matched placebo groups were pooled. Missing data were imputed using the last observation carried forward (LOCF) method.

As indicated, a general linear model tested for differences in change in HbA_{1c} from baseline to study termination across treatments. Factors included treatment (placebo and two active treatment arms), strata of screening HbA_{1c} (<9.0% and ≥9.0%), and site as fixed effects. Fisher's protected testing procedure was applied and the adjusted p-value was presented. The least squares (LS) means (SE), standard errors, and 95% confidence intervals were derived. Change in HbA_{1c} from baseline [Visit 3 (Day 1)] to each of the intermediate visits was analyzed in a similar manner. In addition, the proportion of subjects achieving HbA_{1c} target values of ≤7.0% and ≤8.0% by study termination (Week 30) was compared using the Cochran-Mantel-Haenszel test, using baseline HbA_{1c} strata <9.0% and ≥9.0% as the stratification factor. Time to achieve HbA_{1c} ≤7.0% and time at ≤7.0% were assessed using Kaplan-Meier analysis.

Exenatide, at dosage regimens of 5 and 10 µg BID, administered SC as an adjunct to

metformin and/or a sulfonylurea in subjects with type 2 diabetes, produced clinically and statistically significant reductions from Baseline in HbA_{1c} at Week 30 (Table 1). The magnitude of the reduction with the 10 µg BID dose (0.9-1.0% relative to change in the placebo group) was unrelated to the underlying OAD therapy, and a strong dose relationship to outcome was observed in each study. This magnitude and extent of the HbA_{1c} response in the studied populations represents a meaningful clinical benefit of improved glycemic control. Given that the magnitude of HbA_{1c} reductions tend to be positively proportional to starting HbA_{1c} value, the achieved reductions are especially notable because subjects had relatively low HbA_{1c} (mean baseline HbA_{1c} 8.4%) on entry into these trials. The uniformity of outcome across the studies (patient populations) is consistent with having used maximally effective OAD doses in each study; therefore, the change in HbA_{1c} reflects the true incremental benefit of exenatide treatment over and above the underlying OAD therapy.

The overall mean result is also consistent with the substantial proportion of exenatide-treated subjects (30% and 39% for the exenatide 5 µg and 10 µg groups, respectively) who achieved an HbA_{1c} of ≤7% at Week 30. Similar patterns of response as those seen for changes in HbA_{1c} from Baseline to Week 30 were observed for the secondary endpoints of the study: fasting and postprandial plasma glucose and body weight. The observed loss in body weight in the study subjects reflects an ancillary benefit to overweight patients with type 2 diabetes. As noted, the observed weight loss was not simply secondary to nausea and other gastrointestinal side effects, as weight loss was also observed in those subjects who never experienced these adverse events and there was virtually no correlation between weight change and subjects' total days of nausea. Ability to prevent weight gain is helpful in the overall management of type 2 diabetes.³⁷ Of note, postprandial triglyceride concentrations were reduced, there were also no adverse effects of exenatide treatment on lipid profiles, and blood pressure tended to be unchanged, or slightly reduced.

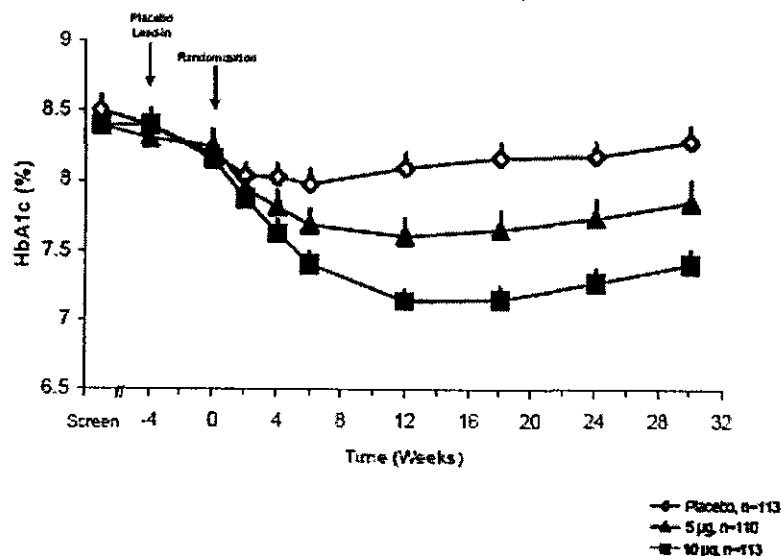
Table 10: Main Efficacy Results of Trials 112, 113 & 115

Study	N	Change From Baseline to Week 30 (LS Mean ± SE)		
		HbA _{1c} (%)	Fasting Plasma Glucose (mg/dL)	Body Weight (kg)
2993-112 (Metformin)				
Placebo	113	-0.00 ± 0.106	14.2 ± 4.69	-0.2 ± 0.42
Exenatide 5 µg	110	-0.46 ± 0.112**	-5.3 ± 4.96*	-1.3 ± 0.45*
Exenatide 10 µg	113	-0.86 ± 0.110**	-10.1 ± 4.88*	-2.6 ± 0.44*
2993-113 (Sulfonylurea)				
Placebo	123	0.06 ± 0.115	5.8 ± 5.21	-0.8 ± 0.32
Exenatide 5 µg	125	-0.51 ± 0.111**	-5.3 ± 5.02	-1.1 ± 0.30
Exenatide 10 µg	129	-0.91 ± 0.110**	-10.8 ± 5.00*	-1.6 ± 0.30*
2993-115 (Metformin + Sulfonylurea)				
Placebo	247	0.12 ± 0.079	12.9 ± 3.61	-0.9 ± 0.21
Exenatide 5 µg	245	-0.66 ± 0.079**	-10.8 ± 3.61*	-1.6 ± 0.21*
Exenatide 10 µg	241	-0.88 ± 0.080**	-12.3 ± 3.69*	-1.6 ± 0.21*

In study 112, Exenatide at doses of 5 µg and 10 µg BID significantly reduced HbA_{1c} in a dose-dependent manner at Week 30 and at each intermediate visit. The LS mean (SE) change in HbA_{1c} from baseline at Week 30 was $-0.46 \pm 0.112\%$ (adjusted $p = 0.0016$) and $-0.86 \pm 0.110\%$ (adjusted $p < 0.0001$) for the exenatide 5 µg and 10 µg groups, respectively, compared with $0.00 \pm 0.106\%$ for the placebo group. A statistically significant dose-effect was demonstrated between exenatide 5 µg and 10 µg for the change in HbA_{1c} at Week 6 through to Week 30 ($p = 0.0053$ at Week 30).

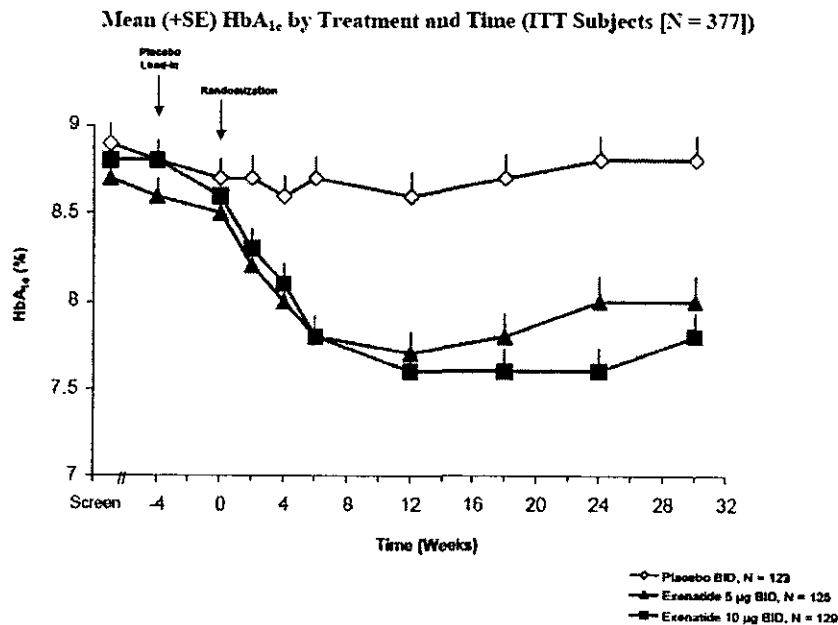
Figure 8:

Mean (+SE) HbA_{1c} by Treatment and Time (ITT Subjects in Study 2993-112 [N=336])



In study 113, glycemic control as measured by HbA_{1c} was significantly improved during 30 weeks of exenatide treatment. LS mean (SE) reductions in HbA_{1c} at Week 30 appeared to be dose-dependent; changes from baseline were $-0.51 (0.111)\%$ for exenatide 5 µg and $-0.91 (0.110)\%$ for exenatide 10 µg compared with an increase of $0.06 (0.115)\%$ for placebo. Pairwise comparisons were statistically significant for exenatide 5 µg versus placebo (adjusted $p = 0.0002$) and exenatide 10 µg versus placebo (adjusted $p < 0.0001$). A statistically significant dose-response effect ($p = 0.0002$ exenatide 5 µg versus placebo, $p = 0.0098$ exenatide 10 µg versus exenatide 5 µg) was observed in the change in HbA_{1c} from baseline to Week 30. Mean HbA_{1c} during 30 weeks of treatment is shown in the figure below. The key efficacy results of study 113 are shown in the following table.

Figure 9:



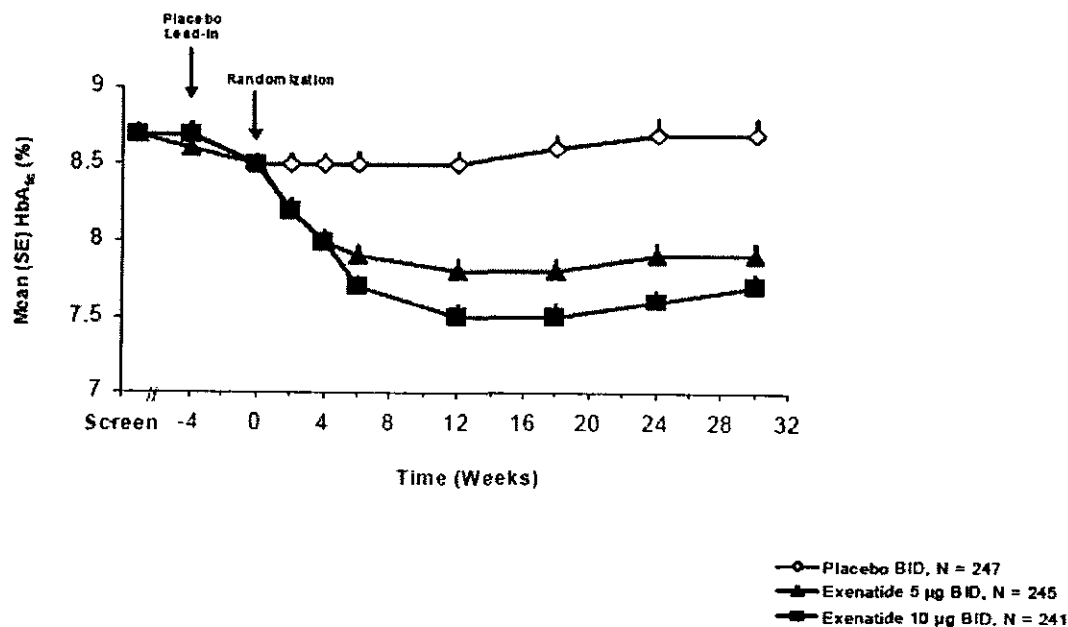
In study 115, Exenatide 5 µg, BID and exenatide 10 µg, BID significantly improved glycemic control in subjects with type 2 diabetes treated with metformin and an SFU as evidenced by dose-dependent reductions in HbA_{1c} over 30 weeks of treatment. Change (LS mean) in HbA_{1c} from baseline at Week 30 for the ITT population was as follows: exenatide 5 µg, -0.66% (adjusted $p < 0.0001$); exenatide 10 µg, -0.88% (adjusted $p < 0.0001$), compared with placebo, 0.12%. A statistically significant dose-response effect was established upon comparison of the change in mean HbA_{1c} (baseline to Week 30) for the exenatide 5 µg, BID and exenatide 10 µg, BID treatments (adjusted $p = 0.0299$).

Mean HbA_{1c} over time is shown in the following figure.

Figure 10:

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Mean (+SE) HbA_{1c} by Treatment and Time (ITT Subjects [N = 733])



Comparison and Analysis of Results Across Studies

For purposes of comparison and analysis, efficacy results from the three long-term, controlled studies are displayed in this section. Also included are results from analysis of the pooled data from these three studies. Pooling was considered appropriate since the studies had similar protocols, were conducted within the same time period, and were qualitatively and quantitatively very similar in terms of results, despite the difference among studies in the OAD onto which exenatide therapy was added.

The statistical methods used for purposes of the analyses for the three studies combined are detailed in a separate Statistical Analysis Plan provided as an Appendix to the Integrated Summary of Efficacy, located in Module 5, Section 5.3.5.3.2.

The main efficacy results of the three long-term controlled studies are summarized in Table 10, and the details for each parameter are described in the subsections that follow.

HbA_{1c} and Change From Baseline HbA_{1c}

Clinically and statistically significant improvements in glucose control (i.e., reductions in

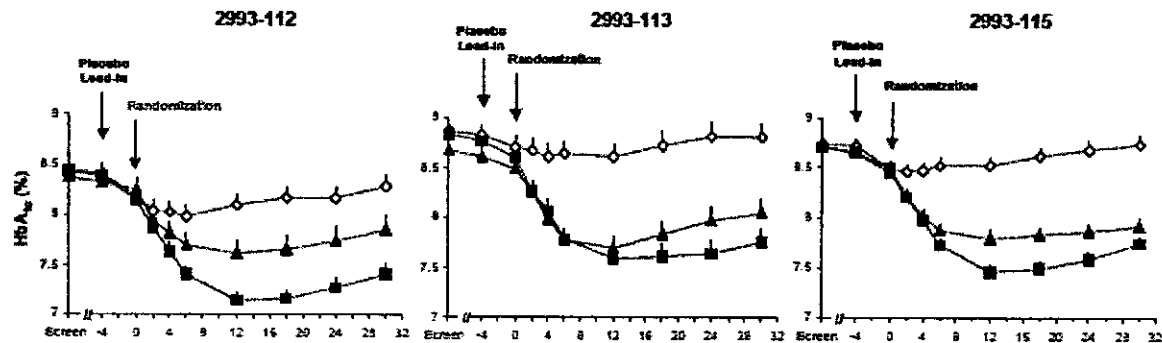
HbA_{1c}) were detected for subjects treated with either exenatide 5 µg or 10 µg BID in each of the three long-term controlled studies, 2993-112, 2993-113, and 2993-115. Furthermore, results across the 3 studies demonstrate a consistent effect independent of the background OAD therapy employed by the subjects. In each of the three long-term controlled studies, mean HbA_{1c} values at baseline were comparable among the three treatment groups within a given study and between studies.

Mean HbA_{1c} in all three treatment groups decreased during the 4-week placebo lead-in period prior to randomization, possibly reflecting a study effect due to the therapeutic discipline imposed by virtue of entering a clinical trial. Although subjects had HbA_{1c} values that were higher than clinically desirable in the management of type 2 diabetes (goal HbA_{1c} <7%) these values were, nonetheless, relatively stable and consistent across both treatment groups and studies.

Following randomization, subjects in the placebo groups, treated only with metformin (2993-112), sulfonylurea (2993-113) or a combination of metformin/sulfonylurea (2993-115) had only minor changes from baseline in HbA_{1c}, indicating that their HbA_{1c} remained relatively stable while being maintained on maximally effective doses of their prior oral antidiabetic therapy during the study period and contributed little, if any, to the difference in mean HbA_{1c} values observed. In contrast, subjects who had exenatide 5 µg BID or 10 µg BID added to their existing oral antidiabetic therapy exhibited decreases from baseline in HbA_{1c}.

In each study, statistically significant mean decreases from baseline were observed in both exenatide treatment groups from Week 2 onward, with the maximum decreases appearing in the timeframe of approximately 12 to 18 weeks. There were small increases in HbA_{1c} in each long-term, controlled study from this point to Week 30 in both exenatide groups. These increases were parallel to those observed in the placebo groups and are to be expected in long-term, clinical studies of subjects with type 2 diabetes. The uniformity of outcome across the studies demonstrates that the effects of exenatide to lower HbA_{1c} are expressed independent of other background therapies.

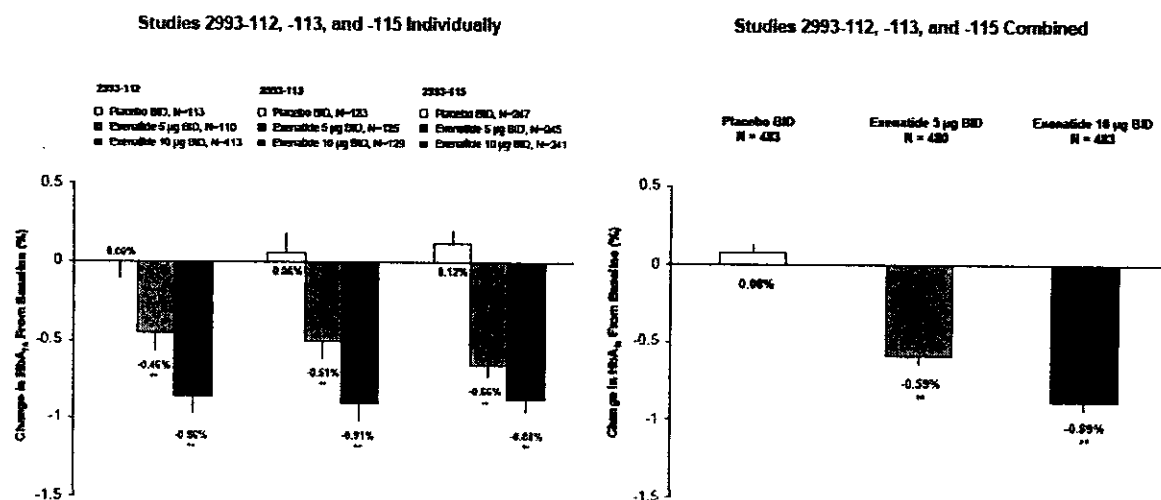
Figure 11: Mean (SE) HbA_{1c} and From Baseline Over Time for Studies 2993-112, 2993-113, and 2993-115 Individually (ITT Population [N = 336; N = 377; N = 733])



Change From Baseline in HbA_{1c} at 30 Weeks of Exposure

Mean change from baseline in HbA_{1c} at Week 30 was the primary endpoint in each long-term, controlled study. The LS mean reductions from baseline in HbA_{1c} at Week 30 with exenatide treatment in each of the three long-term controlled studies 2993-112, 2993-113, and 2993-115 individually and combined are illustrated in Figure 1. Subjects treated with 5 μ g BID and 10 μ g BID exenatide added to their existing therapy for 30 weeks experienced LS mean reductions in HbA_{1c} values at Week 30 of between -0.46% to -0.66% in the exenatide 5 μ g BID group and between -0.86% to -0.91% in the exenatide 10 μ g BID group. These mean reductions in HbA_{1c} at Week 30 in subjects treated with exenatide were consistently observed across all three long-term, controlled studies, regardless of the existing therapy to which exenatide was added (i.e., maximally effective doses of metformin, sulfonylurea, or maximally effective doses of both metformin and a sulfonylurea). In contrast, LS mean reductions in HbA_{1c} values with placebo treatment ranged from 0.0% to +0.12%. The results in all three studies clearly demonstrate a consistent, dose-dependent and statistically significant reduction in HbA_{1c} when compared with placebo either individually or as a combined long-term dataset.

Figure 12: Bar Graph for LS Mean (SE) Change in HbA_{1c} From Baseline to Week 30 for Studies 2993-112, 2993-113, and 2993-115 Individually and Combined (ITT Population [N = 336; N = 377; N = 733; N = 1446])



As evidenced by the results in these tables and by graphic display of the treatment effect sizes (i.e., placebo-subtracted LS mean change from baseline in HbA_{1c}) in each long-term, controlled study, each exenatide dosage regimen, 5 µg and 10 µg, produced a reduction in HbA_{1c} that was both clinically and statistically superior to treatment with the corresponding placebo regimen, i.e., either metformin alone, sulfonylurea alone, or the combination of metformin and a sulfonylurea. Results for the three long-term controlled studies combined reinforced the individual study results. Further, the dose response was again evident and was confirmed by statistical analysis.

Number and Percent of Subjects Reaching Target HbA_{1c} of 7% at Week 30

In all three long-term, controlled studies, the proportions of evaluable subjects with baseline HbA_{1c} >7% achieving HbA_{1c} ≤7% at Week 30 were consistently higher in the exenatide groups compared with the placebo group, and the pairwise comparison between each exenatide dose group and the placebo group was statistically significant. Across the three studies, only 9% to 13% of placebo subjects achieved HbA_{1c} ≤7% at Week 30, whereas 27% to 33% of subjects on exenatide 5 µg and 34-46% of subjects on exenatide 10 µg achieved this HbA_{1c} level. In each of the studies, the proportion of subjects in the exenatide 5 µg BID and 10 µg BID groups achieving HbA_{1c} ≤7% was dose-dependent.

Table 11: Proportion of Subjects Achieving HbA_{1c} ≤7% at Week 30 for Studies 2993-112, 2993-113 and 2993-115 Individually (Population: Evaluable)

	Placebo	5 ug	10 ug
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{Byetta (Exenatide)}

2993-112			
Total n	77	79	84
N (%) attained HbA _{1c} of $\leq 7\%$, P	10 (13.0)	25 (31.6), .009	39 (46.4), <.0001
2993-113			
Total n	68	86	80
N (%) attained HbA _{1c} of $\leq 7\%$, P	6 (8.8)	28 (32.6), .0002	33 (41.3), <.0001
2993-115			
Total n	174	197	179
N (%) attained HbA _{1c} of $\leq 7\%$, P	16 (9.2)	54 (27.4), <.0001	60 (33.5), <.0001

For the three pivotal Phase 3 studies combined, there was also a highly significant difference between each exenatide dose group and placebo in the proportion of subjects achieving an HbA_{1c} of $\leq 7\%$ at Week 30. Only 10% of placebo subjects achieved this HbA_{1c} value, compared with 30% and 39% of subjects in the exenatide 5- μ g BID and 10- μ g BID treatment groups, respectively.

Reduction in Postprandial Glucose Excursions

Clinically and statistically significant improvements in postprandial glucose excursions after 4 and 30 weeks of exenatide treatment were determined with combined analysis of the evaluable standardized meal-tolerance test cohort (SMTT) from the three long-term controlled studies. At Week 4 of treatment, exenatide (5 μ g or 10 μ g BID) significantly reduced the postprandial rise in plasma glucose compared with placebo. This treatment effect was sustained through 30 weeks of therapy.

The evaluable SMTT cohort consisted of 36, 25 and 77 subjects in Studies 2993-112, 2993-113, and 2993-115, respectively. Because the number of subjects in the SMTT cohort of each study was relatively small, particularly within Study 2993-113, the discussion below focuses on the analysis of the three studies combined.

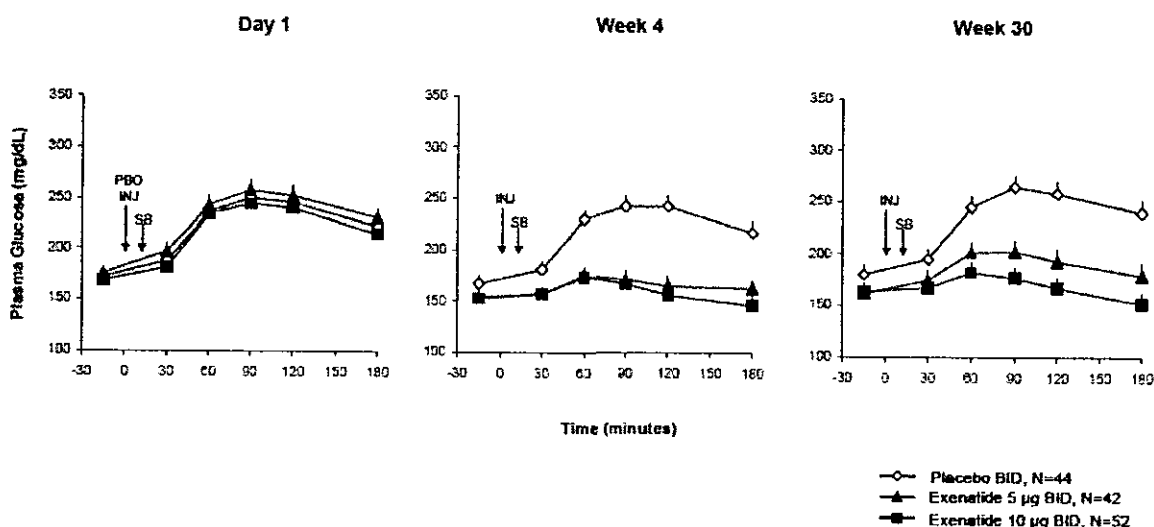
At Day 1, subjects in all three treatment groups received an injection of placebo at t = 0 min. Following ingestion of the standardized meal at t = 15 min, mean glucose concentrations rose progressively over time and were similar among the treatment groups reaching a peak at 90 min. The mean glucose concentrations throughout the 3-hour sampling period remained above those measured at the -15 min time point for all three groups.

At Week 4, subjects received randomized study medication at t = 0 min. For subjects in the exenatide 10- μ g BID group, this was the first injection of 10 μ g received following the

exenatide 5- μ g BID initiation period. Following the standardized meal, mean glucose concentrations in the placebo group rose and remained above that measured at the -15 min time point throughout the 180 minute sampling period, similar to that observed at Day 1. In contrast, the exenatide 5- μ g BID and 10- μ g BID groups had only a small rise in mean glucose concentrations following the standardized meal. Mean postprandial plasma glucose concentrations were similar between the exenatide 5- μ g BID and 10- μ g BID groups following the standardized meal, and the mean glucose concentrations at 180 minutes were the same or lower than those measured at the -15 min time point.

At Week 30, subjects received randomized study medication at t = 0 min. The mean glucose concentration at the -15 min time point remained higher for the placebo group compared with the exenatide 5- μ g BID and 10- μ g BID groups. Following the standardized meal, mean glucose concentrations in the placebo group rose and remained above those concentrations measured at the -15 min time point throughout the 180 minute sampling period, similar to those concentrations observed at Day 1 and Week 4. In contrast to results seen in the placebo group, the mean glucose concentrations following the standardized meal in the exenatide 5- μ g BID and 10- μ g BID groups showed a dose-dependent ability to blunt the rise in postprandial plasma glucose concentrations. Only marginal increases relative to baseline were observed, and glucose concentrations returned to baseline or lower concentrations at the later time points.

Figure 13: Mean (SE) Postprandial Plasma Glucose Following Injection of Exenatide or Placebo Twice Daily in Subjects With Type 2 Diabetes for Studies 2993-112, 2993-113, and 2993-115 Combined (Evaluable Meal Tolerance Test Population [N = 138])

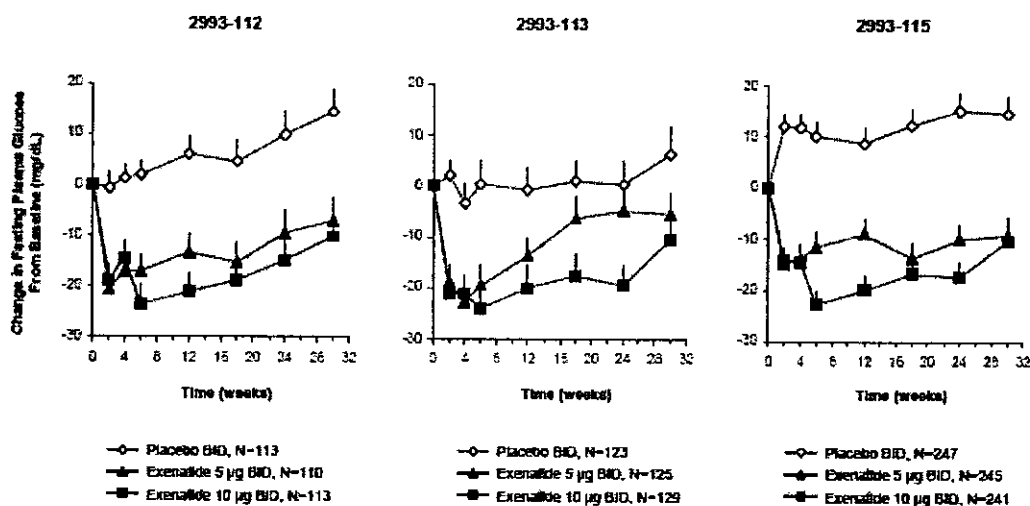


Postprandial plasma glucose AUC_(15-180 min) was reduced from Day 1 to Week 4 for both exenatide treatment groups. The geometric LS mean (SE) ratio of Week 4 to Day 1 was

0.67 ± 0.029 (i.e., 67% of the baseline value) and 0.71 ± 0.027 for the exenatide 5-µg BID and 10-µg BID groups, respectively, compared with 0.96 ± 0.040 for the placebo group. The pairwise comparisons demonstrated a statistically significant difference between the exenatide 5-µg BID group and placebo (p < 0.0001) and between the exenatide 10-µg BID group and placebo (p < 0.0001).

Within each study, mean FPG concentrations at baseline were comparable among the three treatment groups with the exception of Study 2993-113 wherein mean FPG concentrations were higher at baseline Visit 3 (Day 1) for placebo subjects (194.0 mg/dL) compared with exenatide 5 µg (180.3 mg/dL) and exenatide 10 µg (178.2 mg/dL) subjects. Among the three studies, mean baseline FPG concentrations were slightly lower in Study 2993-112 (168.4 to 176.0 mg/dL) than in Study 2993-113 (178.2 to 194.0 mg/dL) or Study 2993-115 (178.1 to 182.3 mg/dL). Mean FPG concentrations in the three treatment groups across studies tended to stay the same or decrease slightly during the 4-week placebo lead-in period (the only exception being the exenatide 5 µg BID group in Study 2993-112).

Figure 14: Plot for Mean (SE) Change in Fasting Plasma Glucose Concentrations From Baseline to Week 30 and Each Intermediate Visit for Studies 2993-112, 2993-113, and 2993-115 Individually
 ITT Population



Following randomization, subjects in the placebo groups, treated only with metformin (2993-112), sulfonylurea (2993-113) or a combination of metformin/sulfonylurea (2993-115) tended to show mean increases over time in FPG concentrations, while subjects treated with exenatide 5 µg BID or 10 µg BID added to their existing oral antidiabetic therapy exhibited sharp decreases from baseline in mean FPG. Of note is the increase in FPG observed following randomization in

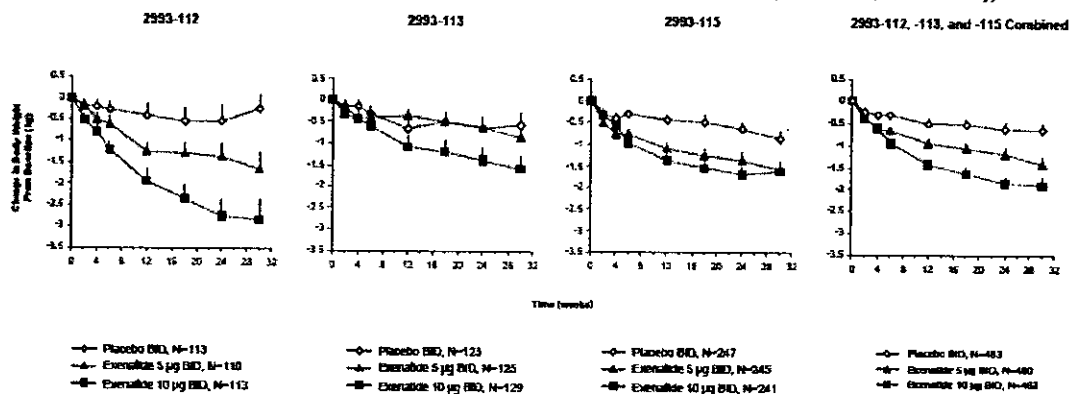
the placebo arm of Study 2993-115, which is driven largely by subjects randomized to the MinRD (minimum recommended dose of sulfonylurea) treatment group, as would be anticipated from the significant reduction in sulfonylurea dose. Despite the drop in SFU dose in half the subjects, the exenatide treatment groups assigned to either MinRD or MaxED SFU treatment groups still demonstrated a clinically meaningful decrease in FPG from baseline.

In each study, statistically significant mean decreases from baseline compared with placebo were observed in both exenatide treatment groups from Week 2 onward with the exception of the 5- μ g treatment group of 2993-113, which demonstrated a statistically significant reduction at all visits up to Week 18. The maximum decreases with the 10- μ g treatment groups were observed in each study at approximately Week 6 of randomized treatment. The difference from placebo is generally maintained and is statistically significant.

Effects on Body Weight

Reductions in body weight were detected for subjects treated with exenatide 5 μ g BID or 10 μ g BID in each of the three long-term, controlled studies, 2993-112, 2993-113, and 2993-115; and in two of the three studies (2993-112 and 2993-113), the reduction in body weight appeared to be dose-dependent. Figure 15 illustrates the mean reductions from baseline in body weight at each study visit by dose group for the three long-term, controlled studies 2993-112, 2993-113, and 2993-115 individually and combined.

Figure 15: Mean (SE) Change in Body Weight From Baseline Over Time for Studies 2993-112, 2993-113, and 2993-115 Individually and Combined (ITT Population [N = 336; N = 377; N = 733; N = 1446])



In Study 2993-112, the LS mean (\pm SE) change in body weight from baseline at Week 30 was -1.3 ± 0.45 kg and -2.6 ± 0.44 kg for the exenatide 5 μ g BID and 10 μ g BID, groups, respectively, compared with -0.2 ± 0.42 kg for the placebo group. The parametric analysis of body weight demonstrated statistically significant reductions from baseline compared with placebo at each visit from Week 2 up to and including Week 30 for the exenatide 10 μ g BID group. Statistically

significant reductions from baseline compared with placebo were also observed at Week 30 for the exenatide 5 µg BID group; however at the intermediate visits the differences between the exenatide 5 µg BID group and the placebo group did not achieve statistical significance.

In Study 2993-113, the LS mean (\pm SE) change in body weight from baseline at Week 30 was -1.1 ± 0.30 kg and -1.6 ± 0.30 kg for the exenatide 5-µg BID and 10-µg BID groups, respectively, compared with -0.8 ± 0.32 kg for the placebo group. Pairwise comparisons demonstrated a statistically significant difference in the change in body weight at Week 30 for exenatide 10 µg BID versus placebo, but the difference was not statistically significant for exenatide 5 µg BID versus placebo. No statistically significant differences in the change in body weight were noted between exenatide 5 µg BID subjects and placebo subjects or between exenatide 10 µg BID subjects and placebo subjects at any intermediate visit.

In Study 2993-115, the LS mean (\pm SE) change in body weight from baseline at Week 30 was -1.6 ± 0.21 kg and -1.6 ± 0.22 kg for the exenatide 5-µg BID and 10-µg BID groups, respectively compared with -0.9 ± 0.21 kg for the placebo group. The parametric analysis of body weight demonstrated statistically significant reductions from baseline compared with placebo at each visit from Week 4 up to and including Week 30 for the exenatide 5 µg BID group, and from Week 6 up to and including Week 30 for the exenatide 10 µg BID group.

For the three long-term, controlled studies combined, the LS mean (\pm SE) change in body weight from baseline at Week 30 was -1.4 ± 0.16 kg and -1.9 ± 0.16 kg for the exenatide 5-µg BID and 10-µg BID groups, respectively, compared with -0.7 ± 0.16 kg for the placebo group. Pairwise comparisons demonstrated a statistically significant difference in the change in body weight at Week 30 for both exenatide 5 µg BID and 10 µg BID versus placebo ($p = 0.0005$ and $p < 0.0001$, respectively). The parametric analysis of body weight demonstrated statistically significant reductions from baseline for both treatment groups compared with placebo from Week 4 up to and including Week 30.

Thus, reductions in body weight at Week 30 in subjects treated with exenatide were consistently observed across all three long-term, controlled studies, regardless of the existing therapy to which exenatide was added (i.e., metformin, sulfonylurea, or a combination of metformin and sulfonylurea).

Long-Term Effects on Beta Cell

In the two long-term, controlled studies (2993-112 and 2993-113) where evaluations of beta-cell effects were made for all subjects, treatment with 5 µg BID and 10 µg BID exenatide for 30 weeks showed statistically significant improvements in HOMA-B compared with placebo. Pairwise comparisons demonstrated a statistically significant difference between the exenatide 10 µg BID group and placebo for the ratio of the HOMA-B value at every visit, and between the exenatide 5 µg BID and placebo group for every visit (except Week 24 in

Study 2993-112). HOMA-B was only assessed in a subset of subjects in Study 2993-115; the magnitude of the effect was similar to that seen in Studies 2993-112 and 2993-113, but was not statistically significant possibly due to the smaller sample size.

The fasting (predose) proinsulin to insulin ratio provides an indication as to the amount of proinsulin to insulin conversion in the pancreatic beta cells prior to secretion. Patients with type 2 diabetes have increased proinsulin concentrations compared with patients not having diabetes, both in absolute terms and relative to the amount of secreted insulin (proinsulin to insulin ratio). A statistically significant reduction in the proinsulin to insulin ratio from Baseline to Week 30 was observed in Studies 2993-112 and 2993-113 with exenatide 10 µg BID treatment compared to placebo. As with the HOMA-B measure described above, proinsulin and insulin were measured in only a subset of subjects in Study 2993-115, making interpretation of the results difficult.

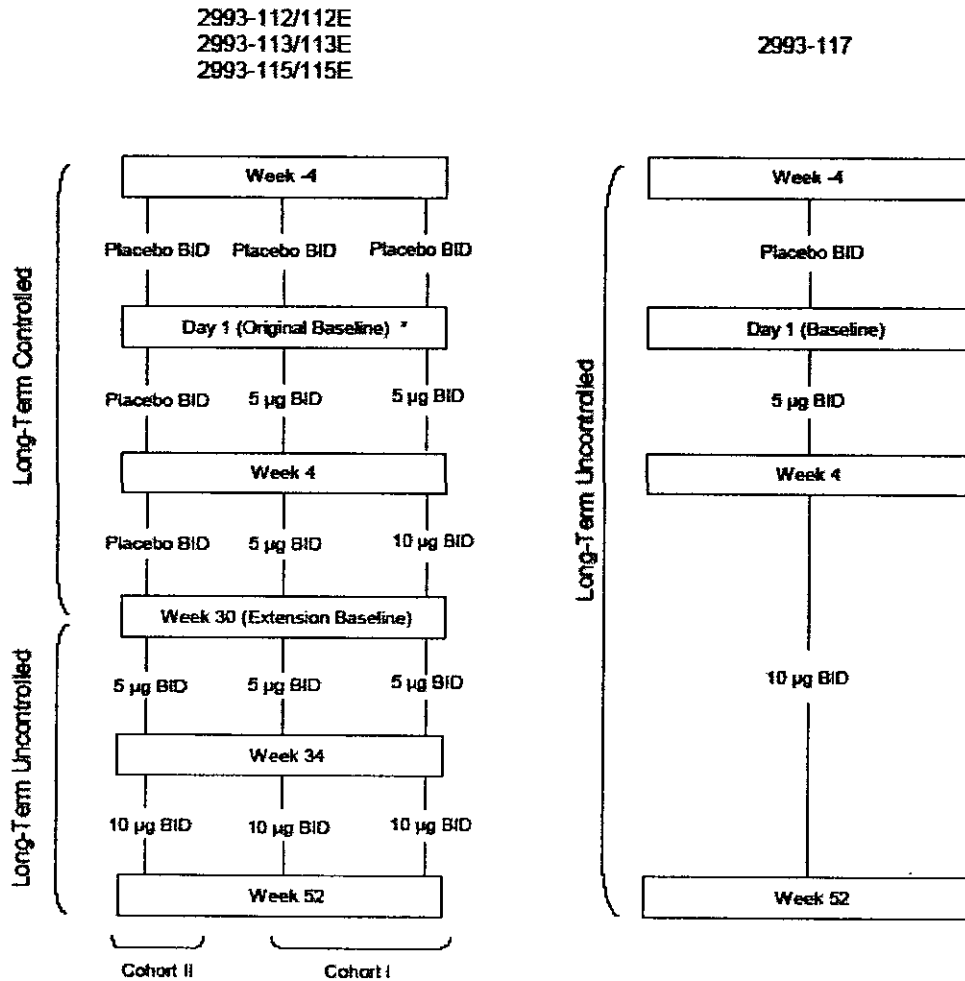
Durability of Exenatide Treatment Effect

The long-term, uncontrolled studies included open-label extensions (2993-112E, 2993-113E, 2993-115E) of the three long-term, controlled studies, and a long-term open-label trial (2993-117). These four studies are treated, in part, as though they were completed studies and in part as ongoing studies, since subjects are continuing their participation in these studies to gain data on exenatide exposure beyond 52 weeks.

The effect of exenatide on HbA_{1c} was shown to be durable through 52 weeks of treatment in four uncontrolled trials. Since the designs and individual study outcomes were shown to be so comparable, it is reasonable to pool data across the three long-term trials and their extensions. In these studies, Cohorts I and II refer to subjects treated with exenatide or placebo, respectively, during the 30-week, controlled trial preceding the open-label extension.

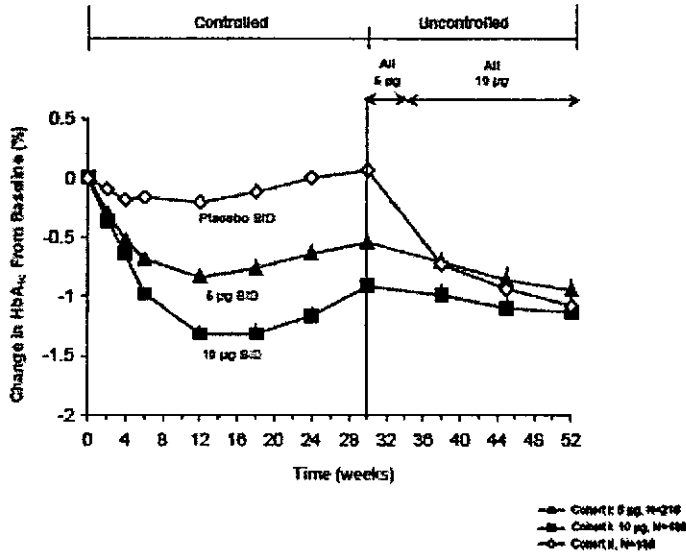
Figure 16: Structure of the Extension Trials 112E, 113E & 115E and the uncontrolled Trial #117

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Of the 1125 patients who completed the 7-month placebo-controlled trials, 86.8% elected to participate in open-label extension studies. The mean change in HbA_{1c} at Week 30 achieved by subjects treated with exenatide 10 µg BID in the controlled studies was clearly maintained throughout the subsequent 22-week open-label period (Cohort I, 10 µg). Subjects originally treated with either placebo (Cohort II) or exenatide 5 µg (Cohort I, 5 µg) in the controlled studies achieved changes in HbA_{1c} by Week 52 comparable to those observed for subjects continuously treated with a 10-µg dose. The reductions from baseline HbA_{1c}, fasting plasma glucose, and body weight observed during the placebo-controlled trials of exenatide were maintained through 52 weeks during the extension studies.

Figure 17: Mean (SE) Change in HbA_{1c} From Original Baseline Over Time for Studies 2993-112/112E, 2993-113/113E, and 2993-115/115E Combined



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Factors That Could Affect Efficacy Outcome

Gender

The treatment-by-gender interaction was significant for the metformin study ($p=0.01$) (Fig. 18). Female patients in the 5 µg and placebo groups experienced similar HbA_{1c} changes from baseline at endpoint. Table 12 displays the mean and standard deviation of HbA_{1c} change from baseline to endpoint by gender.

Figure 18 HbA_{1c} change from baseline by visit and gender

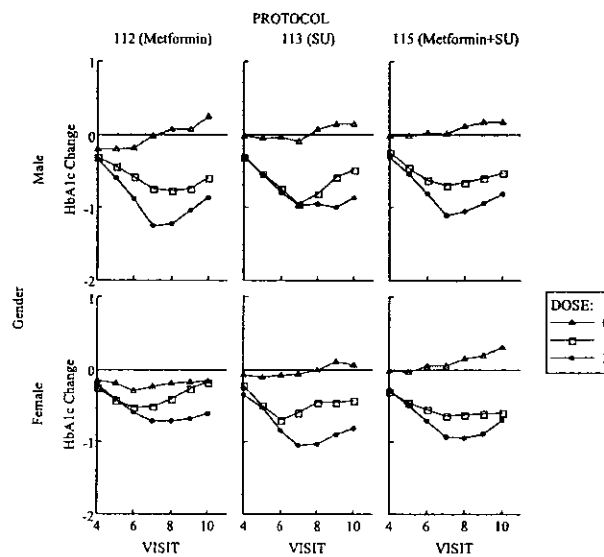


Table 12 Mean HbA_{1c} (%) change from baseline to endpoint by gender – Metformin

	Placebo		5 µg		10 µg	
	Male	Female	Male	Female	Male	Female
Metformin	n=67	n=42	n=57	n=53	n=68	n=45
baseline	8.06 (1.02)	8.41 (1.04)	8.23 (1.19)	8.29 (1.06)	8.26 (1.09)	8.06 (0.85)
change	+0.24 (1.06)	-0.17 (0.99)	-0.59 (1.17)	-0.18 (1.01)	-0.86 (1.04)	-0.61 (1.04)

Race

When 6 race categories were used in the model the overall treatment-by-race interaction was not significant in change from baseline HbA_{1c} for the 3 studies (p=0.9, 1.0, 0.2). However, when only 2 categories were used in the model (Caucasian and Black) the treatment-by-race interaction was significant for study 115 (p=0.07). Figure 19 displays the mean HbA_{1c} change from baseline over time and Figure 8 the median change at endpoint for the 3 races with the most patients, Caucasian, Black and Hispanic patients. Table 9 displays mean and median HbA_{1c} change from baseline for Caucasian and Black patients. The percentages of Caucasians, Blacks, and Hispanics were 68% (494), 11% (82) and 16% (117), respectively. From the descriptive statistics of HbA_{1c} change, the treatment effect is smaller in Black patients in the 5 µg bid group compared to Caucasian and Hispanic patients.

Figure 19: Mean HbA_{1c} change from baseline (%) over time by race

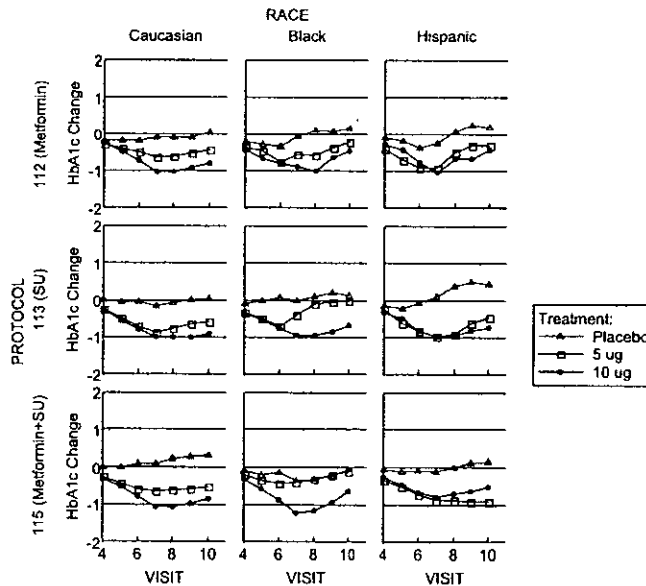


Figure 20: Median HbA_{1c} change from baseline at endpoint by race

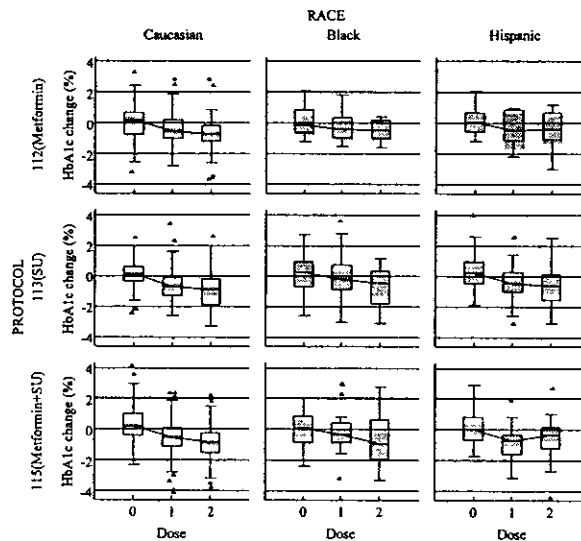


Table 13: Mean, Median of baseline HbA_{1c} & HbA_{1c} change (%) by race

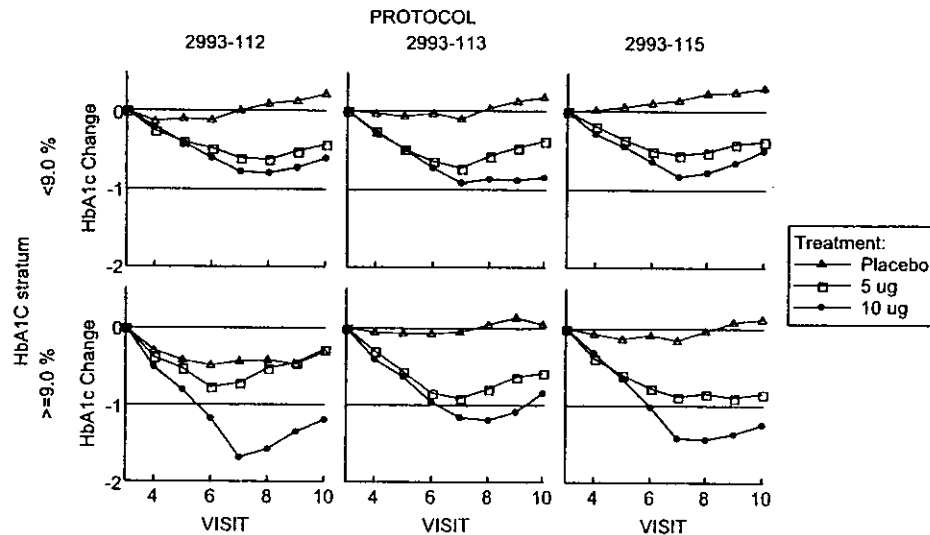
	Placebo				5 µg				10 µg			
	Caucasian n=82		Black n=15		Caucasian n=85		Black n=12		Caucasian n=89		Black n=10	
Metformin												
mean	8.07	+0.04	8.47	+0.18	8.20	-0.43	8.66	-0.21	8.12	-0.79	8.21	-0.45
median	7.85	+0.2	8.6	-0.1	8.0	-0.5	8.5	-0.4	8.0	-0.7	8.25	-0.45
SFU												
mean	8.56	+0.03	9.1	+0.13	8.32	-0.58	8.79	-0.02	8.38	-0.91	9.06	-0.67
median	8.2	+0.1	8.85	+0.25	8.1	-0.7	8.7	-0.2	8.3	-0.9	8.50	-0.5
Metformin+SFU												
mean	8.47	+0.31	8.57	-0.06	8.41	-0.53	8.5	-0.1	8.44	-0.85	8.42	-0.63
median	8.3	+0.2	8.5	+0.1	8.2	-0.5	8.7	-0.3	8.2	-0.85	8.3	-0.9

The treatment-by-age interaction was not significant.

Other Special/Subgroup Populations

The overall treatment-by-HbA_{1c} stratum interaction was significant for the metformin study (p=0.056) and the metformin+SFU study (p=0.027) (Fig. 2 and 9). For the pairwise comparisons, the interaction was significant between the placebo group and the 10 µg group and the 5 µg group and the 10 µg group in the metformin study and between the placebo group and the 5 µg group in the metformin+SFU study. In the metformin study, the difference between 5 µg and placebo in HbA_{1c} change from baseline at endpoint was -0.61% and +0.07% for the HbA_{1c} <9% stratum and the ≥9% stratum respectively (Table 6). The difference between 10 µg and 5 µg was -0.2% and -0.89% for the 2 HbA_{1c} strata. In the metformin+SFU study the treatment difference between 10 µg and placebo was -0.8% and -1.37% for the 2 HbA_{1c} strata, respectively.

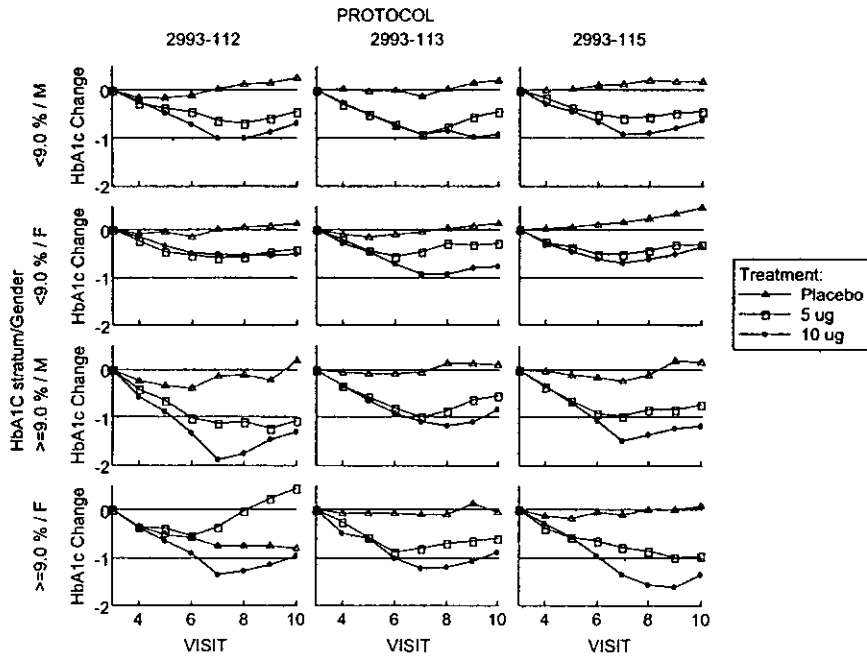
Figure 21 HbA_{1c} change from baseline over time by stratum and protocol



The treatment-by-stratum-by-gender interaction was significant for the metformin study ($p=0.0003$) and the metformin+SFU study ($p=0.08$). The qualitative interaction in the metformin alone study was caused by decreases in the placebo group ($n=15$) and increases in the 5 μg group ($n=14$) of HbA_{1c} in the female and $\text{HbA}_{1c} \geq 9\%$ stratum subgroup (Fig 10, 18). There was a quantitative interaction involving the placebo and 10 μg groups for the metformin+SFU study (Fig 10). However, the sample size was small and gender and HbA_{1c} stratum might be confounded.

Figure 22 HbA_{1c} change from baseline (%) by HbA_{1c} stratum and gender

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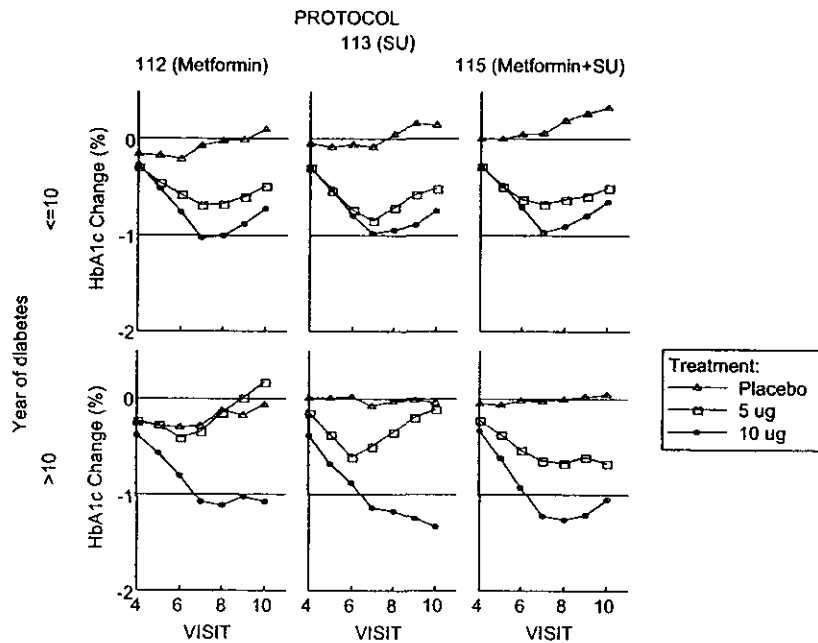


Treatment-by-years of diabetes (>10 or ≤ 10 yrs) interaction was significant for studies 112 and 113 (Fig 11). Patients in the $5\mu\text{g}$ group with >10 years of diabetes was similar to placebo at endpoint in HbA_{1c} change from baseline for studies 112 and 113. 15% of patients had >10 years of diabetes in studies 112 and 113, 31% in study 115 (Table 10).

Table 14: HbA_{1c} (%) in patients with >10 or ≤ 10 years of diabetes

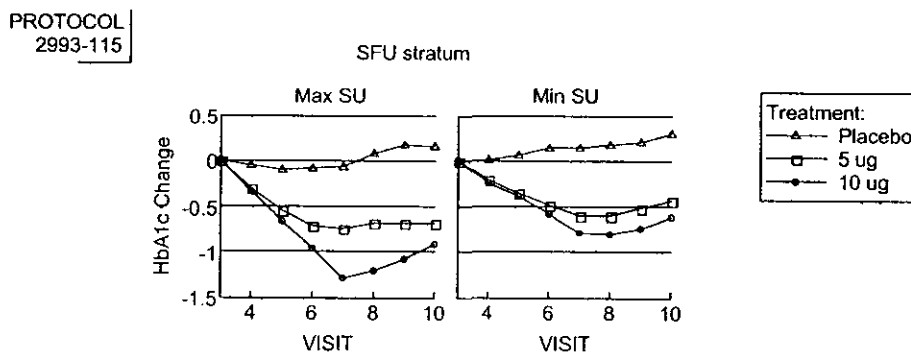
	Placebo		5 μg		10 μg	
	≤ 10	>10	≤ 10	>10	≤ 10	>10
Metformin	n=93	n=20	n=94	n=16	n=99	n=14
baseline	8.1	8.9	8.2	8.9	8.2	8.3
change	0.1	-0.1	-0.5	0.2	-0.7	-1.1
SFU	n=104	n=19	n=108	n=17	n=109	n=20
baseline	8.7	8.6	8.5	8.2	8.6	8.6
change	0.1	-0.04	-0.5	-0.1	-0.7	-1.3
Metformin+SFU	n=161	n=86	n=173	n=72	n=173	n=68
baseline	8.5	8.5	8.6	8.2	8.4	8.7
change	0.3	0.04	-0.5	-0.7	-0.6	-1.0

Figure 23: HbA_{1c} change from baseline by years of diabetes diagnosis



Patients in the metformin+SFU study were randomized to continue on to the maximum effective dose or reduce the SFU to the minimum recommended dose. The treatment-by-SFU (maximum or minimum dose) stratum interaction was not significant at endpoint in HbA_{1c} change from baseline (Fig 12).

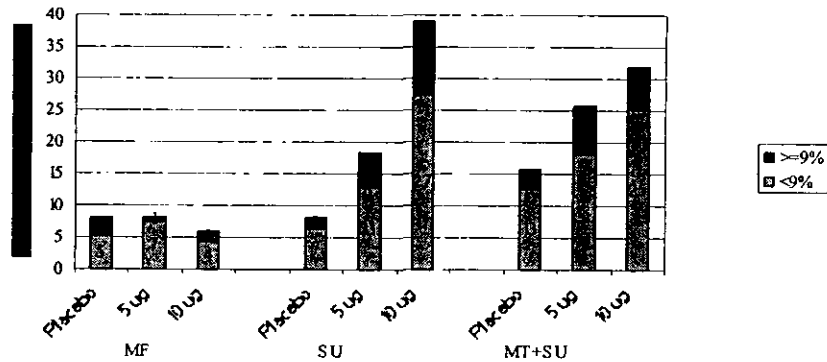
Figure 24: Mean HbA_{1c} change from baseline by visit and SFU stratum – metformin+SFU study



Hypoglycemia

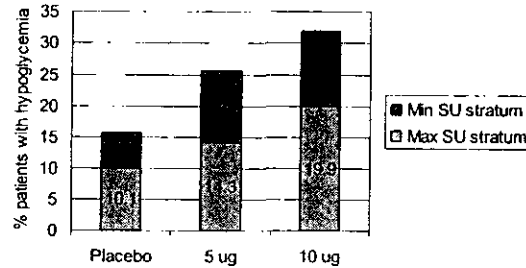
For all studies, there was a greater percentage of patients with hypoglycemia in the screening HbA_{1c} <9% stratum than in the ≥9% stratum (Fig 13).

Figure 25: Percent of patients with hypoglycemia by HbA_{1c} stratum – 3 studies



For the metformin+SFU study, there was a more pronounced dose response for hypoglycemia in patients randomized to the maximum effective dose SFU than patients randomized to the minimum recommended dose SFU (Figure 14).

Figure 1 Percent of patients with hypoglycemia by SFU stratum – Metformin+SFU study (#115)



Anti-exenatide antibody

At endpoint, the treatment groups were significantly different in percentage of patients with anti-exenatide antibodies (Table 11).

Table 15: Percent of patients with anti-exenatide antibodies at endpoint – All studies

	Placebo	5 µg	10 µg	p-value
Metformin alone	3/113 (3%)	44/109 (40%)	51/112 (46%)	<0.0001
SFU alone	2/120 (2%)	46/122 (38%)	51/125 (41%)	<0.0001
Metformin+SFU	13/242 (5%)	120/244 (49%)	107/240 (45%)	<0.0001

Table 12 displays mean and median HbA_{1c} change from baseline for 2 categories of antibody titer at endpoint (<125 or ≥125). Patients in the active treatment groups experienced reduction of HbA_{1c} in both antibody categories compared to placebo. However, the effect was smaller in the antibody titer ≥125 patients than in the antibody titer <125 patients. Note that antibody titer and HbA_{1c} were both outcome variables. Subgroups defined by antibody titer are not subgroups in the usual sense; therefore caution should be used in interpreting the results.

Table 16: Mean HbA_{1c} change (%) by antibody titer category – all studies

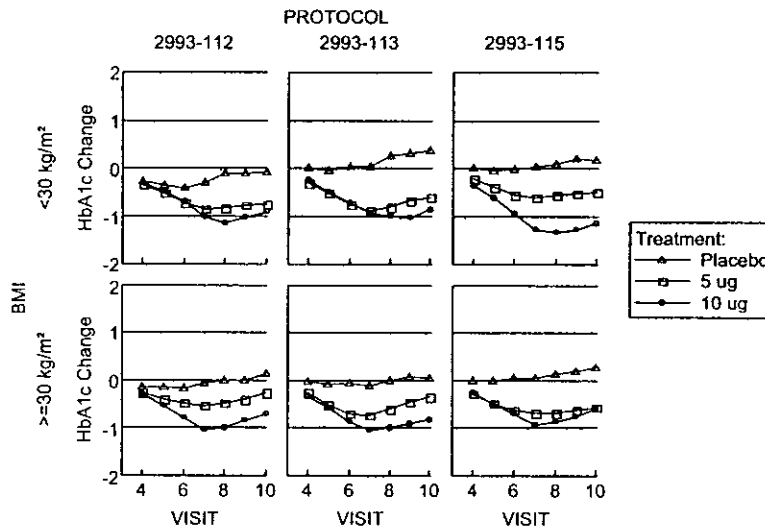
	Placebo		5 µg		10 µg	
	<125	≥125	<125	≥125	<125	≥125
Metformin alone	n=134	n=1	n=112	n=15	n=113	n=16

Mean (SD)	+0.1 (1.0)	+0.2	-0.4 (1.1)	-0.1 (0.7)	-0.7 (1.0)	-0.5 (1.1)
Median	+0.2	+0.2	-0.5	-0.3	-0.6	-0.3
SFU alone	n=156	n=5	n=131	n=15	n=131	n=27
Mean (SD)	+0.2 (1.0)	-0.8 (1.2)	-0.5 (1.2)	-0.5 (1.3)	-0.8 (1.2)	-0.5 (1.2)
Median	+0.2	-1.1	-0.5	-0.6	-0.7	-0.5
Metformin+SFU	n=290	n=2	n=233	n=48	n=227	n=47
Mean (SD)	+0.3 (1.1)	+0.5 (0.3)	-0.6 (1.1)	-0.2 (1.2)	-0.8 (1.1)	-0.3 (1.3)
Median	+0.2	+0.5	-0.5	-0.2	-0.8	-0.2

BMI

The treatment-by-BMI at screening (≥ 30 , < 30) interaction was significant in the metformin+SFU study ($p=0.03$). The interaction was significant between 10 μg and placebo and between 10 μg and 5 μg (Fig 15).

Figure 26: Mean HbA_{1c} change from baseline by screening BMI



In summary, treatment-by-subgroup analyses are exploratory without sufficient power. There were no consistent significant interaction findings in the subgroups among studies; however, the sample sizes of the studies vary. In general, the significant treatment-by-subgroup interactions were quantitative, not qualitative in nature and occurred mostly in the 5 μg group vs. placebo group. The label stated that “Based on clinical response, the dose of BYETTA can be increased to 10 mcg BID” after 1 month of 5 μg therapy. This may address the lack of efficacy for the 5 μg bid treatment observed in some subgroups.

Study 2993-120

2 Page(s) Withheld

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

§ 552(b)(5) Deliberative Process

§ 552(b)(5) Draft Labeling

6.1.5 Clinical Microbiology

Please see the microbiology review.

6.1.6 Efficacy Conclusions

HbA1c

The addition of Exenatide to a regimen of metformin, a sulfonylurea, or both, resulted in statistically significant reductions from baseline HbA1c at Week 30 compared with patients receiving placebo added to these agents in the three long term controlled trials (Table 1). In addition, a statistically significant dose effect was observed between 5 mcg and 10 mcg Exenatide groups for the change from baseline HbA1c at Week 30 in the three studies.

Fasting and Postprandial Glucose

Long term use of Exenatide in combination with metformin, a sulfonylurea, or both, reduced both fasting and postprandial plasma glucose concentrations in a statistically significant, dose dependent manner through Week 30. A statistically significant reduction from baseline in both mean fasting and postprandial glucose concentrations was observed at Week 30 in both

Exenatide groups compared with placebo in data combined from the three long term controlled trials. The change in fasting glucose concentration at Week 30 compared with baseline was 8 mg/dL for Exenatide 5 mcg BID and 10 mg/dL for Exenatide 10 mcg BID, compared with +12 mg/dL for placebo (p <0.0001). The change in 2 h postprandial glucose concentration following administration of Exenatide at Week 30 compared with baseline was 63 mg/dL for 5 mcg BID and -71 mg/dL for 10 mcg BID, compared with +11 mg/dL for placebo (p <0.0001).

Proportion of Patients Achieving HbA_{1c} <7%

Exenatide in combination with metformin, a sulfonylurea, or both, resulted in a greater, statistically significant proportion of patients achieving an HbA_{1c} <7% at Week 30 compared with patients receiving placebo in combination with these agents (Table 1).

Body Weight

In the three 7 month studies, a decrease from baseline body weight at Week 30 was associated with Exenatide 10 mcg BID compared with placebo BID in patients with type 2 diabetes (Table 1).

Table 18: Results of Seven-Month Placebo-Controlled Trials of Exenatide in Patients With Inadequate Glucose Control Despite the Use of Metformin, a Sulfonylurea, or Both

	Placebo BID	Exenatide 5 mcg BID	Exenatide 10 mcg BID
In Combination With Metformin			
Intent-to-Treat Population (N)	113	110	113
HbA_{1c} (%), Mean			
Baseline	8.2	8.3	8.2
Change at Week 30	+0.1	-0.4*	-0.8**
Proportion Achieving HbA_{1c} ≤7%^b	13.0%	31.6%*	46.4%*
In Combination With a Sulfonylurea			
Intent-to-Treat Population (N)	123	125	129
HbA_{1c} (%), Mean			
Baseline	8.7	8.5	8.6
Change at Week 30	+0.1	-0.5*	-0.9**
Proportion Achieving HbA_{1c} ≤7%^b	8.8%	32.6%*	41.3%**
In Combination With Metformin and a Sulfonylurea			
Intent-to-Treat Population (N)	247	245	241
HbA_{1c} (%), Mean			
Baseline	8.5	8.5	8.5
Change at Week 30	+0.2	-0.6**	-0.8**

Proportion Achieving HbA_{1c} ≤ 7%^b 9.2% 27.4%** 33.5%**

^a Exenatide 5 mcg twice daily (BID) for 1 month followed by 10 mcg BID for 6 months before the morning and evening meals.

^b Patients eligible for the analysis had baseline HbA_{1c} > 7%.

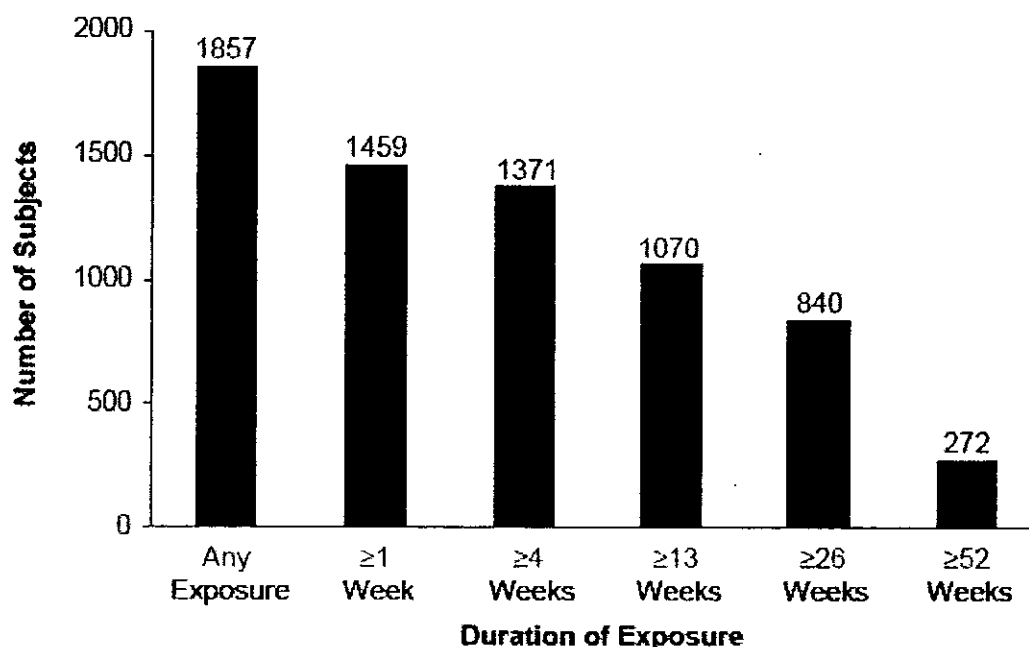
* p ≤ 0.05 based on least square (LS) mean difference (placebo reference group).

** p ≤ 0.0001 based on LS mean difference (placebo reference group).

7 INTEGRATED REVIEW OF SAFETY

The clinical development program exposed male and female subjects in the target population to a range of doses of exenatide, including the recommended dosage regimens of 5 µg BID and 10 µg BID, with a mean duration of exposure of 22 weeks. A total of 1857 subjects, 1083 males and 774 females, were exposed to exenatide in the studies included in the Integrated Safety Database. Of these 1857 subjects, 840 were treated for 6 months and 272 for 12 months. Of the 1857 subjects exposed to exenatide, 443 (23.9%) received a maximum total daily dose of 10 µg (5 µg BID) and 996 (53.6%) received a maximum total daily dose of 20 µg (10 µg BID) at some time during the development program. A total of 167 subjects (9.0%) were exposed to total daily doses in excess of 20 µg.

Figure 29: Cumulative Number of Subjects Exposed to Exenatide at Various Times (All Studies; Intent-to-Treat [N = 1857])



7.1 Methods and Findings

7.1.1 Deaths

Five deaths (3 exenatide, 2 placebo) have occurred during the entire exenatide clinical development program. The events leading to death were 2 motor vehicle accidents (1 exenatide, 1 placebo), which were due to reasons independent of exenatide therapy, 2 myocardial infarctions (1 exenatide, 1 placebo), and 1 bladder cancer (exenatide). None of the events was deemed by the investigator as related to study drug. Neither of the subjects who died secondary to motor vehicle accidents was experiencing hypoglycemia at the time of the accident.

Table 19: Deaths During the Exenatide Clinical Development Program, Including History of Reporting to the Agency

Subject No.	Event	Treatment	Relatedness	Method of Communication (Date)
2993-107-026-009	Death, Injury from Motor Vehicle Accident	Placebo	Unrelated	Fax (3/21/01)
2993-115-018-018	Death, Myocardial Infarction	Placebo	Unrelated	Fax (11/11/02)
2993-113E-077-008	Death, Acute Myocardial Infarction	10 µg exenatide	Probably Not Related	Annual Report
2993-117-241-003	Death, Motor Vehicle Accident	10 µg exenatide	Unrelated	Annual Report
2993-117-241-009	Death, Cancer	10 µg exenatide	Unrelated	Annual Report

Brief narratives describing the deaths:

Subject 2993-107-026-009 (Placebo): Injury From Motor Vehicle Accident; Death. This 65-year-old Black male died during the placebo lead-in period prior to randomization. On [REDACTED] 2001, approximately 19 days after starting placebo lead-in medication, the subject was hospitalized for injuries sustained in a motor vehicle accident in which the subject's vehicle was hit while stopped at a traffic light. The subject sustained multiple injuries including an aortic tear, fractures to both ankles, hip, and vertebrae. The subject died on [REDACTED] 2001 as a result of these injuries. The investigator and the sponsor assessed the event as unrelated to exenatide given the circumstances of the accident and the fact the subject was on placebo.

Subject 2993-115-018-018 (Placebo): Myocardial Infarction; Death. This 43-year-old Caucasian male died on [REDACTED] 2002 approximately 18 days following randomization to study medication (placebo). During the placebo lead-in period, the subject experienced chest pain without radiation followed by dyspnea upon exertion, two-pillow orthopnea, and paroxysmal nocturnal dyspnea. Five days following randomization, the subject had an electrocardiogram finding that was consistent with an acute anteroseptal myocardial infarction. Cardiac catheterization revealed severe three-vessel coronary artery disease. Percutaneous transluminal coronary angioplasty was performed with stent placement and the subject was discharged and scheduled for coronary artery bypass surgery. Six days following

stent placement the subject collapsed at home and was brought to the emergency room in cardiac arrest where resuscitative attempts were unsuccessful. Study medication (placebo) had been discontinued on the day following the subject's discharge from the hospital for angioplasty; the subject's total exposure to study medication was 14 days. The investigator assessed the event as unrelated to study medication (placebo); upon review of all relevant information related to the event, the sponsor assessed the event as not related to exenatide given that the subject was receiving placebo; the event was most likely attributable to a pre-existing condition secondary to multiple cardiovascular risk factors present at study entry.

Subject 2993-113E-077-008 (Exenatide 10 µg BID): Acute Myocardial Infarction; Death. This 76-year-old Caucasian female died approximately 168 days after receiving the first dose of open-label study medication. On [REDACTED] 2003 (165 days after the first dose of study medication), the subject experienced acute chest pain and was transported to the emergency room where the subject went into cardiac arrest. The subject was revived and transferred to the intensive care unit. Over the next several days the subject received cardiac catheterization and angioplasty for a total occlusion of the circumflex artery and was treated with bolus doses of dopamine and epinephrine. The subject developed acute renal failure and deteriorating respiratory status that culminated in the subject's death due to multisystem organ failure, sepsis, and shock on [REDACTED] 2003. The investigator assessed the acute myocardial infarction as probably not related to study medication use; upon review of all relevant information related to the event the sponsor assessed the event as probably not related to exenatide and most likely attributable to pre-existing vascular disease. The subject had received placebo in the original study (2993-113).

Subject 2993-117-241-003 (Exenatide 10 µg BID): Motor Vehicle Accident; Death. This 66-year-old Caucasian male died prior to the data cut-off date [REDACTED] 2003) 404 days after study initiation, after he was struck by an automobile while crossing a street. The subject suffered severe cerebral injuries and multiple fractures of the extremities and was admitted to the hospital in an unconscious state. CT scan of the head revealed a brain stem contusion with "wedging-in" and X-ray examinations revealed extensive right-sided skull fracture, fractures of the right upper arm and left forearm, segmental fractures of the left leg, and fracture of the right seventh rib. The subject's condition worsened during CT examination and the subject was rushed to surgery where he died 5 hours following the accident. The subject had completed 52 weeks of study treatment. This event was unrelated to exenatide given the nature of the accident and no evidence of hypoglycemia.

Subject 2993-117-241-009 (Exenatide 10 µg BID): Bladder Cancer; Death. This 61-year-old Caucasian male was withdrawn from the study 61 days after study initiation due to hospitalization for treatment of bladder cancer. The subject was admitted to the hospital with a 4-month history of dysuria and hematuria, which the subject had failed to disclose during screening. The subject was withdrawn from the study at the time of hospitalization for palliative transurethral resection of the bladder tumor. The subject's condition gradually deteriorated and he was readmitted 48 days following discharge for the initial hospitalization and died the following day on [REDACTED] 2002 due to pneumonia, acute pyelonephritis, urinary bladder tumor, cerebral edema, and cardiac decompensation. The subject had received 60 days of study treatment prior to withdrawal from the study. The bladder cancer is unrelated to exenatide therapy as evidenced by the presence of hematuria for 4 months prior to entry into the study.

7.1.2 Other Serious Adverse Events

A serious adverse event was defined as any adverse event that occurred at any dose that resulted in any of the following outcomes:

- Death
- Life-threatening
- Inpatient hospitalization or prolongation of inpatient hospitalization
- Persistent or significant disability or incapacity

- . . Congenital anomaly or birth defect
- . . Important medical events that may not have resulted in death, been life-threatening, or required hospitalization but may have jeopardized the subject and required medical or surgical intervention to prevent one of the listed outcomes, based upon appropriate medical judgment (e.g., allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that did not result in inpatient hospitalization, or the development of drug dependency or drug abuse)

Serious TEAEs were infrequent throughout the development program and their incidence in exenatide treated subjects was generally comparable to their incidence in the placebo treated subjects. A total of 29 (6%) placebo-treated subjects, in the long-term, controlled studies, experienced serious adverse events. The only system organ class with 2% or more placebo-treated subjects experiencing serious adverse events was cardiac disorders (2%) and the most commonly reported serious adverse event in the system organ class was myocardial infarction (1%). Serious adverse events occurred in 4 (1%) exenatide-treated subjects in the Clinical Pharmacology Studies, 5 (2%) exenatide-treated subjects in the short-term, controlled studies, 42 (4%) exenatide-treated subjects in the long-term, controlled studies and 24 (4%) exenatide-treated subjects in the uncontrolled studies. Across all study groups, among exenatide-treated subjects who had a serious adverse event, the only system organ class with 2% or more exenatide-treated subjects experiencing serious adverse events was cardiac disorders (2%) in the uncontrolled study group. The most frequently occurring serious adverse event in cardiac disorders in the uncontrolled studies was coronary artery disease (1%).

Although cardiovascular serious treatment-emergent adverse events were the most frequently occurring serious adverse events in the long-term, controlled studies, the number of subjects reporting serious cardiac disorders was similar in subjects receiving exenatide (8 subjects; 1%) and in subjects receiving placebo (9 subjects; 2%). Cardiovascular events are common and not unexpected for a population with type 2 diabetes.

The highest incidence of other serious treatment-emergent adverse events was encountered in the long term controlled trials as shown in the following table. Gastrointestinal adverse events occurred in 1% and 1%, serious infections occurred in 1% and 1%, and neoplasms occurred in 1% and 0%, of exenatide and placebo treated subjects, respectively. The number and percentage of subjects reporting serious adverse events in these studies is too small to draw any conclusions regarding the relationship of dose or duration of treatment to onset of the serious adverse event.

Table 20: Number (%) of Subjects With Any Serious TEAE

System Organ Class	Clinical		Controlled				Uncontrolled	Other	
	Pharmacology		Short-term		Long-term			Exenatide (N=660)	Exenatide (N=109)
	Exenatide (N=328)	Placebo (N=200)	Exenatide (N=204)	Placebo (N=61)	Exenatide (N=963)	Placebo (N=483)			
Number (%) of Subjects With Any Serious TEAE	4 (1)	0 (0)	5 (2)	0 (0)	42 (4)	29 (6)	24 (4)	0 (0)	0 (0)
Cardiac Disorders	0 (0)	0 (0)	0 (0)	0 (0)	8 (1)	9 (2)	10 (2)	0 (0)	0 (0)
Ear and Labyrinth Disorders	0 (0)	0 (0)	0 (0)	0 (0)	1 (<1)	0 (0)	0 (0)	0 (0)	0 (0)
Eye Disorders	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (<1)	0 (0)	0 (0)	0 (0)
Gastrointestinal Disorders	0 (0)	0 (0)	1 (<1)	0 (0)	8 (1)	3 (1)	1 (<1)	0 (0)	0 (0)
General Disorders and Administration Site Conditions	0 (0)	0 (0)	3 (1)	0 (0)	1 (<1)	2 (<1)	0 (0)	0 (0)	0 (0)
Hepatobiliary Disorders	0 (0)	0 (0)	0 (0)	0 (0)	3 (<1)	1 (<1)	2 (<1)	0 (0)	0 (0)
Infections and Infestations	0 (0)	0 (0)	0 (0)	0 (0)	7 (1)	6 (1)	3 (<1)	0 (0)	0 (0)
Injury, Poisoning and Procedural Complications	3 (1)	0 (0)	1 (<1)	0 (0)	3 (<1)	0 (0)	1 (<1)	0 (0)	0 (0)
Metabolism and Nutrition Disorders	1 (<1)	0 (0)	0 (0)	0 (0)	1 (<1)	1 (<1)	0 (0)	0 (0)	0 (0)
Musculoskeletal and Connective Tissue Disorders	0 (0)	0 (0)	0 (0)	0 (0)	2 (<1)	1 (<1)	3 (<1)	0 (0)	0 (0)
Neoplasms Benign, Malignant and Unspecified (Incl Cysts and Polyps)	0 (0)	0 (0)	0 (0)	0 (0)	5 (1)	0 (0)	2 (<1)	0 (0)	0 (0)
Nervous System Disorders	0 (0)	0 (0)	1 (<1)	0 (0)	4 (<1)	1 (<1)	1 (<1)	0 (0)	0 (0)
Renal and Urinary Disorders	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	2 (<1)	1 (<1)	0 (0)	0 (0)
Reproductive System and Breast Disorders	0 (0)	0 (0)	0 (0)	0 (0)	2 (<1)	1 (<1)	0 (0)	0 (0)	0 (0)
Surgical and Medical Procedures	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (<1)	0 (0)	0 (0)	0 (0)
Vascular Disorders	0 (0)	0 (0)	0 (0)	0 (0)	1 (<1)	1 (<1)	0 (0)	0 (0)	0 (0)

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7.1.3 Dropouts and Other Significant Adverse Events

7.1.3.1 Overall profile of dropouts

While the number and percentage of subjects who withdrew due to treatment-emergent adverse events in these studies is small, it is of interest that approximately 30% of all subjects who withdrew due to an adverse event did so within the first week of treatment with exenatide. Also of note is that half of the subjects who withdrew were receiving exenatide 5 µg BID and half were receiving exenatide 10 µg BID at the time of withdrawal. Treatment-emergent adverse events leading to withdrawal were captured by adverse event CRF page with action taken equal to "Withdrawal from study". In some instances, there were multiple adverse events leading to withdrawal.

7.1.3.2 Adverse events associated with dropouts

In general, the percentage of subjects who withdrew due to adverse events was low across the clinical development program. Of the subjects treated with exenatide in the clinical development program, the following discontinued due to treatment-emergent adverse events: 9 (3%) subjects in the Clinical Pharmacology Studies, 14 (7%) subjects in the short-term, controlled studies, 67 (7%) in the long-term, controlled studies, 39 (6%) in the uncontrolled studies and 7 (6%) in Study 2993-108. Across all study groups, among exenatide-treated subjects who discontinued due to an adverse event, the system organ class with the highest percentage of subjects reporting treatment-emergent adverse events was the gastrointestinal system; this reflects mostly withdrawals due to nausea. In the long-term, controlled studies the most frequently reported treatment-emergent adverse event leading to withdrawal for exenatide-treated subjects was nausea, which was reported by 26 subjects (3%), the corresponding placebo rate was <1%. Another notable difference is in the incidence of relevant neoplasms (7 subjects (1%) exenatide, 0 placebo). Neoplasms, both malignant and benign, reported in the clinical program were reviewed. In the short-term, controlled studies the incidence rates were <1% in the exenatide group and 0% in the placebo group. In the long-term, controlled studies the incidence rates were 2% in the exenatide group and 1% in the placebo group. In the long-term, uncontrolled studies of exenatide, the incidence was 1%. Considering each report of neoplasm, both malignant and benign, as well as the nonclinical data, there is no evidence that exenatide increases the risk for neoplasm.

Of the subjects treated with placebo in the clinical development program, the following discontinued due to treatment-emergent adverse events: 2 (1%) subjects in the Clinical Pharmacology Studies, 0 (0%) subjects in the short-term, controlled studies, 15 (3%) in the long-term, controlled studies. Six (10%) subjects in Study 2993-108 (Other category) were receiving placebo at the time of withdrawal due to an adverse event. Across all study groups, among

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placebo-treated subjects who withdrew due to an adverse event, the system organ class with the highest percentage of subjects reporting treatment-emergent adverse events was cardiac disorders. In the long-term, controlled studies no treatment-emergent adverse event leading to withdrawal was reported in $\geq 1\%$ of placebo-treated subjects.

Table 21: Number (%) of Subjects With Treatment-Emergent Adverse Events Leading to Withdrawal System Organ Class Summary [1]; All Studies (Population: ITT)

System Organ Class	Efficacy and Safety							
	Clinical Pharmacology		Controlled				Uncontrolled	
	Exenatide (N=328)	Placebo (N=200)	Exenatide (N=204)	Placebo (N=61)	Exenatide (N=963)	Placebo (N=483)	Exenatide (N=660)	Exenatide (N=660)
Number (%) of Subjects With TEAE Leading to Withdrawal	9 (3)	2 (1)	14 (7)	0 (0)	67 (7)	15 (3)	39 (6)	7
Cardiac Disorders	0 (0)	0 (0)	0 (0)	0 (0)	4 (<1)	6 (1)	5 (1)	0
Ear and Labyrinth Disorders	0 (0)	0 (0)	0 (0)	0 (0)	1 (<1)	0 (0)	0 (0)	0
Gastrointestinal Disorders	3 (1)	0 (0)	12 (6)	0 (0)	38 (4)	2 (<1)	27 (4)	7
General Disorders and Administration Site Conditions	0 (0)	0 (0)	1 (<1)	0 (0)	3 (<1)	1 (<1)	1 (<1)	0
Infections and Infestations	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (<1)	0 (0)	0
Injury, Poisoning and Procedural Complications	3 (1)	0 (0)	0 (0)	0 (0)	1 (<1)	0 (0)	1 (<1)	0
Investigations	0 (0)	2 (1)	0 (0)	0 (0)	2 (<1)	1 (<1)	1 (<1)	0
Metabolism and Nutrition Disorders	1 (<1)	0 (0)	1 (<1)	0 (0)	3 (<1)	1 (<1)	2 (<1)	0
Musculoskeletal and Connective Tissue Disorders	0 (0)	0 (0)	0 (0)	0 (0)	1 (<1)	1 (<1)	0 (0)	0
Neoplasms Benign, Malignant and Unspecified (Incl Cysts and Polyps)	0 (0)	0 (0)	0 (0)	0 (0)	7 (1)	0 (0)	1 (<1)	0
Nervous System Disorders	2 (1)	0 (0)	0 (0)	0 (0)	2 (<1)	0 (0)	1 (<1)	0
Psychiatric Disorders	0 (0)	0 (0)	0 (0)	0 (0)	1 (<1)	2 (<1)	0 (0)	0
Renal and Urinary Disorders	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (<1)	0 (0)	0
Respiratory, Thoracic and Mediastinal Disorders	0 (0)	0 (0)	0 (0)	0 (0)	1 (<1)	0 (0)	0 (0)	0
Skin and Subcutaneous Tissue Disorders	0 (0)	0 (0)	1 (<1)	0 (0)	3 (<1)	0 (0)	0 (0)	0
Vascular Disorders	0 (0)	0 (0)	0 (0)	0 (0)	1 (<1)	0 (0)	0 (0)	0

7.1.3.3 Other significant adverse events

Hypoglycemic Adverse Events

The use of any anti-hyperglycemic agent is associated with a potential increased risk of hypoglycemia as the prevailing glucose concentration approaches the normal range. While the glucose-dependent nature of the insulinotropic action of exenatide may minimize the risk of hypoglycemia, a comprehensive evaluation of the risk of hypoglycemia with exenatide therapy is required to adequately assess the safety profile of exenatide.

Treatment-emergent hypoglycemic adverse events were recorded in the three long-term, controlled studies according to categories prospectively defined in the study protocols. Subjects were instructed to obtain a blood glucose value prior to treatment when they experienced

symptoms commonly associated with hypoglycemia. If the subject's blood glucose value was ≥ 60 mg/dL (3.3 mmol/L), the specific symptoms (e.g., dizziness, feeling jittery, nausea) were recorded, but the adverse event was not recorded as hypoglycemia. Conversely, if the subject's blood glucose value was < 60 mg/dL (3.3 mmol/L) or if no blood glucose value was obtained, the event was recorded as hypoglycemia and the symptoms were collapsed into one event. If hypoglycemia was recorded as an adverse event, the severity was reported as follows:

- **MILD/MODERATE HYPOGLYCEMIA:** Subject reports symptoms consistent with hypoglycemia that may or may not have been documented by glucose monitoring data and does not require the assistance of another person. The general intensity definition was used to distinguish between mild and moderate intensity events, as follows:

MILD: Usually transient, requires no special treatment, and does not interfere with the subject's daily activities

MODERATE: Usually causes a low level of inconvenience or concern to the subject and may interfere with daily activities, but is usually ameliorated by simple therapeutic measures

- **SEVERE HYPOGLYCEMIA:** Subject required the assistance of another person to obtain treatment for the event; subject may have been treated for the event with intravenous glucose or intramuscular glucagon; subject was in a life-threatening situation as a result of the episode (e.g., seizure or loss of consciousness while driving a car). For studies conducted by Eli Lilly, the requirement for assistance had to be accompanied by a blood glucose measurement of < 50 mg/dL or prompt recovery after administration of oral carbohydrate, glucagon, or intravenous glucose to be categorized as severe.

- **SERIOUS HYPOGLYCEMIA:** A severe hypoglycemia event was rated as a serious adverse event if it was life-threatening or required the subject to be admitted to a hospital.

The incidence of treatment-emergent hypoglycemic adverse events in the long-term, controlled studies is summarized in Table.

Table 22: Incidence of Treatment-Emergent Hypoglycemic Adverse Events in Efficacy and Safety Studies; Long-Term, Controlled Studies Only (Population: ITT)

Intensity of Hypoglycemic Events	5 μ g BID (N=480)	10 μ g BID (N=483)	All Exenatide (N=963)	Placebo (N=483)
Total Number (%) of Subjects Experiencing Hypoglycemic Events	70 (15)	119 (25)	189 (20)	41 (8)
Mild	50 (10)	94 (19)	144 (15)	27 (6)
Moderate	25 (5)	40 (8)	65 (7)	19 (4)
Severe	1 (< 1)	0 (0)	1 (< 1)	0 (0)

Overall, 189 (20%) of subjects treated with exenatide in the long-term, controlled efficacy and safety studies experienced treatment-emergent hypoglycemic adverse events compared with 41 (8%) of placebo-treated subjects. Among subjects treated with exenatide, the incidence of treatment-emergent hypoglycemic adverse events appeared to be dose-related, with 15% and

25% of subjects reporting treatment-emergent hypoglycemic adverse events in the exenatide 5- μ g and 10- μ g groups, respectively. Of the 189 exenatide-treated subjects who experienced a treatment-emergent hypoglycemic adverse event in the long-term, controlled trials, 144 (76%) experienced at least one hypoglycemic adverse event judged to be mild and 65 (34%) experienced at least one hypoglycemic adverse event judged to be moderate in severity. Only 3 severe treatment-emergent hypoglycemic adverse events were experienced in the entire clinical development program. One of these events was in the context of a 10-fold (100 μ g) overdose in Study 2993-118. One event was reported by a subject using both metformin and a sulfonylurea in long-term, controlled study 2993-115 (5 μ g exenatide), and the third event was reported by a subject using a sulfonylurea in long-term, uncontrolled study 2993-113E while receiving exenatide 5 μ g BID.

Exenatide treatment resulted in a higher incidence and event rate of hypoglycemic adverse events compared with placebo; the event rates for the exenatide 5- μ g and 10- μ g groups appeared to be dose-related. The event rate \pm SE per subject-year of observation was 0.60 ± 0.049 and 1.31 ± 0.073 for subjects in the exenatide 5- μ g and 10- μ g groups, respectively, compared with 0.35 ± 0.039 for subjects in the placebo group. The event rate \pm SE per subject-month of observation was 0.05 ± 0.004 and 0.11 ± 0.006 for subjects in the exenatide 5- μ g and 10- μ g groups, respectively, compared with 0.03 ± 0.003 for subjects in the placebo group.

The incidence of treatment-emergent hypoglycemic adverse events over time in the long-term controlled efficacy and safety studies is calculated based on the number of subjects remaining in the trial during each of the defined intervals. The highest incidence in the exenatide treatment groups occurred within the initial 4 weeks of treatment, during which subjects all received 5 μ g exenatide in addition to their previous oral antidiabetic medication. During this period, 6.3% and 9.3% of subjects randomized to the exenatide 5- μ g and 10- μ g groups, respectively, experienced hypoglycemic adverse events, compared with 2.1% of subjects in the placebo group. The apparent difference in the incidence of hypoglycemia between subjects randomized to the exenatide 5- μ g and 10- μ g groups during the initial 4 weeks of treatment was investigated and found to be primarily due to a difference in the rate of events between the groups in Study 2993-113 (8.0% and 15.5% incidence in subjects randomized to the exenatide 5- μ g and 10- μ g groups, respectively). There were no differences in baseline or demographic characteristics between the subjects in these groups; i.e., no bias, and no differences in study conduct that account for this difference. The incidence of hypoglycemic adverse events in the exenatide groups tended to decrease over time throughout the remainder of the studies, although the incidence remained higher in the exenatide 10- μ g group compared with the exenatide 5- μ g group. After 28 weeks, the incidence of treatment-emergent hypoglycemic adverse events in the exenatide groups was approximately the same as that in the placebo group.

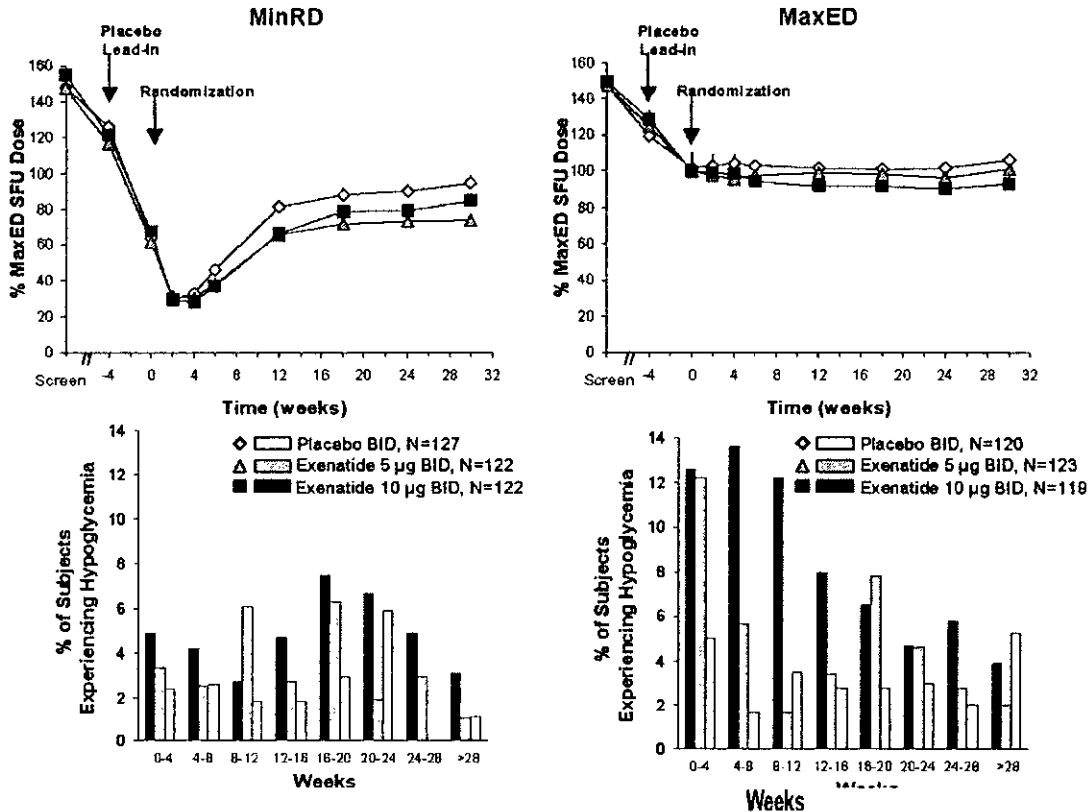
A strong association was noted between the type of OAD therapy used and the occurrence and time course of hypoglycemia. In all three long-term, controlled efficacy and safety studies, subjects continued to receive their previous OAD therapy in addition to their assigned dose of study medication. In Study 2993-112, this OAD therapy was metformin, while in Study 2993-113, the OAD therapy was an SFU. In Study 2993-115, the subjects received both metformin and an SFU. In all 3 of these studies, subjects were required to have been on a maximally effective dose of the OAD agent (or both OAD agents, in Study 2993-115) for 3 months prior to study entry. In Studies 2993-113 and 2993-115 (MaxED arm), subjects were required to reduce their SFU dose to the protocol-defined maximally effective dose (MaxED) at Week -4 if they exceeded MaxED at study entry. Standardization at study entry was done so that efficacy of SFU agents would be maintained; positioning all subjects at the maximum effective dose rather than the maximum recommended dose was required so that any reduction in SFU dose due to hypoglycemic events would actually result in a meaningful reduction in the risk of additional events.

In all 3 of these studies, it was recommended that subjects reduce their OAD therapy in response to hypoglycemia (single event with documented blood glucose <60 mg/dL or two symptomatic events without documented blood glucose values). In Study 2993-112, subjects were instructed to decrease their daily metformin dose by 50% in response to hypoglycemia, while in Studies 2993-113 and 2993-115, subjects were instructed to decrease their daily SFU dose by 50%. This reduction could be repeated multiple times (including allowing the subjects to discontinue their OAD therapy completely) in response to repeated hypoglycemic events.

Study 2993-115 included a design feature to evaluate the impact of two different SFU-management strategies upon the occurrence of hypoglycemia. Subjects were randomly assigned to either remain on the maximum effective dose of their SFU (MaxED SFU-management group), or reduce the SFU dose upon randomization (Day 1) from MaxED to the minimum recommended dose (MinRD SFU-management group), allowing subsequent upward adjustments in the SFU dose based on fasting plasma glucose measurements. A gradual increase in mean SFU dose was observed in the MinRD SFU-management group; at Week 30 subjects treated with exenatide were receiving approximately 74% (exenatide 5 µg) to 84% (exenatide 10 µg) of the MaxED (up from approximately 30% of MaxED at Week 2 for both treatments). For subjects in the MaxED SFU-management group there was a slight trend for decreasing the SFU dose for subjects receiving exenatide 10 µg, reflecting SFU dose reductions in response to hypoglycemia in a subset of subjects. At study termination, subjects in the MaxED SFU-management group receiving exenatide 10 µg BID in Study 2993-115 were receiving a mean of 93% of the MaxED (Figure 6).

Figure 30: SFU Doses Over Time and Incidence of Treatment-Emergent Hypoglycemia Over Time in the MinRD and MaxED SFU-Management Groups (Population: ITT, Includes 2993-115 Only [N=

733]



Source: Supporting Data Summary 5.39.1 from ISS and Supporting Data Summary 1.5.7 from 2993-115 CSR
 Treatment: 5 µg BID=exenatide 5 µg (4 weeks) followed by exenatide 5 µg (26 weeks); 10 µg=exenatide 5 µg (4 weeks) followed by 10 µg (26 weeks). Percentages are based on number of subjects who remained in the trial during the defined period. Each hypoglycemic event is attributed to a defined period according to the event onset date and resolution date.

There was a notable difference in the incidence of hypoglycemic adverse events between the long-term, controlled studies. No difference from placebo in the incidence of hypoglycemic events was noticeable when subjects were on metformin only; the event rate in both the exenatide and placebo groups was 0.01 events per subject-month of observation. The fact that in these subjects, the incidence of hypoglycemia does not increase despite improved glycemc control on exenatide supports the mode of action of exenatide on the stimulation of insulin secretion only at hyperglycemic levels. In contrast, subjects treated with exenatide plus an SFU in Study 2993-113 and exenatide plus an SFU and metformin in Study 2993-115 had higher incidence rates of hypoglycemic adverse events than subjects in the corresponding placebo groups. Because the SFU dose recommendations were identical between Study 2993-113 and the MaxED SFU-management group of Study 2993-115, data from these subject groups were combined for the purpose of exploring the relationship between SFU dose and hypoglycemia. The event rates for hypoglycemia were higher for exenatide-treated subjects in the MaxED SFU-

management group (0.12 events per subject-month) in Studies 2993-113 and 2993-115 compared with the event rate for exenatide-treated subjects in the MinRD SFU-management group (0.06 events per subject-month) in Study 2993-115. These event rates for exenatide-treated subjects in both SFU-management groups were higher than those for placebo-treated subjects in these same subgroups (0.04 and 0.03 events per subject-month for MaxED and MinRD SFU-management groups, respectively).

Thus, it appears that hypoglycemia associated with exenatide treatment is heavily influenced by the concomitant OAD. The increased hypoglycemia observed when exenatide is used in combination with SFUs is consistent with the demonstrated effect of SFUs to stimulate endogenous insulin secretion over a wide range of glucose concentrations. The increased risk can be reduced if the dose of SFU is reduced as exenatide treatment is initiated, but as demonstrated by the results of the MinRD SFU-management group, the reduction in hypoglycemia may come at the expense of some loss of efficacy.

Comparisons of the incidence of treatment-emergent hypoglycemic adverse events and the corresponding mean SFU doses over time in the MinRD and MaxED SFU-management subgroups in Study 2993-115 are summarized in Figure 6. As shown, subjects who entered Study 2993-115 and were randomized to the MinRD SFU-management group decreased their mean dose of SFU on Day 1 by ~70% as required by the protocol. These mean SFU doses then gradually increased over the course of the study based on fasting plasma glucose concentrations until, by the end of the study, the mean SFU doses in subjects treated with exenatide were between 74-84% of the MaxED doses. The incidence of hypoglycemia was initially low for this subgroup, but as the SFU doses were increased in response to elevated fasting plasma glucose concentrations there was a corresponding increase in the incidence of hypoglycemia, which dropped again as subjects acclimated to the higher SFU dose.

In contrast, subjects randomized to the MaxED SFU-management group maintained their SFU doses after an initial mean reduction to protocol-defined MaxED at Week -4. Throughout the study medication-dosing period, mean SFU doses remained at approximately 100% of the published MaxED for subjects receiving placebo, and decreased only slightly in the exenatide groups towards the end of the study as a subset of subjects reduced their dose due to hypoglycemic events. The corresponding incidence of hypoglycemia in the MaxED SFU-management group shows the highest rates over the first 4 weeks (exenatide 5 µg BID) or 12 weeks (exenatide 10 µg BID) after initiation of exenatide treatment compared with placebo. Then, as subjects acclimated to the exenatide and SFU combination and/or titrated their SFU dose down to achieve proper glycemic control, the incidence of hypoglycemia decreased and approached that observed for subjects treated with SFU and metformin assigned to placebo. Thus, it appears that the incidence of hypoglycemia was associated with SFU dose in Study 2993-115, suggesting that reductions in SFU dose in response to hypoglycemia reduces the risk of hypoglycemia. Lower mean SFU doses in the MinRD SFU-management group during the initial weeks of exenatide treatment were associated with lower incidence rates of hypoglycemia

compared to the MaxED SFU-management group, especially among subjects in the exenatide 10 µg BID group. However, from Week 16 through the end of the study, the incidence of hypoglycemia was similar between exenatide 10 µg BID subjects randomized to the MaxED and MinRD SFU-management groups. For subjects treated with 5 µg BID exenatide, the difference in hypoglycemia events between the MaxED and MinRD SFU-management groups were apparent during the first 4 weeks of treatment, but beyond that there was no consistent pattern. Overall, for both doses of exenatide, the incidence of hypoglycemia varied over time in the study, and appeared to be related to SFU dose.

Given the known mechanism of action of exenatide, hypoglycemia would be expected to be most apparent in subjects using sulfonylureas. The observed pattern of mild and moderate hypoglycemia is consistent with the effects of exenatide to increase insulin secretion in a glucose-dependent manner. Since metformin has not been shown to exert a significant effect on insulin secretion, no increase in hypoglycemia is observed when exenatide is added to metformin therapy. In contrast, when exenatide is added to sulfonylureas, which are agents that increase insulin secretion independent of the prevailing glucose concentration, one sees an increase in mild and moderate hypoglycemia not only in exenatide subjects, but in placebo subjects as well. These episodes of hypoglycemia are consistent with the known effects of the sulfonylureas to stimulate insulin secretion even when plasma glucose concentrations are approaching the hypoglycemic range. This interpretation is also supported by the observations in Study 2993-115 indicating that the occurrence of hypoglycemia is reduced when the sulfonylurea dose is reduced to the minimum recommended dose at the time exenatide is initiated. Importantly, as only one severe hypoglycemic event occurred in the long-term, controlled studies, it is clear that the combination of exenatide and SFU is rarely associated with hypoglycemic events which are greater than mild to moderate in severity.

Another group that might be expected to have a higher incidence of hypoglycemia is the renal impairment subjects. A summary of the incidence of hypoglycemic adverse events in subjects with mild renal impairment (creatinine clearance rate of 51 -≤80 mL/min calculated using the Cockcroft-Gault formula) follows. The incidence of hypoglycemia is not presented for subjects with calculated creatinine values indicating moderate renal impairment because there were only five such subjects in the long-term, controlled studies. There were no subjects with severe renal impairment. In Study 2993-115, there appeared to be an increase in the incidence of hypoglycemic adverse events among subjects with mild renal impairment compared with subjects with normal renal function. The incidence of hypoglycemia among subjects with normal renal function at baseline in the placebo, exenatide 5-µg and exenatide 10-µg groups was 12%, 18%, and 26%, respectively, and among subjects with impaired renal function at baseline was 20%, 29%, and 43%, respectively. The fact that the increase in the incidence of hypoglycemic adverse events among subjects with mild renal impairment was observed for

subjects in the placebo group as well as subjects in the exenatide group suggests that this is not strictly a drug (exenatide)-disease interaction but may be related in part to altered SFU pharmacokinetics in subjects with impaired renal function. In Study 2993-113, the increased incidence of hypoglycemic adverse events for subjects with mild renal impairment was only observed in the exenatide 5- μ g group (12% normal vs. 33% mild impairment). None of the hypoglycemic adverse events reported in subjects with mild renal impairment at baseline in either study were considered severe. A trend for an increase in hypoglycemic adverse events among subjects with mild renal impairment was not observed in Study 2993-112, where the overall incidence of hypoglycemic adverse events (ranging from 0% to 10% of subjects) was much lower than in Studies 2993-113 or 2993-115. It should be noted that these data are based on a relatively small number of subjects in each treatment group.

Sulfonylurea agents are primarily eliminated via the kidney)is this true for all of them?). Consequently, patients with impaired renal function may be more sensitive to the glucose-lowering effects of sulfonylurea agents. Further, subjects with mild renal impairment appeared to have marginally better reductions in mean HbA_{1c} at each dose compared with subjects having normal renal function. This may, in part, explain the increased incidence of hypoglycemia reported in this population compared with subjects receiving exenatide plus placebo or exenatide plus metformin. This interpretation is supported by observations in Study H8O-EW-GWAB, a study examining the pharmacokinetics of exenatide in renally impaired subjects in which no concomitant sulfonylurea agents were used and in which no hypoglycemic events were observed.

There were only three subjects who reported severe hypoglycemia in the clinical development program. Severe hypoglycemia was defined using the criteria developed for the Diabetes Control and Complications Trial (DCCT), which captured events requiring the assistance of another individual. In studies conducted by Eli Lilly, the requirement for assistance had to be accompanied by a blood glucose measurement of <50 mg/dL or prompt recovery after administration of oral carbohydrate, glucagon, or intravenous glucose to be categorized as severe. In the clinical pharmacology trials, severe hypoglycemia was not observed during the administration of up to 0.4 μ g/kg once per day to subjects with type 2 diabetes who had discontinued their OADs. In the long-term, controlled studies, there was only one severe hypoglycemic event in a patient on both metformin and an SFU who was randomized to the 5- μ g exenatide group.

In summary, the data from the clinical development program demonstrate that, as with all agents that reduce circulating glucose concentrations, there may be an increased risk of hypoglycemia with exenatide treatment. This risk of increased hypoglycemia is limited to the use of exenatide with an SFU, as the incidence of hypoglycemia over 30 weeks was the same in exenatide (4.9%) and placebo (5.3%) treated subjects on the background of metformin alone. In subjects taking a maximally effective dose of an SFU, the incidence of hypoglycemia was higher on exenatide treatment (26.6%) compared to placebo (9.1%). This increased risk can be reduced with a

reduction of the SFU dose, however some loss of glycemic effectiveness may accompany the SFU dose-reduction. Only 3 severe hypoglycemic events in exenatide-treated subjects were reported in the entire clinical development program, indicating that the glucose-dependent nature of the actions of exenatide provides a safeguard against very low plasma glucose concentrations, which place individuals at risk for bodily harm. Based on all available information from the clinical development, there is no clear indication that SFU dose should be reduced at the time exenatide therapy is initiated. However, both health care providers and patients should be aware of the potential for hypoglycemia and take appropriate measures, including dose-reduction of SFU.

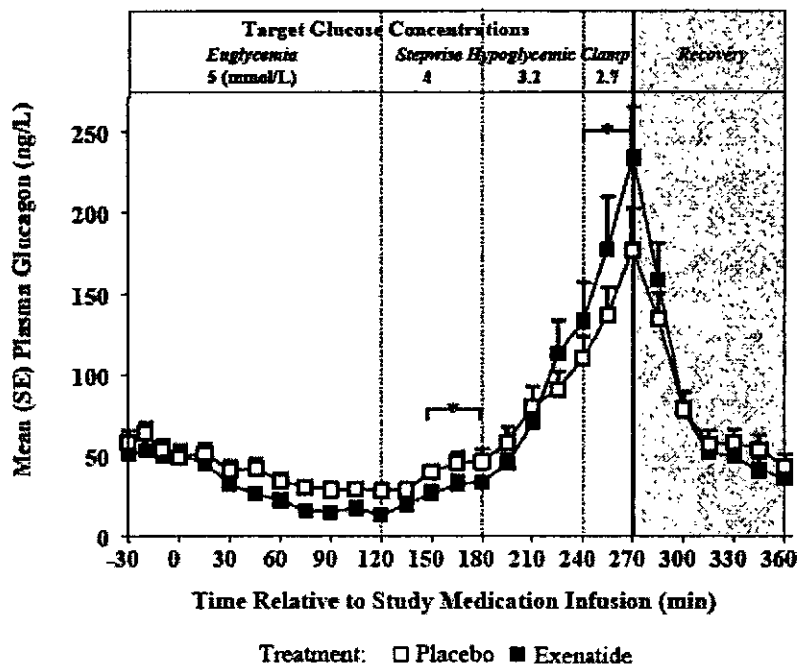
Counter-Regulatory Response to Hypoglycemia

The data from Study 2993-111 indicate that the counter-regulatory hormone response is intact during hypoglycemia when exenatide is present in the circulation at therapeutic concentrations. Glucagon, growth hormone, cortisol, and catecholamines are important counter-regulatory hormones that protect individuals from hypoglycemia. As exenatide has been shown to suppress glucagon during hyperglycemia, it was important to assess its effects on glucagon and other counter-regulatory hormones during hypoglycemia. To that end, Study 2993-111 examined the potential effect of exenatide on the counter-regulatory response to hypoglycemia in a controlled glucose-clamp setting.

Each subject underwent 360-minute intravenous infusions of exenatide and placebo on different days separated by 4 to 6 weeks. A euglycemic hyperinsulinemic clamp followed by a stepwise hypoglycemic clamp was performed from 0 to 270 minutes. Circulating concentrations of glucagon, growth hormone, epinephrine, norepinephrine, and cortisol were measured prior to the clamp and throughout the infusion period. Mean insulin secretion rates were assessed to demonstrate the glucose-dependent insulinotropic effect.

At glucose concentrations of approximately 5 mmol/L, mean plasma glucagon concentrations were lower (Figure) during exenatide treatment. When glucose concentrations were lowered to approximately 4 mmol/L, the mean plasma glucagon concentrations increased for both treatments with lower concentrations still observed with exenatide treatment. With glucose concentrations lowered to approximately 3.2 mmol/L, slightly higher concentrations of glucagon were observed with exenatide treatment. The difference was statistically significant (geometric least square mean 205.86 ng/L for exenatide versus 157.36 ng/L for placebo).

Figure 31: Plasma Glucagon Concentration Time Curve by Treatment During Glycemic Step (Study2993-111; Evaluable [N = 11]; Healthy Volunteers)

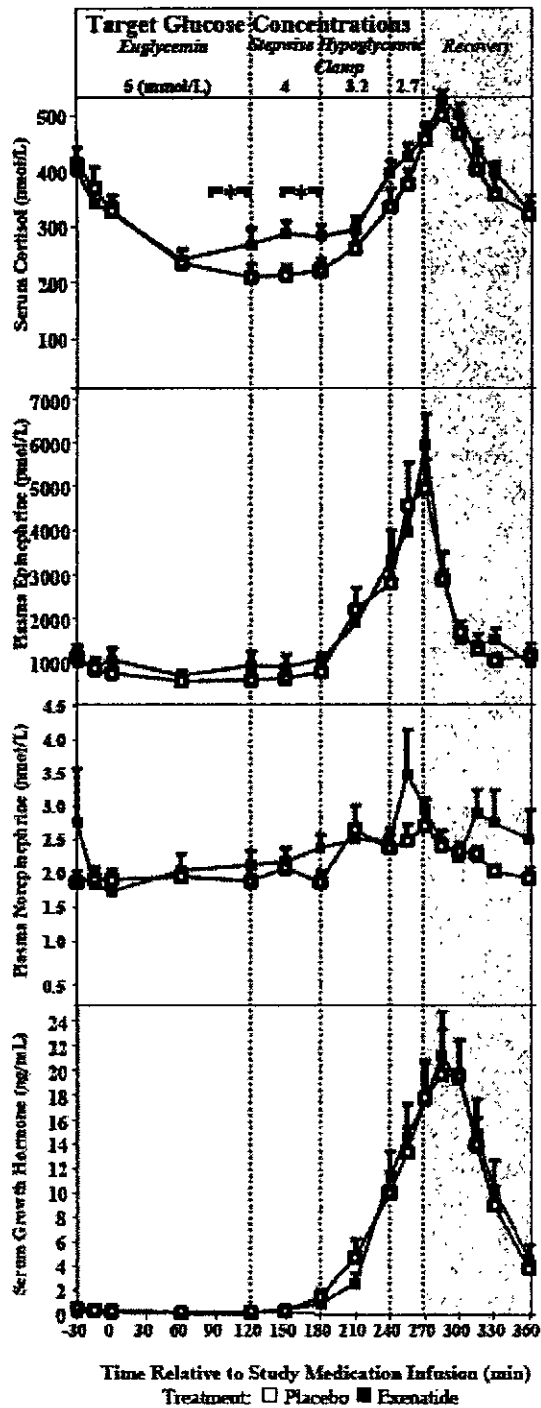


Mean serum growth hormone concentrations were similar prior to injection and throughout the clamp period for placebo and exenatide (Figure 4, bottom panel). A similar pattern of response was observed for epinephrine (Figure 4, panel 2) and norepinephrine (Figure 4, panel 3). However, mean serum cortisol concentrations, while similar prior to treatment injection, were higher for exenatide treatment when glucose concentrations were 5 mmol/L to 2.7 mmol/L (Figure 4, top panel).

In addition, the time to recover from hypoglycemia was assessed when the insulin infusion was stopped. There was no difference in recovery time between exenatide and placebo treatment.

Figure 32: Mean (SE) Serum Cortisol, Plasma Epinephrine, Plasma Norepinephrine, and Serum Growth Hormone Concentration Time Curves During Glycemic Step (Study 2993-111; Evaluable [N = 11]; Healthy Volunteers)

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Effects on Ability to Drive or Operate Machinery or Impairment of

Mental Ability

No studies were performed to specifically evaluate the potential for exenatide to impair the senses or coordination or any other factor that would result in diminished ability to drive a vehicle, operate machinery, or impair mental ability.

However, hypoglycemia can result in symptoms that could impair the senses or coordination or result in diminished ability to drive a vehicle, operate machinery, or impair mental ability. Because exenatide is associated with an increase in mild to moderate hypoglycemia when used with sulfonylureas, this combination has the potential to impair the senses or coordination in a manner that could result in diminished ability to drive a vehicle, operate machinery, or impair mental ability. When hypoglycemia occurs in patients using both exenatide and an SFU, a reduction in SFU dose should be considered.

Table summarizes the treatment-emergent adverse events in the Efficacy and Safety Studies in subjects with type 2 diabetes that could be indicative of impairment of the senses or coordination. Based on the low incidence of severe hypoglycemia in the clinical program (3 cases), and the ability to manage hypoglycemia risk by reducing the sulfonylurea dose, together with the low incidence of other treatment-emergent adverse events that could be indicative of impairment of the senses or coordination, the potential for exenatide treatment to result in diminished ability to drive a vehicle, operate machinery, or impair mental ability is considered minimal.

Table 23: Treatment-Emergent Adverse Events in Efficacy and Safety Studies Potentially Indicative of Impairment of the Senses or Coordination (Population: ITT)

Preferred Term	Controlled				Uncontrolled Exenatide (N=660)
	Short-term		Long-term		
	Exenatide (N=204)	Placebo (N=61)	Exenatide (N=963)	Placebo (N=483)	
Hypoglycemia	14 (7)	0 (0)	189 (20)	41 (8)	106 (16)
Feeling Jittery	3 (1)	0 (0)	90 (9)	20 (4)	45 (7)
Road Traffic Accident*	1 (<1)	0 (0)	7 (1)	2 (<1)	0 (0)
Vision Blurred	1 (<1)	0 (0)	8 (1)	4 (1)	3 (<1)
Fatigue	2 (1)	2 (3)	39 (4)	16 (3)	16 (2)
Balance Disorder	0 (0)	0 (0)	0 (0)	1 (<1)	0 (0)
Cerebrovascular Accident	0 (0)	0 (0)	1 (<1)	0 (0)	1 (<1)
Convulsion	0 (0)	0 (0)	2 (<1)	0 (0)	0 (0)
Dizziness	11 (5)	2 (3)	84 (9)	30 (6)	28 (4)
Dizziness Postural	0 (0)	0 (0)	1 (<1)	0 (0)	1 (<1)
Loss of Consciousness	0 (0)	0 (0)	1 (<1)	0 (0)	0 (0)
Somnolence	0 (0)	0 (0)	6 (1)	1 (<1)	2 (<1)
Syncope	0 (0)	0 (0)	5 (1)	0 (0)	0 (0)
Syncope Vasovagal	0 (0)	0 (0)	1 (<1)	0 (0)	1 (<1)
Transient Ischemic Attack	0 (0)	0 (0)	1 (<1)	1 (<1)	1 (<1)
Confusional State	1 (<1)	0 (0)	6 (1)	2 (<1)	3 (<1)
Disorientation	0 (0)	0 (0)	3 (<1)	0 (0)	2 (<1)
Nervousness	1 (<1)	0 (0)	5 (1)	1 (<1)	2 (<1)

7.1.4 Other Search Strategies

The following list of adverse events was compiled from the FDA Guidance for Industry – on the adverse reactions section of labeling (rare, serious events) and FDA Safety Reporting Proposed Rule (always expedited reports).

Congenital Anomalies¹
Acute Renal Failure^{1,2}
Acute Respiratory Failure¹
Sclerosing Syndromes¹
Ventricular Fibrillation¹
Pulmonary Hypertension¹
Torsades de Pointe¹
Pulmonary Fibrosis¹
Malignant Hypertension¹
Confirmed or Suspected Transmission of Infectious Agent by
Marketed Product¹
Seizure¹
Agranulocytosis^{1,2}
Confirmed or Suspected Endotoxin Shock¹
Aplastic Anemia¹
Significant Hemolytic Anemia²
Toxic Epidermal Necrolysis¹
Thrombocytopenia²
Liver Necrosis¹
Rhabdomyolysis²
Acute Liver Failure^{1,2}
Idiopathic Thrombocytopenic Purpura²
Anaphylaxis¹
Intussusception²

1

Safety Reporting Requirements for Human Drug and Biological Products; Proposed Rule, Federal Register: March 14, 2003 (Volume 68, Number 50).

2

FDA Guidance for Industry-Content and Format of the Adverse Reactions Section of Labeling for Human Prescription Drugs and Biologics Guidance for Industry Labeling, May 2000.

The integrated adverse event database was systematically reviewed to identify any events (preferred terms or verbatim terms) that could be categorized as one of the events shown above. There were no adverse events found to have the potential of being malignant hypertension, aplastic anaemia, toxic epidermal necrolysis, liver necrosis, significant hemolytic anemia, rhabdomyolysis, idiopathic thrombocytopenic purpura or intussusception. There were no events of Torsades de Pointe. The term "Confirmed or Suspected Transmission of Infectious Agent by Marketed Product" is not applicable to investigational drugs and was not, therefore, included in the search.

A total of 37 treatment-emergent adverse events were identified in 33 subjects as having the potential to be one of these adverse event terms; 24 of these treatment-emergent adverse events were reported in 22 subjects while on exenatide therapy. None of the noted events among exenatide subjects (seizure [2 subjects], acute renal failure [3 subjects], Sjogren's syndrome [1 subject], pulmonary fibrosis [1 subject]) could be attributed to a direct effect of exenatide treatment. None of the events exhibited any features of an event that would qualify as "serious, very unusual in the absence of drug therapy". Each of the adverse events that could possibly have been consistent with one of the terms listed above was reviewed and none was considered to be a *bona fide* case related to exenatide administration.

In addition the LAR and Ongoing Studies were reviewed for the occurrence of treatment-emergent adverse events that have the potential to require expedited reporting or generally considered unusual in the absence of drug therapy and no such cases were found.

7.1.5 Common Adverse Events

Nausea, Vomiting, Headache, Dizziness

Nausea was the most common adverse event across all of the study groups. The percentage of exenatide-treated subjects who experienced nausea ranged from 37% in the short-term, controlled studies to 62% in study 2993-108. The comparatively high incidence of nausea in Study 2993-108 was expected as it reflects the objective and design of the study, which was to compare the incidence of nausea in subjects receiving an initial high dose of exenatide with those who had gradual exenatide dose-escalation prior to the high dose. The percentage of exenatide-treated subjects reporting nausea was consistently higher than that in placebo-treated subjects across all of the study groups. The percentage of exenatide-treated subjects reporting vomiting

was also consistently higher than that in placebo-treated subjects. In the long-term, controlled studies, diarrhea was reported more frequently in the exenatide-treated subjects than in the placebo-treated subjects. Nausea, and to a lesser extent vomiting and diarrhea, were the dose-limiting adverse events associated with exenatide treatment.

Table 24: Common Adverse Events

	Clin Pharmacology		Short Term		Long Term		Uncont.	Other Studies	
	Exenatide	Placebo	Exenatide	Placebo	Exenatide	Placebo		Exenatide	Placebo
Preferred Term	(N=328)	(N=200)	(N=204)	(N=61)	(N=963)	(N=483)	(N=660)	(N=109)	(N=61)
Arthralgia	1 (<1)	1 (1)	3 (1)	0 (0)	32 (3)	26 (5)	20 (3)	1 (1)	0 (0)
Decreased Appetite	6 (2)	0 (0)	1 (<1)	0 (0)	13 (1)	1 (<1)	2 (<1)	7 (6)	3 (5)
Diarrhea	9 (3)	5 (3)	8 (4)	0 (0)	124 (13)	30 (6)	56 (8)	10 (9)	6 (10)
Dizziness	42 (13)	5 (3)	11 (5)	2 (3)	84 (9)	30 (6)	28 (4)	5 (5)	4 (7)
Dyspepsia	20 (6)	2 (1)	5 (2)	0 (0)	60 (6)	15 (3)	28 (4)	3 (3)	1 (2)
Feeling Jittery	0 (0)	0 (0)	3 (1)	0 (0)	90 (9)	20 (4)	45 (7)	0 (0)	0 (0)
Headache	87 (27)	17 (9)	16 (8)	1 (2)	82 (9)	30 (6)	29 (4)	10 (9)	4 (7)
Hypoglycemia	14 (4)	2 (1)	14 (7)	0 (0)	189 (20)	41 (8)	106 (16)	0 (0)	0 (0)
Injection Site Bruising	0 (0)	1 (1)	3 (1)	1 (2)	48 (5)	21 (4)	2 (<1)	4 (4)	5 (8)
Nasopharyngitis	0 (0)	0 (0)	2 (1)	2 (3)	64 (7)	39 (8)	32 (5)	1 (1)	0 (0)
Nausea	162 (49)	6 (3)	75 (37)	4 (7)	419 (44)	87 (18)	257 (39)	68 (62)	17 (28)
Sinusitis	0 (0)	0 (0)	4 (2)	0 (0)	55 (6)	28 (6)	19 (3)	2 (2)	0 (0)
Somnolence	21 (6)	3 (2)	0 (0)	0 (0)	6 (1)	1 (<1)	2 (<1)	0 (0)	0 (0)
URI	2 (1)	1 (1)	7 (3)	1 (2)	122 (13)	72 (15)	71 (11)	0 (0)	1 (2)
Vomiting	99 (30)	1 (1)	18 (9)	1 (2)	123 (13)	18 (4)	64 (10)	43 (39)	3 (5)

Two preferred terms within the gastrointestinal body system had a $\geq 2\%$ difference in the incidence rate between subjects treated with exenatide and subjects treated with placebo in the long-term controlled studies. These two terms of dyspepsia and gastroesophageal reflux disease are discussed below. In the long-term controlled studies, dyspepsia was reported in 6% of subjects receiving exenatide and 3% of subjects receiving placebo. Only one subject (receiving exenatide 10 μg BID) reported dyspepsia with an intensity of severe. In the long-term uncontrolled studies, the incidence of dyspepsia was 4%. Dyspepsia was also reported with an increased incidence in the clinical pharmacology studies (6% in exenatide-treated subjects, 1% in placebo-treated subjects), short-term controlled studies (2% in exenatide-treated subjects, 0% in placebo-treated subjects), and Study 2993-108, categorized as other (3% in exenatide-treated subjects, 2% in placebo-treated subjects). Gastroesophageal reflux disease (GERD) was reported in 3% of exenatide-treated subjects in the long-term controlled studies, compared with 1% of subjects treated with placebo. Only one subject (receiving exenatide 5 μg BID) reported gastroesophageal reflux disease of severe intensity. Three percent of exenatide-treated subjects in the long-term uncontrolled studies also reported gastroesophageal reflux disease. The only other occurrence of GERD in the exenatide development program was in the short-term controlled studies, where it was reported in 1% of exenatide-treated subjects and 0% of placebo treated

subjects.

Exenatide, similar to GLP-1, slows gastric emptying as demonstrated in the clinical pharmacology studies. This effect may accentuate dyspepsia and other GERD symptoms in some subjects. This effect did not lead to an increase in adverse events of impaired gastric emptying. In the entire exenatide clinical development program, 2 adverse events (<1%) of impaired gastric emptying were reported, both in subjects receiving exenatide 10 µg BID in the long-term controlled studies. One of these events was reported as moderate in intensity, and the second was reported as severe.

Other gastrointestinal adverse events that occurred at an incidence >1%, with higher incidence in exenatide-treated subjects than placebo-treated subjects in the long-term controlled studies, although not with ≥2% difference in incidence, are as follows: abdominal distension, abdominal pain, and flatulence.

7.1.5.1 Eliciting adverse events data in the development program

The overall safety profile of exenatide, including both nonclinical and clinical data, was reviewed from an organ system perspective, with particular emphasis on the hepatic, renal, gastrointestinal, and cardiovascular systems. The potential for the drug to act as a carcinogen was also systematically reviewed.

7.1.6 Less Common Adverse Events

Table provides a summary, by study grouping, of the number and percent of subjects with any treatment-emergent adverse event and the number and percent of subjects with a treatment-emergent adverse event in each system organ class. The majority of treatment-emergent adverse events reported across all studies were mild or moderate in intensity and most were considered related to treatment.

Table 25: Number (%) of Subjects With Treatment-Emergent Adverse Events by System Organ Class [1]; All Studies (Population: ITT)

System Organ Class	Controlled						Uncontrolled	Exer (N=)
	Clinical Pharmacology		Short-term		Long-term			
	Exenatide (N=328)	Placebo (N=200)	Exenatide (N=204)	Placebo (N=61)	Exenatide (N=963)	Placebo (N=483)		
Number (%) Of Subjects With Any TEAE	234 (71)	52 (26)	144 (71)	27 (44)	873 (91)	396 (82)	546 (83)	92
Blood and Lymphatic System Disorders	1 (<1)	1 (1)	1 (<1)	0 (0)	18 (2)	7 (1)	10 (2)	0
Cardiac Disorders	11 (3)	0 (0)	2 (1)	0 (0)	26 (3)	25 (5)	19 (3)	2
Congenital, Familial and Genetic Disorders	0 (0)	0 (0)	0 (0)	0 (0)	1 (<1)	0 (0)	0 (0)	0
Ear and Labyrinth Disorders	2 (1)	0 (0)	1 (<1)	0 (0)	24 (2)	15 (3)	8 (1)	0

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Endocrine Disorders	1 (<1)	0 (0)	2 (1)	0 (0)	5 (1)	1 (<1)	2 (<1)	0
Eye Disorders	4 (1)	1 (1)	3 (1)	2 (3)	39 (4)	22 (5)	23 (3)	2
Gastrointestinal Disorders	191 (58)	12 (6)	95 (47)	8 (13)	560 (58)	163 (34)	329 (50)	80
General Disorders and Administration Site Conditions	61 (19)	15 (8)	21 (10)	4 (7)	258 (27)	85 (18)	114 (17)	18
Hepatobiliary Disorders	0 (0)	0 (0)	0 (0)	0 (0)	5 (1)	4 (1)	3 (<1)	0
Immune System Disorders	0 (0)	0 (0)	0 (0)	1 (2)	17 (2)	4 (1)	11 (2)	2
Infections And Infestations	6 (2)	2 (1)	29 (14)	8 (13)	387 (40)	213 (44)	211 (32)	7
Injury, Poisoning and Procedural Complications	6 (2)	1 (1)	6 (3)	3 (5)	93 (10)	44 (9)	42 (6)	4
Investigations	5 (2)	2 (1)	5 (2)	1 (2)	122 (13)	54 (11)	51 (8)	13
Metabolism and Nutrition Disorders	29 (9)	3 (2)	17 (8)	1 (2)	236 (25)	66 (14)	149 (23)	9
Musculoskeletal and Connective Tissue Disorders	18 (5)	7 (4)	5 (2)	2 (3)	167 (17)	94 (19)	98 (15)	7
Neoplasms Benign, Malignant and Unspecified (Incl Cysts and Polyps)	0 (0)	0 (0)	1 (<1)	0 (0)	20 (2)	6 (1)	8 (1)	0
Nervous System Disorders	137 (42)	25 (13)	28 (14)	3 (5)	227 (24)	76 (16)	89 (13)	18
Psychiatric Disorders	7 (2)	1 (1)	9 (4)	2 (3)	73 (8)	23 (5)	33 (5)	2
Renal And Urinary Disorders	3 (1)	1 (1)	1 (<1)	1 (2)	31 (3)	18 (4)	19 (3)	2
Reproductive System and Breast Disorders	0 (0)	1 (1)	0 (0)	0 (0)	31 (3)	9 (2)	12 (2)	1
Respiratory, Thoracic and Mediastinal Disorders	5 (2)	0 (0)	7 (3)	2 (3)	134 (14)	52 (11)	42 (6)	3
Skin And Subcutaneous Tissue Disorders	11 (3)	2 (1)	18 (9)	1 (2)	111 (12)	50 (10)	40 (6)	4
Social Circumstances	0 (0)	0 (0)	0 (0)	0 (0)	2 (<1)	0 (0)	0 (0)	0
Surgical and Medical Procedures	0 (0)	0 (0)	0 (0)	0 (0)	14 (1)	5 (1)	3 (<1)	0
Vascular Disorders	12 (4)	3 (2)	1 (<1)	1 (2)	54 (6)	21 (4)	23 (3)	3

Clinical laboratory and adverse event data from the Efficacy and Safety Studies consisting of the short-term (28-day), and long-term (30 weeks of treatment), controlled studies and the long-term uncontrolled (up to 52 weeks of treatment including time spent on drug in the long-term controlled studies) studies provided the best opportunity to search for signals of exenatide-induced renal toxicity. Overall, the number of subjects with potentially clinically significant renal function changes was small, and considered to be normal in this population of subjects with type 2 diabetes. The treatment-emergent adverse event database was also searched for subjects with treatment-emergent adverse events in the Renal and Urinary Disorders system organ class for evidence of potential renal toxicity. Across all study categories (clinical pharmacology, short-term, controlled, long-term, controlled, long-term, uncontrolled, and other) the incidence of renal and urinary disorders was small (4% or less), and was not higher in exenatide-treated subjects than in subjects assigned to placebo. None of the results suggested that exenatide is toxic to the kidney.

7.1.7 Laboratory Findings

Overall, the percentage of subjects with potentially clinically important laboratory abnormalities was low and generally similar for subjects treated with exenatide and subjects treated with placebo. No clinically meaningful changes from Baseline to Last Visit were noted in hematology, chemistry, or urinalysis assessments for exenatide or placebo for any of the Efficacy and Safety Studies. These data are supported by the results of the individual clinical study reports for the Efficacy and Safety Studies.

7.1.8 Vital Signs

Overall, across all study groupings, no clinically meaningful vital sign changes from Baseline were noted for exenatide- or placebo-treated subjects. In the Efficacy and Safety Studies the incidence rates for potentially clinically important blood pressure readings were generally low and similar for exenatide- and placebo-treated subjects. Some reports of postural hypotension in the early clinical pharmacology study were typically symptomatically identified but were not corroborated with a blood pressure measurement. Adverse events associated with vital sign abnormalities were generally mild, and none resulted in study discontinuation. Despite the fact that increased blood pressure is common in subjects with type 2 diabetes, incidence rates for vital sign related adverse events were 5% or less across all treatment groups in each of the 3 study groupings. Across the long-term, controlled studies, no clinically meaningful vital sign changes from Baseline were noted for exenatide or placebo. Generally the incidence rates for potentially clinically important blood pressure readings were low and similar for exenatide and placebo subjects. Notably, a mean reduction in sitting systolic (range of means -2.4 to -3.6 mm Hg) and diastolic (range of means -1.1 to -2.6 mm Hg) blood pressures from extension baseline to Week 52 was observed for the ITT populations of 2993-112E, 2993-113E, and 2993-115E.

7.1.9 Electrocardiograms (ECGs)

Exenatide was not associated with an overall increase in cardiovascular adverse events, including treatment-emergent coronary artery disease (CAD)-related adverse events. Further, the clinical course and nature of the cardiac events in the exenatide-treated subjects were reviewed and were not thought to be clinically unusual in any way compared to those events seen in placebo-treated subjects or in the general population of patients with type 2 diabetes. A systematic investigation of abnormal vital signs and ECGs including treatment-emergent adverse events likely to be diagnosed by ECG did not reveal an exenatide effect on these parameters. There were no cases of Torsades de Pointe and no evidence to suggest that exenatide results in prolongation of the QTc interval.

Electrocardiogram data were collected at different times in each study in the exenatide clinical program, employing a number of different methods. A meta-analysis of QT intervals and plasma exenatide concentrations was also done. The data from that analysis along with the clinical observations in the studies indicate that there are no ECG issues with exenatide treatment.

The clinical pharmacology studies included a diverse group of 17 studies, most of which included ECG evaluations either at screening or at both screening and at the end of the study. No

clinically important ECG changes were observed in the clinical pharmacology studies. One of the clinical pharmacology studies, the lovastatin interaction study, H8O-EW-GWAG, had a 12-lead ECG performed around the time of the peak exenatide concentrations. These ECGs were carefully evaluated. No evident correlation between Fridericia's or Bazett's corrected QTc or change in QTc and exenatide plasma concentrations was observed.

ECGs were systematically performed in the Efficacy and Safety Studies in accordance with the schedule outlined in Table .

Table 26: Schedule of ECG Evaluations in Efficacy and Safety Studies

Protocol Number	Schedule
Short-term, controlled	
2993-107	Screening (Baseline), Day 28 (Term or Early Term)
2993-116	Week -2 (Baseline), Day 28 (Term or Early Term)
Long-term, controlled	
2993-112, -113, -115	Screening, Week -4 (Baseline), Week 30 (or Early Term)
Long-term, uncontrolled	
2993-112E, -113E, -115E	Week 30 of corresponding long-term controlled study (taken as Baseline for Cohort II [1] of the corresponding long-term uncontrolled study), Termination (or Early Term)
2993-117	Day 1 (Baseline), Termination (or Early Term)

A treatment-emergent ECG abnormality was defined as an abnormality observed after administration of the first randomized dose or the first administration of exenatide in an open-label trial. These include changes from normal to abnormal (clinically significant or not) and abnormal (non-clinically significant) to abnormal (clinically significant). In the short-term and long-term controlled studies, the incidence of treatment-emergent ECG abnormalities was approximately the same in both the exenatide and placebo groups (10-14%); and in the long-term uncontrolled studies, the incidence of treatment-emergent ECG abnormalities was also 14%. The incidence of clinically significant treatment-emergent ECG abnormalities among exenatide-treated subjects was <1% in the controlled studies and 1.4% in the uncontrolled studies. A total of 16 subjects (7 exenatide and 9 placebo) had clinically significant ECG abnormalities. Most of the abnormalities in placebo-treated subjects related to electrical conduction (6 of the 9 placebo-treated subjects); the most frequent abnormality in exenatide-treated subjects could be categorized as ST-T changes. A review of the specific ECG abnormalities for subjects with clinically significant treatment-emergent findings showed no difference between the exenatide- and placebo-treated groups and was consistent with the underlying cardiovascular status of the type 2 diabetes patient population under investigation.

In the Other Study, 2993-108, ECGs were performed at screening, Visit 6, and Termination. No clinically meaningful ECG changes were observed.

To complement the review of ECG abnormalities *per se*, a review of treatment-emergent adverse events usually diagnosed by an ECG was done to highlight any treatment-emergent adverse event that could be considered clinically consistent with an electrophysiological effect on the myocardium. These treatment-emergent adverse event data, found primarily in the cardiovascular and investigations groupings, represent more objective data than other symptomatic adverse event data. There was no increase in the frequency of treatment-emergent adverse events likely to be diagnosed by ECG for subjects receiving exenatide compared to those on placebo.

To further assess any potential effect of exenatide on QTc interval, a retrospective meta-analysis of QT intervals and plasma exenatide concentrations for the 105 subjects that constituted the meal-tolerance cohort for Studies 2993-112, 2993-113, and 2993-115 and had a Baseline and Week 30 ECG determination was performed. This cohort was selected because ECGs and plasma exenatide concentrations were prospectively and systematically collected during the 4-hour period after exenatide dosing, a time interval when systemic exenatide concentrations were expected to be in the therapeutic range. For these subjects, ECG assessments were done between 1 and 240 minutes after administration of study medication. Most ECG measurements were collected between 115 and 175 min (mean = 122.7 min) following the dose, which approximates the time of maximum plasma exenatide concentration (median exenatide T_{max} = approximately 120 min).

This meta-analysis allowed the potential relationship between QT intervals and systemic exenatide exposure to be assessed. The meta-analysis indicates that 30 weeks of twice daily dosing with exenatide does not lead to prolongation of the QT or QTcF intervals even when assessed at peak circulating concentrations of exenatide. Differences between the placebo group and the 5- μ g and 10- μ g groups were not statistically significant or clinically meaningful, as assessed by the 95% confidence intervals for the difference in change from baseline. The scatter plots of change in QT and QTcF intervals from baseline versus plasma exenatide concentrations did not show any obvious pattern, and no slope estimates from the regression calculations against exenatide concentration were statistically different from 0, implying no relationship between these variables. The absence of an exenatide effect on the QT interval was also supported by the lack of dose-related effects on QT prolongation and in the plots of plasma exenatide concentrations and QT change from baseline. Furthermore, these observations were supplemented by no gender difference in change from baseline. Consequently, based on this meta-analysis, no cardiovascular risks relative to QT intervals should be associated with exenatide administration at the recommended doses.

7.1.10 Immunogenicity

Consistent with the potentially immunogenic properties of protein and peptide pharmaceuticals, patients may develop anti-exenatide antibodies following treatment with Exenatide. Patients who developed anti-exenatide antibodies had similar rates and types of adverse events as those with no anti-exenatide antibodies. Forty-four percent of subjects in the long-term, controlled trials developed anti-exenatide antibodies, with the majority (86% of the anti-exenatide-positive subjects) exhibiting titers of 1/5 to 1/125 by Week 30 of treatment. For this lower titer group, the level of glycemic control (HbA_{1c}) was generally comparable to that observed in those without antibody titers. For the 14% of anti-exenatide-positive subjects with higher antibody titers (1/625 to 1/15,625) still present at Week 30, glycemic responses were diminished for about half of the subjects while the rest had no apparent decrease in efficacy. A comparison of adverse event profiles for subjects with any level of anti-exenatide antibody titer versus those who never exhibited an antibody response did not reveal evidence of antibody-specific safety events or acute allergic reactions. There were no events that might be related to an IgE response. Examination of antibody-positive specimens from a long-term (52-week), uncontrolled study (2993-117) revealed no significant treatment-emergent cross-reactivity with structurally similar endogenous peptides (glucagon, GLP-1).

An examination of efficacy in the 30-week studies based on both titer and dose reveals that in the 5- μ g group subjects who were antibody negative had a reduction in HbA_{1c} of -0.55% at week 30, and those with low titers had a similar reduction (-0.53%). In contrast, those subjects with higher antibody titers had an overall increase in HbA_{1c} (0.16%). Similar results were seen for the 10- μ g group; subjects who were antibody negative had a reduction in HbA_{1c} of -0.89%, and those with low titers had a similar reduction (-0.79%). However, those subjects with higher antibody titers had an overall increase in HbA_{1c} (0.11%). When both doses were pooled, subjects who were antibody negative had a reduction in HbA_{1c} of -0.72%, and those with low titers had a nearly identical reduction (-0.67%). Those subjects with higher antibody titers had an overall increase in HbA_{1c} (0.14%).

When a similar analysis of HbA_{1c} response based on antibody titer was done for subjects in the 52-week long-term uncontrolled studies, a similar pattern of reduced efficacy was observed for those subjects with titers \geq 1/625. Subjects who were

antibody negative had a reduction in HbA_{1c} of -1.17%, and those with low titers had a similar reduction (-0.97%). Those subjects with higher antibody titers had no mean change in HbA_{1c} (0.01%)

7.1.11 Human Carcinogenicity

Exenatide was not tumorigenic in mice or rats when administered SC for up to 24 months at doses resulting in exposures >90 times that of human systemic exposure at 10 mcg BID.

Exenatide was devoid of mutagenic effects, with or without metabolic activation, in both in vitro (Ames bacterial reverse mutation, chromosomal aberration in mammalian cells) and in vivo (mouse micronucleus formation) assays.

7.1.12 Special Safety Studies

In patients with end-stage renal disease receiving dialysis, single doses of Exenatide 5 mcg were not well tolerated due to gastrointestinal side effects. Exenatide is not recommended for use in patients with end-stage renal disease or severe renal impairment (creatinine clearance <30 mL/min).

7.1.13 Withdrawal Phenomena and/or Abuse Potential

Because there is no pharmacologic evidence to suggest an abuse potential for exenatide, no specific animal or human studies have been conducted to assess the dependence potential of the drug.

The duration of action of exenatide is relatively short as evidenced by no accumulation occurring with BID dosing. Exenatide is detectable in plasma for approximately 10 hours post-dose, leading to low or undetectable plasma levels before the subsequent dose. Thus, if rebound reactions were to occur, it would be evident between each dose. In the clinical trials there was no evidence of any rebounds. Therefore no rebound is expected on withdrawal of treatment.

7.1.14 Human Reproduction and Pregnancy Data


Nonclinical data

Exenatide produced no impairment of fertility, sperm concentration, or sperm motility in male mice, or fertility or estrous cycling in female mice at doses resulting in exposures 400 times that of human systemic exposure at 10 mcg BID. In lactating mice exposed to >400 times the expected human systemic exposure, low concentrations of exenatide were detected in milk.

Clinical data

No adequate and well-controlled studies of exenatide have been conducted in pregnant women.

However, during the course of the clinical development program, information on unintended study subject pregnancies was obtained from study sites. This information was obtained in a timely fashion after site personnel became aware of the pregnancy. Although not always captured as adverse events, the Amylin Clinical Safety Department actively tracked and followed-up each pregnancy through outcome, and each event has been described in a detailed subject narrative in the clinical study reports.

Four pregnancies occurred in exenatide clinical studies as of the "pregnancy cut off date" of 15 December 2003. A by-subject listing with details for each case was submitted. All four subjects became pregnant while being treated with exenatide. Three of the pregnancies were in Study 2993-112E (2 in the interim ITT population and one in the ongoing portion of the study); the fourth pregnancy occurred in ongoing study 2993-119. Two pregnancies produced healthy newborns (Subject 2993-112E-009-011 and Subject 2993-119-116-234-001). One pregnancy was ongoing (Subject 2993-112E-083-010) and one pregnancy (Subject 2993-112E-103-001) was electively terminated on  (planned abortion). There was no suggestion that exenatide adversely affects pregnancy or the fetus.

It is unknown whether exenatide is excreted in human milk.

7.1.15 Assessment of Effect on Growth

The effects of exenatide on growth have not been assessed.

7.1.16 Overdose Experience

Nonclinical data

Exenatide caused no lethality and minimal toxic responses when administered as a single,

IV dose in mice at doses up to 1500 µg/kg exenatide, as a SC dose in rats up to 30,000 µg/kg exenatide, and as a SC dose in monkeys up to 5000 µg/kg exenatide. Of note were observations of reduced food consumption in the monkey at doses ≥ 3000 µg/kg exenatide.

Clinical data

In the completed studies, 8 of 1857 subjects (0.4%) received an overdose (MedDRA Preferred Terms of Accidental Overdose or Overdose NOS) of exenatide: 3 in a clinical pharmacology study and 5 in the long-term, controlled studies. One additional subject, in a long-term, controlled study experienced a probable overdose. Of these 8 cases of overdose, only one resulted in a report of severe hypoglycemia. No overdoses were reported in the ongoing studies.

In Clinical Pharmacology Study, 2993-118, three subjects (2993-118-229-002, 2993-118-229-003, and 2993-118-229-004) received study medication overdoses of exenatide 100 µg SC, a dose 10-fold the protocol-specified dose; these doses were administered after a meal. Effects noted secondary to the overdose included nausea and aggravated nausea of severe intensity, vomiting of severe intensity, and rapidly decreasing blood glucose. One of the three overdosed subjects, one (2993-118-229-003) developed severe hypoglycemia (lowest measured blood glucose was 36 mg/dL) requiring the assistance of another person in the form of IV glucose administration. The other two subjects did not experience hypoglycemia as a result of the overdose; the lowest blood glucose levels recorded approximately 1-hour post dose for these subjects were 68 mg/dL and 88 mg/dL. All three subjects were treated with concomitant medications including an antiemetic and continuous IV 5% dextrose solution (D5W) infusion administered as hypoglycemia prophylaxis. The intensity of effects secondary to the overdose (e.g., nausea) was associated with plasma exenatide concentration with the severest effects occurring at the highest plasma exenatide concentrations. The intensity of the effects subsided as plasma exenatide concentrations declined.

In Study 2993-112 in which exenatide was administered with metformin, one subject (2993-112-033-006) inadvertently administered a dose of 75 µg. The subject experienced overdose effects including mild dizziness and pyrexia and moderate nausea. All three adverse events associated with the overdose resolved on the same day and were considered probably related to study medication by the investigator. In Study 2993-113 in which exenatide was administered with sulfonylurea, three subjects (2993-113-017-021, 2993-113-253-002, and 2993-113-257-001) reported an adverse event of accidental overdose with exenatide. In Study 2993-115 in which exenatide was administered with metformin and sulfonylurea, two subjects (2993-115-177-006 and 2993-115-195-002) reported an adverse event of accidental overdose with exenatide. One additional subject in long-term, controlled study 2993-115 received a probable overdose, but the investigator declined to record an adverse event of overdose. All of these six events were considered to reflect relatively minor overdoses secondary to either incorrect use of the pen-

injector or pen-injector malfunction, without serious consequences to the study subjects.

The experience in the above cases would suggest that a prudent recommendation in the event of overdosage would be to initiate appropriate supportive treatment (i.e., oral carbohydrate, and in the rare event of a resulting event of severe hypoglycemia, IV glucose or IM glucagon), according to the patient's clinical signs and symptoms.

7.1.17 Postmarketing Experience

Not applicable. As of the time of this application, exenatide is not marketed anywhere in the world.

7.2 Adequacy of Patient Exposure and Safety Assessments

7.2.1 Description of Primary Clinical Data Sources (Populations Exposed and Extent of Exposure) Used to Evaluate Safety

As of the data cutoff date (15 October 2003) the exenatide clinical development program consisted of the 27 completed studies. A total of 2252 unique subjects participated in the 27 completed studies. Across all study groups, 1857 subjects received exenatide and 805 subjects received placebo. Some subjects were treated with both exenatide and placebo and are counted in both groups. The number of subjects exposed to at least one dose of exenatide within the aforementioned completed studies (including the subjects in the long-term, uncontrolled studies who met the "study completion" criteria) is 1857, with 840 subjects and 272 subjects having been exposed to exenatide for 6 months and for 12 months, respectively, as of the 15 October 2003 data cut-off. These values for subject exposure exceed the requirements of the ICH E1 guideline on the "Extent of Population Exposure."

Male and female subjects in the target population were exposed to a range (0.01 to 0.4 µg/kg) of exenatide doses, including the recommended dosage regimens of 5 µg BID and 10 µg BID. The mean duration of exposure was over 22 weeks. A total of 1857 subjects, 1083 males and 774 females, were exposed to at least one dose of exenatide in the studies included in the Integrated Safety Database. Of these, 840 subjects (497 males, 343 females) were treated for at least 6 months and 272 (161 males, 111 females) for at least 12 months.

The most substantial exposure to exenatide was in the Efficacy and Safety Studies. In these studies, a total of 1420 subjects (795 males and 625 females) received exenatide. Of these, 840

(497 males, 343 females) received the drug for at least 26 weeks and 272 (161 males, 111 females) received the drug for at least 52 weeks.

7.2.1.1 Study type and design/patient enumeration

Table 27: Study type and design/patient enumeration and duration of exposure to exenatide

Study Grouping	Any Exposure	Less than 1-Wk	Cumulative Number (%) of Total Weeks of Exposure				
			≥1	≥4	≥13	≥26	≥52
Clinical Pharmacology Studies							
Human PK (BA/BE)	28	28 (100.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Human PK/Safety Tolerance (Healthy)	30	30 (100.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Human PK/PD (Special Populations/Intrinsic Factors)	31	31 (100.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Human PK (Drug Interaction/Extrinsic Factors)	105	105 (100.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Human Mechanism of Action	34	34 (100.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Human PK/Safety Tolerance (Diabetic)	100	88 (88.0)	12 (12.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Subtotal	328	316 (96.3)	12 (3.7)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Efficacy and Safety Studies							
Short-term, Controlled	204	11 (5.4)	193 (94.6)	151 (74.0)	0 (0.0)	0 (0.0)	0 (0.0)
Long-term, Controlled	963	14 (1.5)	949 (98.5)	932 (96.8)	849 (88.2)	784 (81.4)	230 (23.9)
Long-term, Uncontrolled Studies	253	9 (3.6)	244 (96.4)	235 (92.9)	221 (87.4)	56 (22.1)	42 (16.6)
Subtotal	1420	34 (2.4)	1386 (97.6)	1318 (92.8)	1070 (75.4)	840 (59.2)	272 (19.2)
Other Studies	109	48 (44.0)	61 (56.0)	53 (48.6)	0 (0.0)	0 (0.0)	0 (0.0)
Grand Total	1857	398 (21.4)	1459 (78.6)	1371 (73.8)	1070 (57.6)	840 (45.2)	272 (14.6)

Substantially fewer subjects were exposed to placebo than to exenatide during the clinical development program. A total of 805 subjects (483 males, 322 females) were exposed to placebo, 356 for at least 26 weeks (exposure to placebo was limited to a maximum of 30 weeks based on the design of the long-term, controlled studies). Of the 805 subjects exposed to placebo, 200 were exposed in the Clinical Pharmacology Studies, 544 were exposed in the Efficacy and Safety Studies, and 61 were exposed in Other Studies

Table 28: Exposure to exenatide and placebo by study group

Study Grouping	Number of Studies	Number of Subjects	Number Exposed (Previously)	
			Exenatide	Placebo
Clinical Pharmacology Studies				
Human PK (BA/BE)	1	28	28 (0)	0
Human PK/Safety Tolerance (Healthy)	1	40	30 (0)	10
Human PK/PD (Special Populations/Intrinsic Factors)	1	31	31 (0)	0
Human PK (Drug Interaction/Extrinsic Factors)	4	105	105 (0)	58

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 {Byetta (Exenatide)}

Human Mechanism of Action	3	49	34 (0)	47
Human PK/Safety Tolerance (Diabetic)	7	101	100 (0)	85
Subtotal	17	354	328	200
Efficacy and Safety Studies				
Short-term, Controlled	2	265	204 (0)	61
Long-term, Controlled	3	1446	963 (0)	483
Long-term, Uncontrolled Studies	4	660	660 (407)	0
Subtotal	9	1775	1420	544
Other Studies	1	123	109 (0)	61
Grand Total	27	2252	1857	805

7.2.1.2 Demographics

The total ITT population comprised 1857 subjects treated with exenatide and 805 subjects treated with placebo in the clinical development program. There were fewer females (41%) than males (59%) overall, with a similar distribution among exenatide- and placebo-treated subjects. Most of the subjects were Caucasian (68%). Hispanic and Black subjects comprised 16% and 11% of the population, respectively. The mean age in both the exenatide and placebo groups was 53 years. The majority of subjects were ≥ 18 to < 65 years of age (85%). The percentage of subjects 65 years of age or over was 15% in both the exenatide and placebo groups. Subjects 75 years of age or over comprised only 1.1% of the ITT population. There were no subjects under 18 years of age. The mean BMI of subjects was 32.5 kg/m² and 32.6 kg/m² in the exenatide and placebo groups, respectively. The majority of the subjects (64.2%) had a BMI of ≥ 30 kg/m².

The demographic characteristics for each category of clinical studies were similar to those for all studies combined, except for the Clinical Pharmacology Studies. In those studies there was a higher percentage of Hispanic subjects and fewer Caucasian, Black, and Asian subjects compared with the Efficacy and Safety Studies or Other Study. Also, mean age was lower among subjects in the Clinical Pharmacology Studies (range of means across treatments = 45.7 to 48.1 years) compared with the other categories of clinical studies. Mean BMI among subjects in the Clinical Pharmacology Studies was lower, which was expected among a population including a substantial number of healthy volunteers, as opposed to the exclusively type 2 diabetes population in the Efficacy and Safety Studies.

Table 29: Demographic characteristic of the population in the development program

Clinical Review
 {K. Eddie Gabry, M.D.}
 {NDA 21,773}
 {Byetta (Exenatide)}

Demographic Category	Efficacy and Safety												
	Clinical Pharmacology		Controlled				Uncon- trolled		Other		Total		
	Exenatide (N=328)	Placebo (N=200)	Short-term		Long-term		Exenatide (N=660)	Placebo (N=61)	Exenatide (N=109)	Placebo (N=61)	Exenatide (N=1857)	Placebo (N=805)	Total (N=2252)
Gender - n (%)													
Male	242 (73.8)	138 (69.0)	103 (50.5)	34 (55.7)	561 (58.3)	282 (58.4)	381 (57.7)	46 (42.2)	29 (47.5)	1083 (58.3)	483 (60.0)	1321 (58.7)	
Female	86 (26.2)	62 (31.0)	101 (49.5)	27 (44.3)	402 (41.7)	201 (41.6)	279 (42.3)	63 (57.8)	32 (52.5)	774 (41.7)	322 (40.0)	931 (41.3)	
Age (yr)													
n	328	200	204	61	963	483	660	109	61	1857	805	2252	
Mean (SD)	45.7 (15)	48.1 (14)	52.6 (10)	52.2 (9.5)	54.6 (10)	53.0 (10)	55.3 (10)	33.8 (7.1)	53.4 (7.4)	52.9 (12)	53.0 (11)	53.0 (12)	
Median	49.0	51.0	54.0	54.0	55.0	55.0	56.0	34.0	53.0	54.0	54.0	54.0	
Min,Max	18.0, 76.0	19.0, 73.0	26.0, 78.0	27.0, 71.0	19.0, 78.0	21.0, 77.0	19.0, 76.0	35.0, 69.0	35.0, 69.0	18.0, 78.0	19.0, 77.0	18.0, 78.0	
Age subgroup - n (%)													
≥18-45	298 (90.9)	180 (90.0)	179 (87.7)	57 (93.4)	795 (82.6)	389 (80.5)	532 (80.6)	102 (93.6)	57 (93.4)	1575 (84.8)	683 (84.8)	1906 (84.6)	
≥65	30 (9.1)	20 (10.0)	25 (12.3)	4 (6.6)	168 (17.4)	94 (19.5)	128 (19.4)	7 (6.4)	4 (6.6)	282 (15.2)	122 (15.2)	346 (15.4)	
≥75	2 (0.6)	0 (0.0)	1 (0.5)	0 (0.0)	11 (1.1)	11 (2.3)	9 (1.4)	0 (0.0)	0 (0.0)	16 (0.9)	11 (1.4)	25 (1.1)	
Race - n (%)													
Caucasian	188 (57.3)	115 (57.5)	134 (65.7)	43 (70.5)	658 (68.3)	333 (68.9)	509 (77.1)	75 (68.8)	44 (72.1)	1254 (67.5)	535 (66.5)	1533 (68.0)	
Black	25 (7.6)	8 (4.0)	26 (12.7)	7 (11.5)	117 (12.1)	57 (11.8)	67 (10.2)	11 (10.1)	5 (8.2)	206 (11.1)	77 (9.6)	245 (10.9)	
Asian	23 (7.0)	1 (0.5)	8 (3.9)	1 (1.6)	26 (2.7)	7 (1.4)	14 (2.1)	7 (6.4)	5 (8.2)	65 (3.5)	14 (1.7)	72 (3.2)	
Native American	0 (0.0)	0 (0.0)	2 (1.0)	0 (0.0)	4 (0.4)	2 (0.4)	1 (0.2)	1 (0.9)	1 (1.6)	4 (0.4)	3 (0.4)	9 (0.4)	
Hispanic	91 (27.7)	76 (38.0)	28 (13.7)	9 (14.8)	147 (15.3)	77 (15.9)	66 (10.0)	12 (11.0)	5 (8.2)	303 (16.3)	167 (20.7)	365 (16.2)	
Other	1 (0.3)	0 (0.0)	6 (2.9)	1 (1.6)	11 (1.1)	7 (1.4)	3 (0.5)	3 (2.8)	1 (1.6)	21 (1.1)	9 (1.1)	29 (1.3)	
BMI (kg/m ²)													
n	325	198	204	61	963	483	655	109	61	1851	803	2249	
Mean (SD)	27.6 (4.6)	28.2 (4.4)	34.2 (5.5)	34.3 (5.2)	33.5 (5.8)	34.1 (5.4)	33.0 (5.6)	33.7 (5.0)	33.6 (5.4)	32.5 (5.9)	32.6 (5.7)	32.7 (5.9)	
Median	26.9	28.0	34.0	33.6	32.7	33.5	32.3	34.0	32.1	32.0	32.0	32.1	
Min,Max	18.6, 50.1	19.2, 42.8	23.4, 52.6	25.6, 46.9	21.1, 53.0	20.7, 56.2	20.9, 51.6	23.6, 46.7	23.6, 45.9	18.6, 53.0	19.2, 56.2	18.6, 56.2	
BMI subgroup - n (%)													
<27	164 (50.0)	83 (41.5)	14 (6.9)	4 (6.6)	111 (11.5)	37 (7.7)	93 (14.1)	3 (2.8)	3 (4.9)	319 (17.2)	127 (15.8)	357 (15.9)	
≥27-30	73 (22.3)	49 (24.5)	33 (16.2)	9 (14.8)	191 (19.8)	85 (17.6)	121 (18.3)	29 (26.6)	15 (24.6)	372 (20.0)	158 (19.6)	447 (19.8)	
≥30-35	69 (21.0)	57 (28.5)	73 (35.8)	23 (37.7)	317 (32.9)	163 (33.7)	231 (35.0)	32 (29.4)	19 (31.1)	576 (31.0)	362 (45.1)	705 (31.3)	
≥35	19 (5.8)	9 (4.5)	84 (41.2)	25 (41.0)	344 (35.7)	198 (41.0)	210 (31.8)	45 (41.3)	24 (39.3)	584 (31.4)	256 (31.8)	740 (32.9)	

7.2.1.3 Extent of exposure (dose/duration)

Of the 1857 subjects exposed to exenatide, 443 (23.9%) received a maximum total daily dose of 10 µg (5 µg BID) and 996 (53.6%) received a maximum total daily dose of 20 µg (10 µg BID) at some time during the development program. A total of 167 subjects (9.0%) were exposed to daily doses in excess of 20 µg.

7.2.2 Secondary Clinical Data Sources Used to Evaluate Safety

7.2.2.1 Other studies

In addition to the 1857 subjects treated with exenatide in the completed studies and included in the integrated safety database, the following additional subject exposure to exenatide has occurred: 82 subjects were treated with exenatide in the LAR studies, 471 subjects were treated with exenatide in the long-term, uncontrolled studies (2993-112E, 2993-113E, 2993-115E, 2993-117), 141 subjects were treated with exenatide in Study 2993-119, 74 subjects were exposed to exenatide in Study 2993-120, and 65 subjects were treated with exenatide in Study H80-MC-GWAA, prior to the data cut-off date of 15 October 2004 as described below.

In the interim clinical study reports for the long-term, uncontrolled studies (Studies 2993-112E, 2993-113E, 2993-115E, 2993-117), data are provided for up to 52 weeks of exposure. Among

the 660 subjects included in the interim clinical study reports, there were some who had exposure to exenatide beyond 52 weeks, yet prior to 15 October 2003, this additional exposure amounts to 180 subjects with 7.2, 127 subjects with 5.9, 289 subjects with 5.1, and 64 subjects with 0.2 additional mean subject-weeks of exposure for Studies 2993-112E, 2993-113E, 2993-115E and 2993-117, respectively.

An additional 380 subjects were exposed to exenatide for less than 52 weeks in Studies 2993-112E, 2993-113E, and 2993-115E by 15 October 2003 who were not included in the integrated safety dataset due to their inability to have reached the Week 52 visit by this date. In Study 2993-112E, an additional 46 subjects were exposed with a mean duration of exposure of 39.8 weeks; 97 additional subjects were exposed for a mean duration of 34.7 weeks in Study 2993-113E, and 237 additional subjects in study 2993-115E were exposed to exenatide for a mean duration of 33.7 weeks. Similarly, in Study 2993-117 an additional 91 subjects were exposed to exenatide for less than 52 weeks by 15 October 2003 that are not included in the integrated safety dataset; their average duration of exposure as of this date was 37.2 weeks.

The extent of exposure, as of 15 October 2003 for Study 2993-119, included 141 subjects with a mean duration of exposure of 25.3 weeks.

Study 2993-120 has been completed since the 15 October 2003 date, and overall in that study, 74 subjects were exposed to exenatide with mean exposure of approximately 28 days.

As of 15 October 2003, there were 65 subjects randomized to exenatide treatment in Study H8O-MC-GWAA with an average exposure of 34.4 days.

7.2.2.2 Postmarketing experience

Not applicable. Exenatide is not yet marketed in the U.S. or around the world.

7.2.2.3 Literature

A literature search was conducted to identify any studies conducted and published by non-Amylin investigators by the data cutoff date of 15 October 2003. The following terms were used to search the Medline, Embase, and Current Contents for Life Sciences databases: exendin-4, exendin4, exendin, and exenatide. In addition to this formal search, non-indexed publications (e.g., abstracts from relevant scientific meetings) were identified from a manual search of the meeting abstract supplements. Publications that primarily focused on exendin [9-39] or exendin-3 were excluded from the search.

The final search results identified 10 published manuscripts and 11 published abstracts that either reported on exendin-4/exenatide clinical trials or nonclinical study results potentially

relevant to understanding the safety of exenatide in humans. Many of the reports focused on the physiological effects of exenatide to stimulate insulin secretion, lower glucose concentrations, and induce satiety/energy intake. When safety was reported on, the findings typically mirrored those seen in the exenatide clinical development program.

There were two reports of exendin-4 having an effect on secretion of thyroid-stimulating hormone (TSH), but the findings were contradictory: an *in vivo* study in rats¹ indicated that exendin-4 acutely suppressed circulating TSH concentrations, while an *in vitro* study² indicated that exendin-4 stimulates secretion of TSH by cultured anterior pituitary cells. Nonclinical (rat) studies conducted by Amylin indicate that exenatide treatment had no effect on thyroid hormone (T3 or T4) concentrations. While potential effects of exenatide on TSH secretion have not been specifically studied in the clinical development program, there has been no indication in the long-term, controlled trials of clinical symptoms that would reflect an adverse effect on pituitary or thyroid function.

Reports of exendin-4 stimulation of the pituitary-adrenocortical axis³ are consistent with the known effect of exenatide to stimulate cortisol secretion. This stimulation of cortisol is an acute, transient phenomenon that is consistent with the rise of other stress hormones; as shown in Study 2993-107, the effect is absent after 4 weeks of repeated dosing with exenatide. Lack of chronic (or acute) changes in cardiovascular function and amelioration (rather than deterioration) of patients' glycemic and metabolic response suggest that this transient stress-like response may be of limited clinical significance. Data from chronic toxicity studies in monkeys do not indicate increased adrenal size, consistent with the absence of a long-term stimulation of cortisol secretion with repeated exenatide treatment.

At least two literature reports^{4,5} suggest that dosing of rodents with exendin-4 acutely increases blood pressure and heart rate. These findings are consistent with nonclinical (rat) studies conducted by Amylin. However, in clinical trials conducted by Amylin there has been no indication of any long-term detrimental effect on hemodynamic parameters.

The publications identified in the literature search are listed below.

Baraboi E-D, Timofeeva E, Richard D. Neuronal activation in response to intraperitoneal administration of exendin-4 in rats. <i>Obes Res</i> 2003;11(suppl):A117. Abstract 483-P.6
Barragan JM, Rodriguez RE, Eng J, Blazquez E. Interactions of exendin-(9-39) with the effects of glucagon-like peptide-1-(7-36) amide and of exendin-4 on arterial blood pressure and heart rate in rats. <i>Regul Pept</i> 1996;67:63-8.4
Beak SA, Small CJ, Ilovaiskaia I, Hurley JD, Ghatei MA, Bloom SR, et al. Glucagon-like peptide-1 (GLP-1) releases thyrotropin (TSH): Characterization of binding sites for GLP-1 on alpha-TSH cells. <i>Endocrinology</i> 1996;137:4130-8.2

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Behme M, Dupre J, McDonald T. Exendin-4 normalizes glycemic excursions in C-peptide-negative type 1 diabetes. <i>Diabetes</i> 2003;52(suppl 1):A110. Abstract 472-P.7
Brynes AE, Edwards CMB, Stanley SA, Davis R, Frost GS, Seal L, et al. Exendin-4 reduces energy intake at a free choice buffet meal in healthy volunteers. <i>Diabet Med</i> 2000;17(suppl 1):69. Abstract P131. 8
Dupre J, Behme MT, Hramiak I, McDonald TJ. Exendin-4 reduces glucose excursions after meals in type 1 diabetes. <i>Diabetes</i> . 2001;50(suppl 2):A110. Abstract 442P.9
Edwards CMB, Stanley SA, Davis R, Brynes AE, Frost GS, Seal LJ, et al. Exendin-4 reduces fasting and postprandial glucose and decreases energy intake in healthy volunteers. <i>Am J Physiol Endocrinol Metab</i> 2001;281:E155-61.10
Edwards CMB, Stanley SA, Davis R, Brynes AE, Frost GS, Seal LJ, et al. Exendin-4 reduces fasting and postprandial glucose in healthy volunteers. <i>Diabet Med</i> 2000;17(suppl 1):69. Abstract P133.11
Egan JM, Clocquet AR, Elahi D. The insulinotropic effect of acute exendin-4 administered to humans: comparison of nondiabetic state to type 2 diabetes. <i>J Clin Endocrinol Metab</i> 2002;87:1282-90.12
Egan JM, Clocquet AR, Elahi D. Insulinotropic effect of exendin-4 in humans. <i>Diabetologia</i> 1999;42(suppl 1):A41. Abstract 148.13
Egan JM, Meneilly GS, Elahi D. Effects of 1-mo bolus subcutaneous administration of exendin-4 in type 2 diabetes. <i>Am J Physiol Endocrinol Metab</i> 2003;284:E1072-9.14
Goke R, Larsen PJ, Mikkelsen JD, Sheikh SP. Identification of specific binding sites for glucagon-like peptide-1 on the posterior lobe of the rat pituitary. <i>Neuroendocrinology</i> 1995;62:130-4.15
Levy JC, Maksoud H, Barrow BA, Carter RD. Subcutaneous exendin-4 reduces postprandial glucose increment in type 2 diabetic subjects. <i>Diabet Med</i> 2000;17(suppl 1):70. Abstract P138. 16
Levy JC, Maksoud J, Barrow BA, Sutton PJ. Subcutaneous exendin-4 improves daytime glucose exposure by reducing postprandial glucose increment in diet treated type 2 diabetic subjects. <i>Diabetes</i> 2000;49(suppl 1):A115. Abstract 464-P.17
Maksoud H, Barrow BA, Carter RD, Levy JC. Subcutaneous exendin-4 improves daytime glucose exposure and beta cell function in type 2 diabetic subjects. <i>Diabet Med</i> 2000;17(suppl 1):5. Abstract A13.18
Maksoud H, Barrow BA, Manley SE, Levy JC. Subcutaneous exendin-4 reduces basal glucose and postprandial glucose increment and improves beta cell function in sulphonylurea treated type 2 diabetic subjects. <i>Diabetes</i> 2000;49(suppl 1):A116. Abstract 471-P.19
Maksoud H, Dudley C, Manley SE, Levy JC. Subcutaneous exendin-4 lowers both post-prandial and fasting plasma glucose in type 2 diabetes. <i>Diabetologia</i> 2000;43:A144. Abstract 556.20
Malendowicz LK, Neri G, Nussdorfer GG, Nowak KW, Zytarska A, Ziolkowska A. Prolonged exendin-4 administration stimulates pituitary-adrenocortical axis of normal and streptozotocin-induced diabetic rats. <i>Int J Mol Med</i> 2003;12:593-6.3
Malendowicz LK, Nowak KW. Preproglucagon derived peptides and thyrotropin (TSH) secretion in the rat: robust and sustained lowering of blood TSH levels in exendin-4 injected animals. <i>Int J Mol Med</i> 2002;10:327-31.1

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Rai A, Singh G, Raffaniello R, Eng J, Raufman JP. Actions of Helodermatidae venom peptides and mammalian glucagon-like peptides on gastric chief cells. *Am J Physiol* 1993;265:G118-25. 21

Yamamoto H, Lee CE, Marcus JN, Williams TD, Overton JM, Lopez ME, et al. Glucagon-like peptide-1 receptor stimulation increases blood pressure and heart rate and activates autonomic regulatory neurons. *J Clin Invest* 2002;110:43-52. 5

7.2.3 Adequacy of Overall Clinical Experience

The overall clinical experience was adequate and exceeded the ICH requirements.

7.2.4 Adequacy of Special Animal and/or In Vitro Testing

Please see the pharmacology review.

7.2.5 Adequacy of Routine Clinical Testing

Routine clinical testing of subjects exposed to exenatide in all phases of clinical development was adequate.

7.2.6 Adequacy of Metabolic, Clearance, and Interaction Workup

The metabolism of exenatide and its clearance as well as its interaction with other drugs have been adequately addressed.

7.2.7 Adequacy of Evaluation for Potential Adverse Events for Any New Drug and Particularly for Drugs in the Class Represented by the New Drug; Recommendations for Further Study

Adequate measures were taken to capture any adverse events relevant to this novel class of drugs. All adverse events reported spontaneously by the subject, as well as those noted by the investigator or clinical study-site staff, were to be recorded on source documents and entered on the CRFs. In order to avoid vague, ambiguous, or colloquial expressions, the adverse event was to have been recorded on the CRFs using standard medical terminology rather than the subject's own words. Whenever the investigator was confident in making a unifying diagnosis, all related signs, symptoms, and abnormal test results were to be grouped together as a single adverse event on the CRF (e.g., cough and rhinitis were to be reported as an "upper respiratory infection"). All treatment-emergent adverse events continuing at study termination and clinically significant electrocardiograms (ECG) and clinical laboratory test abnormalities were to have been followed and evaluated until diagnosis of the underlying cause or resolution of the event. Follow-up information should have been recorded on the source documents.

All adverse events and signs and symptoms were to be evaluated by the investigator for intensity, seriousness, and causal relationship to the use of study medication.

7.2.8 Assessment of Quality and Completeness of Data

The overall quality of data is good. Overall, the data is judged by this reviewer as complete.

7.2.9 Additional Submissions, Including Safety Update,

The 4-Month Safety Update provides integrated adverse event data from an additional 648 subjects (127.7 additional subject-years of exposure to exenatide) from 2 additional clinical trials, relative to the data presented in the original NDA. In addition, information on serious adverse events, deaths, and withdrawals due to adverse events from 10 ongoing clinical trials is provided. The observed adverse events remain essentially the same as described in the original NDA submission, with the majority of events being gastrointestinal in nature, mostly nausea that dissipates with time of exposure for most subjects.

After substantial exposure of subjects to exenatide from 2 additional drug substance manufacturers, there is no evidence of differential immunogenicity across drug suppliers

Detailed follow-up on cancer cases among exenatide-treated subjects, including the finding that the rate of incident cancers is decreasing with continued exenatide exposure, is consistent with a lack of causality between exenatide and malignant neoplasms.

Follow-up on the 1 pregnancy that had not yet gone to term as of the original NDA

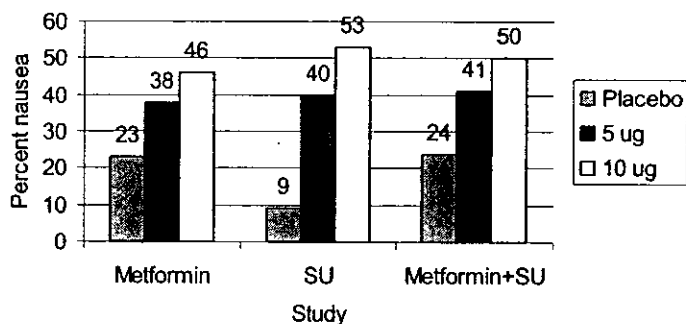
submission indicates that the pregnancy was successful. The baby was delivered by emergency Caesarian section and both infant and mother are currently in good health. The outcome of the 4 pregnancies during the clinical development program is consistent with no detrimental effects of exenatide on pregnant women or the fetus.

7.3 Summary of Selected Drug-Related Adverse Events, Important Limitations of Data, and Conclusions

The clinical development program exposed male and female subjects in the target population to a range of doses of exenatide, including the recommended dosage regimens of 5 µg BID and 10 µg BID, with a mean duration of exposure of 22 weeks. A total of 1857 subjects, 1083 males and 774 females, were exposed to exenatide in the studies included in the Integrated Safety Database. Of these 1857 subjects, 840 were treated for 6 months and 272 for 12 months. Of the 1857 subjects exposed to exenatide, 443 (23.9%) received a maximum total daily dose of 10 µg (5 µg BID) and 996 (53.6%) received a maximum total daily dose of 20 µg (10 µg BID) at some time during the development program. A total of 167 subjects (9.0%) were exposed to total daily doses in excess of 20 µg.

General Adverse Events. The majority of subjects who participated in the exenatide long-term, controlled studies experienced at least one treatment-emergent adverse event (91% and 82% for exenatide- and placebo-treated subjects, respectively). The adverse event profile varied depending on the background oral antidiabetic agent therapy, but adverse events were generally mild to moderate, and the frequency with which they were reported diminished with continued therapy. In the long-term, controlled studies, treatment-emergent adverse events with an incidence of at least 5%, and a greater incidence with exenatide- than placebo-treated subjects, were nausea (44% exenatide, 18% placebo), hypoglycemia (20% exenatide, 8% placebo), vomiting (13% exenatide, 4% placebo), diarrhea (13% exenatide, 6% placebo), feeling jittery (9% exenatide, 4% placebo), dizziness (9% exenatide, 6% placebo), headache (9% exenatide, 6% placebo), and dyspepsia (6% exenatide, 3% placebo).

Figure 33: Percent of patients with nausea by treatment group and study

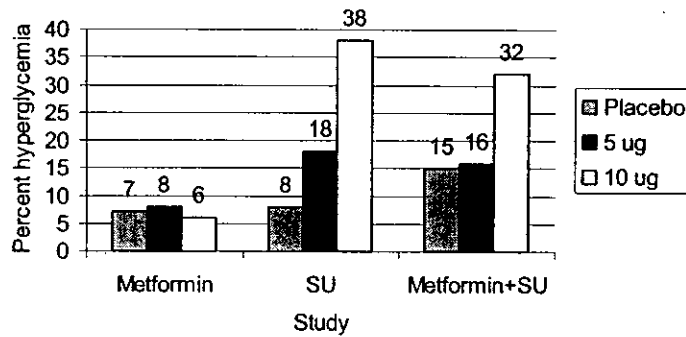


Withdrawals in the long-term, controlled studies due to any adverse event were 7% for exenatide-treated subjects and 3% for placebo-treated subjects.

The incidence of serious adverse events was comparable between exenatide subjects (4%) and placebo subjects (6%) in those same trials. Five deaths were reported in the clinical development program: two placebo subjects (one motor vehicle accident, one cardiac arrest) and three exenatide subjects (one motor vehicle [pedestrian] accident, one myocardial infarction, and one bladder cancer). None of the deaths were attributed by the investigators to the study drug.

Hypoglycemia. When the pooled data from the long-term, controlled studies were broken down to the individual study level, the elevated incidence of hypoglycemia relative to the placebo comparator occurred only in patients receiving exenatide in combination with a sulfonylurea. In Studies 2993-113 (concomitant sulfonylurea) and 2993-115 (concomitant sulfonylurea and metformin), hypoglycemia was observed in 25% (versus 3% in placebo) and 24% (versus 13% in placebo) of the patients, respectively, whereas in Study 2993-112 (concomitant metformin), hypoglycemia was observed in both the exenatide plus metformin and the placebo plus metformin groups at equal frequency (5%). Therefore, patients receiving exenatide in combination with a sulfonylurea may be at increased risk of hypoglycemia, but those receiving exenatide in combination with metformin appear not to be. The vast majority of hypoglycemia events were mild or moderate. Of 189 subjects who experienced hypoglycemia in the long-term, controlled studies, only in one subject was the hypoglycemia rated severe (requiring the assistance of another person) and, in this case, the hypoglycemia was resolved with an oral snack.

Figure 34: Percent of patients with hyperglycemia



Analysis of hyperglycemia

Study	Placebo	5 µg	10 µg	p-value
Metformin	8/113 (7%)	9/110 (8%)	7/113 (6%)	0.80
SFU	10/123 (8%)	23/125 (18%)	49/129 (38%)	<0.0001
Metformin+SFU	37/247 (15%)	63/245 (26%)	77/241 (32%)	<0.0001

To address the management of hypoglycemia, subjects in Study 2993-115 were proactively divided into subgroups that either used the maximally effective dose of their sulfonylurea or reduced to the minimally recommended dose prior to beginning exenatide treatment. The latter subgroup experienced treatment-emergent, mild or moderate hypoglycemic events at approximately one third of the rate observed for those who remained on the maximally effective sulfonylurea dose, although achieved at the expense of some loss in efficacy. Reduction in the dose of the sulfonylurea may therefore be considered as a way to reduce the risk of hypoglycemia associated with its use with exenatide.

Pregnancy. Four pregnancies were reported during the clinical study of exenatide. All subjects were receiving exenatide treatment at the time of conception, and two of the subjects were using an oral contraceptive. All stopped exenatide treatment soon after the determination of pregnancy was made, and exposure of the fetus to exenatide ranged from 16 to 48 days. The pregnancies to date have been uneventful, with two women giving birth to healthy babies, one having a planned abortion not related to exenatide use, and one still awaiting delivery. While exenatide is unlikely to cause any direct, untoward fetal effects given its very low potential to cross the placental barrier, at this time the total exposure information which can be used to draw conclusions is limited.

Other General Safety Measures.

There was no indication from the long-term, controlled trials of any adverse effect of exenatide on clinical laboratory measures, vital signs, electrocardiograms, or circulating cortisol concentrations.

There were no adverse events found to have the potential of being malignant hypertension, aplastic anemia, toxic epidermal necrolysis, liver necrosis, significant hemolytic anemia, rhabdomyolysis, idiopathic thrombocytopenic purpura, or intussusception. There were no events of Torsades de Pointe. A total of 37 treatment emergent adverse events were identified in 33 subjects as having the potential to be one of these adverse event terms; 24 of these treatment-emergent adverse events were reported in 22 subjects while on exenatide therapy. None of the noted events among exenatide subjects (seizure [2 subjects], acute renal failure [3 subjects], Sjogren's syndrome [1 subject], pulmonary fibrosis [1 subject]) could be attributed to a direct effect of exenatide treatment.

7.4 General Methodology

7.4.1 Pooling Data Across Studies to Estimate and Compare Incidence

To facilitate data displays and interpretation, safety data from the 27 completed studies were pooled into an "integrated safety database." Any subject who was in the ITT population in one of the individual studies was included in this integrated safety database. The definitions of ITT were the same as those defined in the individual study statistical analysis plans (SAPs). For crossover and controlled studies, the ITT population was defined as all subjects who received at least one injection of randomized medication. For the long-term uncontrolled studies, the ITT population consisted of all subjects who received at least one injection of open-label medication, and who completed the 52 weeks of treatment by the data cutoff date or who could have achieved 52 weeks of treatment by the data cutoff date but withdrew prior to that date.

7.4.1.1 Pooled data vs. individual study data

The results of the 3 main long term controlled clinical studies mirrored those from the pooled data.

Table 30: Key Safety Findings of Individual Studies

2993-112	2993-113	2993-115
<ul style="list-style-type: none"> No clinically important changes were observed for this study population in clinical laboratory values. Exenatide treatment was not associated with any untoward effects on vital signs, physical exam findings, or ECG recordings. 	<ul style="list-style-type: none"> No clinically important changes were observed for this study population in clinical laboratory values. Exenatide treatment was not associated with any untoward effects on vital signs, physical exam findings, or ECG recordings. 	<ul style="list-style-type: none"> No clinically important changes were observed for this study population in clinical laboratory values. Exenatide treatment was not associated with any untoward effects on vital signs, physical exam findings, or ECG recordings.

<ul style="list-style-type: none"> • Twelve (3.6%) subjects receiving exenatide treatment experienced a serious adverse event during the study. Twelve subjects withdrew due to a treatment-emergent adverse event, the most common being nausea (4 subjects, 1.8%, including 1 subject from the 5-μg exenatide group and 3 from the 10-μg exenatide group). The most common treatment-emergent adverse events with exenatide treatment were transient mild-to-moderate nausea (40.8% compared to 23.0% with placebo), diarrhea (13.9% compared to 8.0% with placebo), and vomiting (11.2% compared to 3.5% with placebo). The nausea was dose-dependent. The incidence of mild to moderate hypoglycemia was comparable between placebo (5.3%) and exenatide-treated subjects (4.9%). No severe hypoglycemic events were reported with long-term use of exenatide. • At Week 30, 76 (43.2%) exenatide-treated subjects had a treatment-emergent anti-exenatide antibody positive result. The majority of antibody-positive subjects had low titer ($\leq 1/125$) anti-exenatide antibodies at Week 30. There were no apparent trends of adverse events among treatment groups or between groups of subjects with or without antibody titers with 	<ul style="list-style-type: none"> • Nineteen subjects (5.0%) experienced 20 serious adverse events during the study (8.1% placebo, 3.2% exenatide 5 μg, and 3.9% exenatide 10 μg). Twenty-six subjects (6.9%) were withdrawn due to a treatment-emergent adverse event; the most common reasons were nausea (8 exenatide subjects, 3.1%) and vomiting (2 exenatide subjects, 0.8%). The most common treatment-emergent adverse events for exenatide subjects were transient mild-to-moderate nausea (45.3% compared to 7.3% with placebo), hypoglycemia (25.2% compared to 3.3% with placebo), and dizziness (15.0% compared to 6.5% with placebo). The incidence of treatment-emergent nausea and hypoglycemia was higher in exenatide subjects than placebo subjects and appeared to be dose-dependent. No severe hypoglycemic events were reported. • At Week 30, 40.8% of exenatide subjects had a treatment-emergent anti-exenatide antibody positive result; the highest incidence was at Week 18 (48.2%). Most treatment-emergent anti-exenatide antibody titers at Week 30 were between 1/5 and 1/125. There were no apparent trends of adverse events among treatment groups or between groups of 	<ul style="list-style-type: none"> • The majority of treatment-emergent adverse events were assessed as mild or moderate in intensity. The most common treatment-emergent adverse events for exenatide-treated subjects were transient mild-to-moderate nausea (43.8% compared to 20.6% with placebo) and hypoglycemia (23.5% compared to 12.6% with placebo). • One subject died during the study. The subject died due to myocardial infarction and was receiving placebo at the time of the event. • One severe hypoglycemic event was reported 23 days after randomization (exenatide 5 μg); the subject recovered within 10 min of eating a snack with the assistance of her husband and completed the study after 210 days. • The incidence of treatment-emergent hypoglycemia exhibited a dose-dependent pattern (placebo, 12.6%; exenatide 5 μg, 19.2%; and exenatide 10 μg, 27.8%). This was not an unexpected finding given addition of the glucose-dependent insulinotropic actions of exenatide to the non-specific insulinotropic effects of a pre-existing sulfonylurea regimen at baseline. Anticipation of this outcome, led to evaluation of the MinRD and MaxED approaches to sulfonylurea therapy
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<p>long-term exenatide treatment. Specific adverse events consistent with an immune response were assessed and there were no indications of a relationship between these adverse events and antibody-positive subjects. No clinically meaningful changes in eosinophil count, an indicator of an acute allergic reaction, were observed. In addition, the presence of anti-exenatide antibodies did not have significant impact on long-term efficacy of exenatide treatment. Results indicate on average a smaller reduction in HbA_{1c} from baseline in anti-exenatide antibody-positive subjects than in anti-exenatide antibody-negative subjects; however, individual antibody status was not predictive of an individual subject's glycemic outcome.</p>	<p>subjects with or without antibody titers with long-term exenatide treatment. Specific adverse events consistent with an immune response were assessed and there were no indications of a relationship between these adverse events and antibody-positive subjects. No clinically meaningful changes in eosinophil count, an indicator of an acute allergic reaction, were observed. In addition, the presence of anti-exenatide antibodies did not have significant impact on long-term efficacy of exenatide treatment. Results indicate on average a smaller reduction in HbA_{1c} from baseline in anti-exenatide antibody-positive subjects than in anti-exenatide antibody-negative subjects; however, individual antibody status was not predictive of an individual subject's glycemic outcome.</p>	<p>in the study.</p> <ul style="list-style-type: none"> • A lower incidence of hypoglycemia was observed for the MinRD group (5 µg, 16.4%; 10 µg, 21.3%) than for the MaxED group (5 µg, 22.0%; 10 µg, 34.5%). Significant improvement (p < 0.0001) in glycemic control was observed for subjects in both sulfonylurea management groups, though the reduction in the risk of hypoglycemia with the MinRD approach comes with some loss of benefit in terms of HbA_{1c} reduction as absolute efficacy results were somewhat lower for subjects in the this sulfonylurea management group. Therefore, the proactive approach reduced the incidence of mild to moderate hypoglycemia by approximately one-third; however, the reduction in the risk of hypoglycemia with this approach comes with some loss of benefit (0.3% less absolute reduction in LS mean HbA_{1c} for MinRD group across treatments). • At Week 30, 48.5% of exenatide subjects had anti-exenatide antibodies. Most treatment-emergent anti-exenatide antibody titers at Week 30 were between 1/5 and 1/125. There were no apparent trends of adverse events among treatment groups or between groups of
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		subjects with or without antibody titers with long-term exenatide treatment. Specific adverse events consistent with an immune response were assessed and there were no indications of a relationship between these adverse events and antibody-positive subjects. No clinically meaningful changes in eosinophil count, an indicator of an acute allergic reaction, were observed. In addition, the presence of anti-exenatide antibodies did not have significant impact on long-term efficacy of exenatide treatment. Results indicate on average a smaller reduction in HbA _{1c} from baseline in anti-exenatide antibody-positive subjects than in anti-exenatide antibody-negative subjects; however, individual antibody status was not predictive of an individual subject's glycemic outcome.
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7.4.2 Explorations for Predictive Factors

7.4.2.1 Explorations for dose dependency for adverse findings

As mentioned above, the drug related adverse effects, e.g. nausea, vomiting, diarrhea, hypoglycemia were dose related.

7.4.2.2 Explorations for time dependency for adverse findings

Study H8O-EW-GWAJ showed that administration of exenatide at various times ranging from

60 minutes before to 60 minutes after a meal produced significant reductions in postprandial glucose exposure. Pre-meal treatments (-60, -15, 0 min) exhibited greater reduction of postprandial glucose excursions compared with postmeal administration (+30 or +60 min). mentioned previously, post-meal administration was associated with transient low glucose concentrations. Therefore, it is recommended that exenatide be administered within the 60-minute period before a meal. Exenatide should not be administered after a meal. Subcutaneous single doses of exenatide 10 µg were safe and fairly well tolerated.

The duration of treatment prior to event onset was also explored for adverse events with an incidence of at least 5%, adverse events leading to withdrawal, and serious adverse events. For selected adverse events, e.g., nausea, vomiting, and hypoglycemia, various approaches were used to characterize the time course of adverse event occurrence. For each of these selected events, the time specific rate of occurrence (incidence) was summarized using the cut points of 0-4 weeks, >4-8 weeks, >8-12 weeks, >12-16 weeks, >16-20 weeks, >20-24 weeks, >24-28 weeks, and >28 weeks to determine whether the chances of the event occurring escalated as the exposure time increased or whether the bulk of the action occurred early and then tapered off.

A Kaplan-Meier plot of the cumulative frequency distribution of the time to first onset of nausea in the long-term, controlled studies was used to estimate the rate of new nausea onset.

7.4.2.3 Explorations for drug-demographic interactions

Review of treatment-emergent adverse events by age category did not indicate any obvious age-related difference.

Overall, females reported a higher incidence of treatment-emergent adverse events than did males in both treatment groups: exenatide (95% females vs. 88% males) and placebo (90% females vs. 77% males). The female vs. male difference was most notable for following events (exenatide incidence rates for female/male): feeling jittery (14%/6%), headache (11%/6%), nausea (57%/34%), and vomiting (20%/8%). Each of these treatment-emergent adverse events was further reviewed by dose group. Even after correcting for the subject incidence rate in the placebo group, nausea and vomiting each occurred more frequently in females than in males in both the 5-µg BID and 10-µg BID exenatide dose groups. Nausea occurred at a higher rate in the 10-µg BID group than in the 5-µg BID group in both females and males. Dose-relatedness for vomiting was only apparent in females. After correcting for the subject incidence rate in the placebo group, feeling jittery occurred at higher subject incidence rate in females than in males only in the 5-µg BID dose group; and headache did not exhibit any substantial gender difference in either dose group.

Within each treatment group, the treatment-emergent adverse event incidence was comparable across the three race categories, with overall incidence rates being 91%, 91%, and 88% in the

Caucasian, Black, and Hispanic exenatide subgroups; and 82%, 81%, and 84% in the corresponding placebo subgroups. Despite these similar overall incidence rates among racial subgroups, there were some differences, most notably the lower incidence of nausea in Black subjects (36%) treated with exenatide compared with Caucasians (44%) and Hispanics (48%) treated with the drug. In contrast, placebo-treated Black subjects had a higher incidence rate of nausea (26%) than placebo-treated Caucasians (17%) or Hispanics (18%).

Overall, in both treatment groups, the incidence rate of treatment-emergent adverse events was approximately the same in subjects with a BMI $<30 \text{ kg/m}^2$ as in subjects with a BMI $\geq 30 \text{ kg/m}^2$: exenatide (90% BMI $<30 \text{ kg/m}^2$ vs. 91% BMI $\geq 30 \text{ kg/m}^2$); placebo (76% BMI $<30 \text{ kg/m}^2$ vs. 84% BMI $\geq 30 \text{ kg/m}^2$). Review of treatment-emergent adverse events occurring at an incidence of at least 5% by BMI category did not suggest any important difference in the adverse event profile by BMI category.

Overall, in both treatment groups, the incidence rate of treatment-emergent adverse events was approximately the same in subjects with normal and with mildly impaired renal function: exenatide (90% normal renal function vs. 95% mildly impaired renal function); placebo (82% normal renal function vs. 80% mildly impaired renal function). Review of treatment-emergent adverse events occurring at an incidence of at least 5% by renal function category indicated that with the exception of hypoglycemia, the adverse event profile of exenatide, including the profile of gastrointestinal adverse events, was not affected by renal function status. Hypoglycemia occurred at a higher incidence in exenatide-treated subjects with mild renal impairment (31%) than in exenatide-treated subjects with normal renal function (18%), and in 3 of 5 exenatide-treated subjects with moderate renal impairment.

7.4.2.4 Explorations for drug-disease interactions

The drug is used for the treatment of one disease, type 2 diabetes, and causes improved glycemic control.

7.4.2.5 Explorations for drug-drug interactions

Given that exenatide is primarily eliminated by the kidneys, it is not expected to have metabolism-based interactions with concomitantly-administered oral medications. However, because it slows gastric emptying, exenatide has the potential to alter the absorption of orally administered drugs. In Study 2993-121, more fully described in Module 2, Section 2.7.2, the greatest effect of exenatide on absorption of orally administered acetaminophen was observed when the acetaminophen was administered 1-2 h after exenatide administration. The effect on absorption tended to be diminished by 4 hours. There were no changes in the acetaminophen pharmacokinetic profile when dosed 1 hour prior to exenatide administration. Based on these data, no dosage adjustment is recommended for any orally-administered concomitant drugs.

However, the timing of exenatide dosing should be a consideration in patients receiving oral medications that require rapid gastrointestinal absorption.

Pharmacokinetic studies were also performed to assess the potential for drug-drug interactions between exenatide and each of the following: digoxin, lovastatin, lisinopril. As anticipated from the results of the acetaminophen marker evaluations, exenatide administered concomitantly at the maximum intended therapeutic dose of 10 µg with oral digoxin (Study H8O-FW-GWAF), lovastatin (Study H8O-EW-GWAG), or lisinopril (Study H8O-EW-GWAE), produced changes in their pharmacokinetic profile that were consistent with slowing of gastric emptying (a lower C_{max} and delayed T_{max} in the presence of exenatide). In each case, concomitant administration of exenatide was generally well-tolerated with the most frequent adverse event being mild to moderate gastrointestinal side-effects that appeared to dissipate over the course of the study. A brief summary of the results of each of these studies is provided below. Based on the results of these studies, no dosage adjustment is recommended for any of the drugs specifically evaluated.

Digoxin (Study H8O-EW-GWAF)

In healthy volunteers, co-administration of repeated doses of exenatide (10 µg BID) decreased the C_{max} of oral digoxin (0.25 mg QD) by 17% and delayed the T_{max} by approximately 2.5 h; however, the overall steady-state pharmacokinetic exposure (AUC) was not changed.

Lovastatin (Study H8O-FW-GWAG)

Concomitant administration of a single dose of lovastatin (40 mg) after SC administration of exenatide (10 µg BID) in healthy volunteers decreased lovastatin AUC and C_{max} by approximately 40% and 28%, respectively. The T_{max} of lovastatin was delayed about 4 h. Additional information on the concomitant use of HMG-CoA reductase inhibitors in the long-term trials is provided in ISS, 5.3.5.3.1, Section 6.3.

Lisinopril (Study H8O-EW-GWAE)

Alterations in the rate of absorption of lisinopril could potentially alter its hemodynamic response; thus justifying a study of their interaction. In nondiabetic patients with mild to moderate hypertension stabilized on lisinopril (5 to 20 mg/day), exenatide (10 µg BID) did not alter steady state C_{max} or AUC of lisinopril. Lisinopril steady-state T_{max} was delayed by 2 h. There were no changes in 24-hour mean systolic and diastolic blood pressure. Thus, the results of this study indicate that there is no significant pharmacodynamic or pharmacokinetic interaction between lisinopril and exenatide.

Clinical efficacy and safety studies, including the long-term, controlled and uncontrolled studies, have been conducted with exenatide at dosages of 5 µg BID or 10 µg BID added to maximally effective doses of oral antidiabetic agents: metformin (Studies 2993-112, 2993-112E, and 2993-117), sulfonylureas (Studies 2993-113, 2993-113E, and 2993-117), or the combination of metformin and sulfonylureas (Studies 2993-115, 2993-115E, and 2993-117). Of these studies, 2993-112, 2993-113, and 2993-115 provide the best opportunity to evaluate potential drug-drug interactions in controlled clinical trial setting. The protocols for these studies were similar with regard to criteria for use of other concomitant medications and required that subjects not take antidiabetic agents other than those stipulated by the study protocol.

Medications for the treatment of high blood pressure were to have been stable with respect to treatment regimen, and blood pressure must have been adequately controlled for 4 weeks prior to screening. No changes to the regimen of lipid-lowering agents were allowed within 6 weeks of screening.

The concomitant medications include all medications used on or after the date of the first randomized dose and include prior medications that continued past the first randomized dose. The most frequently used concomitant medications were approximately evenly distributed among treatment groups. As expected based on the study designs, the two most frequently used classes of drugs were sulfonylureas and metformin. The next most frequent medications classes were ACE inhibitors, HMG-CoA reductase inhibitors, platelet aggregation inhibitors excluding heparin, and propionic acid derivatives. Of the HMG-CoA reductase inhibitors, the most frequently used was atorvastatin, followed by simvastatin, pravastatin, and lovastatin.

When exenatide was used in combination with metformin, the incidence of hypoglycemia was 5% and a 5% incidence of hypoglycemia was also reported with placebo in combination with metformin. In contrast, when exenatide was added to sulfonylurea therapy or to the combination of sulfonylurea and metformin, the incidence of hypoglycemia increased to approximately 25%. In Study 2993-113, the incidence in both exenatide dose groups combined was 25% and the incidence in the placebo (sulfonylurea alone) group was 3%. In Study 2993-115, the incidence in both exenatide dose groups combined was 23% and the incidence in the placebo (metformin plus sulfonylurea) group was 13%. Based on these findings, healthcare providers should be mindful of the concomitant SFU therapy when introducing exenatide to a patient's treatment regimen. Whenever hypoglycemia occurs in patients treated with exenatide and a SFU, a reduction in SFU dose should be considered.

Exenatide did not act synergistically with metformin to increase the incidence of nausea and/or vomiting with metformin alone. The incidence of nausea was relatively constant, approximately 40-45%, among exenatide-treated subjects in the long-term, controlled studies regardless of whether the drug was added to metformin (exenatide, 41%; placebo, 23%), sulfonylurea

(exenatide 45%; placebo 7%), or the combination of metformin and sulfonylurea (exenatide 44%; placebo, 21%). Similarly, the incidence of vomiting was relatively constant, approximately 11-14%, among exenatide-treated subjects in the long-term, controlled studies regardless of whether the drug was added to metformin (exenatide, 11%; placebo, 4%), sulfonylurea (exenatide 11%; placebo 2%), or the combination of metformin and sulfonylurea (exenatide 14%; placebo, 4%).

As described above for hypoglycemia, when exenatide was added to sulfonylurea therapy or to the combination of sulfonylurea and metformin, the incidence rates of feeling jittery and of dizziness, common symptoms of hypoglycemia, were also increased. In Study 2993-112, in which exenatide was added to metformin and in which subjects were prohibited from using sulfonylureas, the incidence of feeling jittery in both exenatide dose groups combined was 3% and the incidence in the placebo (metformin alone) group was 1%. In this same study, the incidence of dizziness in both exenatide dose groups combined was 7% and the incidence in the placebo (metformin alone) group was 6%. In contrast, in Study 2993-113, the incidence of feeling jittery in both exenatide dose groups combined was 13% and the incidence in the placebo (sulfonylurea alone) group was 2%. The incidence of dizziness in this study in both exenatide dose groups combined was 15% and the incidence in the placebo (sulfonylurea alone) group was 7%. In Study 2993-115, the incidence of feeling jittery in both exenatide dose groups combined was 10% and the incidence in the placebo (metformin plus sulfonylurea) group was 7%. Dizziness in this study was reported at an incidence rate in both exenatide dose groups combined of 6% and at the same rate in the placebo (metformin plus sulfonylurea) group. These observations may be attributable to the manner in which investigators were instructed to capture hypoglycemic events versus individual symptoms. When subjects experienced symptoms consistent with hypoglycemia, e.g., feeling jittery, dizziness, etc., but their glucose concentrations were greater than 60 mg/dL, investigators were instructed to record the symptoms themselves as adverse events but not to record hypoglycemia as an adverse event.

For purposes of detecting potentially clinically important interactions between exenatide and the most frequently used concomitant medications (other than sulfonylureas and metformin), there appeared to be an increase in the incidence of some treatment-emergent adverse events, particularly nausea, vomiting, and diarrhea, in subjects taking exenatide concomitantly with H₂-receptor antagonists or proton pump inhibitors. However, H₂-receptor antagonists and proton pump inhibitors were recorded as concomitant medications if they were prescribed on or after the date of the first randomized dose, e.g., to treat the gastrointestinal effects of study drug, as well as if they were being used prior to randomization and continued past the first randomized dose. Therefore, to better assess whether there might be a clinically based drug-drug interaction between either of these classes of drugs and exenatide, the incidence rates (and 95% CIs) of nausea, vomiting, and diarrhea only in subjects who were on the concomitant medication of

interest prior to randomization and continued on the particular medication past the first randomized dose of study drug were determined and contrasted graphically with the incidence rates (and 95% CIs) of these same events in subjects **not taking** the corresponding concomitant medication. Based on an examination of these displays (Figure 8 and Figure 9), there did not appear to be evidence for a drug-drug interaction.

Within the long-term, controlled and uncontrolled studies, 3 subjects (2993-112-077-005, 2993-115-105-011 and 2993-115-112-014) who were using a concomitant HMG-CoA Reductase Inhibitor along with exenatide developed individual transaminase elevations >10x ULN. These cases do not likely reflect exenatide/HMG-CoA Reductase Inhibitor interactions. In the long-term, controlled studies, an HMG-CoA Reductase Inhibitor was concurrently used in 353 (37%) subjects receiving exenatide and in 172 (36%) subjects receiving placebo. The percentages of subjects in these long-term, controlled studies with a potentially clinically important (PCI) transaminase (ALT, AST, GGT) value (>3x ULN), alkaline phosphatase value (>300 U/L) or total bilirubin value (>2 mg/dL) were low and comparable between the exenatide and placebo groups; with PCI values for ALT being recorded in 0.6% of subjects in both the exenatide and placebo groups and PCI values for AST being recorded in 0.3% of exenatide treated subjects and in none of the placebo-treated subjects. In the uncontrolled studies, the incidence of PCI ALT and AST values were 0.5% and 1.0%, respectively. No subject in any of the Efficacy and Safety Studies had both a PCI total bilirubin value and a PCI transaminase value.

Based on information from the long-term, controlled clinical trials of exenatide, the concomitant use of exenatide and HMG-CoA reductase inhibitors was not associated with adverse changes in lipid profiles (HDL-cholesterol, LDL-cholesterol, total cholesterol, and triglycerides), indicating that there is no adverse interaction between exenatide and this class of compounds.

The concurrent use of exenatide with α -glucosidase inhibitors, meglitinides, thiazolidinediones, D-phenylalanine derivatives, or insulin has not been systematically studied.

7.4.3 Causality Determination

The investigator was to determine whether the event was best described as unrelated, probably not related/unlikely, possibly related, probably related or definitely related to the study medication. The following criteria were to be considered for this determination:

- A temporal relationship existed between the adverse event and the use of the study medication,
- Repeat administration of study medication resulted in reappearance or worsening of the adverse

event,

- Previous experience with the study medication resulted in a similar adverse event,
- The adverse event was not related to any concomitant disease, pre-existing condition, other drug therapy, or environmental factors.

Treatment-emergent adverse events were defined as those occurring on or after the date a

subject received the first dose of study medication. All adverse events were recoded relative to coding in the individual CSRs using the Medical Dictionary for Regulatory Activities (MedDRA™, version 6.1). Earlier MedDRA versions or WHOART had been used in the individual clinical study reports.

8 ADDITIONAL CLINICAL ISSUES

8.1 Dosing Regimen and Administration

Single-dose pharmacokinetic/pharmacodynamic studies (2993-102, 2993-104) showed little incremental benefit in postprandial glucose reduction at doses greater than 0.1 µg/kg, with doses exceeding 0.2 µg/kg resulting in increased gastrointestinal side effects. Simulations based on population pharmacokinetic/pharmacodynamic modeling of data from Studies 2993-102 through 2993-105 supported transition from weight-normalized dosing to a fixed-dosing paradigm. A dose of 10 µg was predicted to optimally balance maximal glucose reduction and acceptable gastrointestinal tolerability; a 5-µg dose was predicted to further reduce the probability of gastrointestinal adverse events while still eliciting an acceptable reduction in glucose concentrations for the majority of subjects.

One 28-day controlled study (2993-116) demonstrated that doses in the range 2.5 to 10.0 µg BID elicited dose-related reductions in HbA_{1c}. Also, data from another 28-day controlled study (2993-107) suggest no substantial difference in HbA_{1c} response between BID dosing and TID dosing (with the third dose given at bedtime). Data from a third 28-day controlled trial (2993-120) confirm that 10 µg BID is an effective dose in subjects with type 2 diabetes not using other antidiabetic agents. Another key finding from this study is that once-daily (QD) morning dosing with exenatide is less efficacious (10 µg QD) or less efficacious and not well tolerated (20 µg QD), compared with 10 µg BID dosing regimens. These pharmacodynamic and efficacy outcome findings, together with the exenatide exposure dose-proportionality strongly supported the choice of 5 and 10 µg BID in the long-term, controlled trials, in which dose-related effects on both fasting and postprandial plasma glucose and HbA_{1c} were also observed.

A dose-timing study (H8O-EW-GWAJ) showed that administration of exenatide at various times ranging from 1 hour before to 1 hour after meals resulted in significant reductions in postprandial

glucose exposure. However treatments administered 30 or 60 minutes after a meal were associated with transient, low circulating glucose concentrations and higher excursions in peak postprandial glucose concentrations. As premeal treatments exhibited a better postprandial glycemic control and were not associated with specific safety issues, dosing of exenatide is recommended to occur at any time within 60 minutes prior to a meal, but not after a meal. A forced dose-titration study (2993-108) demonstrated that gradually increasing the exenatide dose to achieve a therapeutic target dose mitigates gastrointestinal side effects as compared to direct administration of the final target dose to an otherwise drug-naive individual. Thus, escalation of the exenatide dose to 10 µg following an initial dosing period with 5 µg was expected to reduce the frequency and severity of gastrointestinal side effects; this expectation was borne out in the results of the long-term, controlled trials. The designs of some of the clinical pharmacology trials precluded the use of dose-escalation as that would have confounded the results. Therefore, the incidence of events such as nausea was higher than it might have been if dose-escalation had been employed.

Dosage Recommendation

- Exenatide therapy should be initiated at 5 mcg 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 mcg BID after 1 month of therapy. Each dose should be administered as a SC injection in the thigh, abdomen, or upper arm.
- When Exenatide is added to a regimen of metformin, a sulfonylurea, or both, the current dose of metformin or sulfonylurea can be continued upon initiation of Exenatide therapy. It is unlikely that the dose of metformin will require adjustment due to hypoglycemia when used with Exenatide. To reduce the risk of hypoglycemia associated with the use of a sulfonylurea, a reduction in the dose of sulfonylurea may be considered.
- Exenatide is a clear and colorless liquid and should not be used if particles appear or if the solution is cloudy or colored. Exenatide should not be used past the expiration date. No data are available on the safety or efficacy of intravenous or intramuscular injection of Exenatide.
- Two separate pens are available, one delivering 5-µg doses and the other 10-µg doses. The pens are distinguishable by their unique colors and labeling. These differences in presentation will help reduce errors in dosing. The current pen-injector device has also been designed to minimize the potential for mechanical risks.

8.2 Drug-Drug Interactions

The effect of Exenatide to delay gastric emptying may affect the rate of absorption of orally administered drugs. In a study using acetaminophen as a marker, the greatest effect on gastric emptying was observed at 1 to 2 h after Exenatide administration. Exenatide should be used with caution in patients receiving oral medications that require rapid gastrointestinal absorption.

1.1.1 Digoxin

Coadministration of repeated doses of Exenatide (10 mcg BID) decreased the C_{max} of oral digoxin (0.25 mg QD) by 17% and delayed the T_{max} by approximately 2.5 h; however, the overall steady state pharmacokinetic exposure (AUC) was not changed.

1.1.2 Lovastatin

Lovastatin AUC and C_{max} were decreased approximately 40% and 28%, respectively, and T_{max} was delayed about 4 h when Exenatide (10 mcg BID) was administered concomitantly with a single dose of lovastatin (40 mg) compared with lovastatin administered alone. In the 7 month controlled clinical trials of Exenatide, the concomitant use of Exenatide and HMG CoA reductase inhibitors was not associated with consistent changes in lipid profiles (HDL cholesterol, LDL cholesterol, total cholesterol, and triglycerides).

1.1.3 Lisinopril

In patients with mild to moderate hypertension stabilized on lisinopril (5 to 20 mg/day), Exenatide (10 mcg BID) did not alter steady state C_{max} or AUC of lisinopril. Lisinopril steady state T_{max} was delayed by 2 h. There were no changes in 24 h mean systolic and diastolic blood pressure.

8.3 Special Populations

8.3.1.1 Pharmacokinetics

8.3.1.1.1 Renal Insufficiency

In patients with mild to moderate renal impairment (creatinine clearance 30 to 80 mL/min), exenatide clearance was only mildly reduced; therefore, no dosage adjustment of Exenatide is required in subjects with mild to moderate renal impairment. However, in patients with end-stage renal disease receiving dialysis, mean exenatide clearance is reduced to 0.9 L/h (compared with 9.1 L/h in healthy subjects).

8.3.1.1.2 Hepatic Insufficiency

No pharmacokinetic study has been performed in patients with a diagnosis of acute or chronic hepatic insufficiency. Because exenatide is cleared primarily by the kidney, hepatic dysfunction is not expected to affect blood concentrations of exenatide (see Pharmacokinetics, Metabolism and Elimination).

8.3.1.1.3 Geriatric

Age does not influence the pharmacokinetic properties of exenatide. Therefore, dosage adjustment is not necessary for elderly patients.

8.3.1.1.4 *Pediatric*

Exenatide has not been studied in pediatric patients.

8.3.1.1.5 *Gender*

No clinically relevant differences in exenatide pharmacokinetics were observed between men and women. Therefore, dosage adjustment based on gender is not necessary.

8.3.1.1.6 *Race*

Population pharmacokinetic analysis of patients including Caucasian, Hispanic, Black, and other ethnic origins suggests that race has no significant influence on the pharmacokinetics of exenatide. Dosage adjustment based on ethnic origin is not necessary.

8.3.1.1.7 *Obesity*

No significant correlation was observed between body mass index (BMI) and exenatide pharmacokinetics. Therefore, dosage adjustment based on BMI is not necessary.

8.3.1.2 *Efficacy*

Efficacy in subgroups of the intent-to-treat population based on demographic (gender, age, and race) and the primary endpoint, i.e., change in HbA_{1c} for data pooled from the three long-term, controlled studies is summarized here.

8.3.1.2.1 *Gender and Age*

For the change in HbA_{1c} values from Baseline to Week 30, there were no apparent gender differences in the response of type 2 diabetes subjects to exenatide. There also were no clear trends indicating age-related differences in the response of type 2 diabetes subjects to exenatide.

8.3.1.2.2 *Race*

There was an apparent difference in the response of type 2 diabetes subjects to exenatide based on race, with Black subjects being less responsive to both 5 µg and 10 µg BID exenatide treatment than either Caucasian or Hispanic subjects. In addition, Hispanic subjects appeared to be equally responsive to the 5 µg and 10 µg BID dosage regimens, in contrast to the observed dose-response in other two race subgroups. The former finding is consistent with the observation that Black subjects seem to have a slightly greater exenatide clearance than those in other ethnic subgroups. This could at least in part account for the somewhat blunted efficacy response as observed in the long-term, controlled trials. However, there is substantial overlap in clinical response both across ethnicities and within each race group, indicating that no dose-adjustment based on race is warranted. The reason for an absence of a dose-response among Hispanic subjects is unknown and was entirely attributable to Study 2993-115, but also does not point to the need for specific dose adjustments simply on the basis of race. Dose-adjustments for all subjects should instead be based on individual subject glycemic outcome and tolerability to exenatide treatment.

8.3.1.2.3 *Baseline HbA_{1c}*

Statistically significant reductions from Baseline to Week 30 in HbA_{1c} were observed in both the 5 µg BID and 10 µg BID exenatide treatment groups for each predefined baseline HbA_{1c} strata subgroups (<9% and ≥9%). As expected, the magnitude of the treatment effect was greater for the subgroup with higher baseline HbA_{1c} concentrations compared with the subgroup with lower baseline HbA_{1c} concentrations. These findings are consistent with the larger reductions in HbA_{1c} for patients with higher pretreatment HbA_{1c} observed with many OADs.

8.3.1.2.4 *Body Weight*

Statistically significant reductions from Baseline to Week 30 in HbA_{1c} were observed in both the 5 µg BID and 10 µg BID exenatide treatment groups for each baseline BMI strata subgroup (<30 kg/m² versus ≥30 kg/m²). The magnitude of the treatment effect was greater for the subgroup with lower baseline BMI compared with the subgroup with higher baseline BMI. Similar trends were observed for the treatment effect sizes in each treatment group. Nevertheless, as for the other subgroups examined, there is substantial overlap in clinical response across BMI strata subgroups, indicating that no dose-adjustment based on BMI is warranted.

8.4 **Pediatrics**

The study of exenatide in pediatric subjects was deferred with the Agency concurrence until after the approval of exenatide for adults.

8.5 **Advisory Committee Meeting**

Not applicable. No advisory committee meeting was warranted.

8.6 **Literature Review**

An updated literature review as of March 24, 2005 of recent published literature has revealed no untoward findings that would point to any previously undetected safety issue. Overall, the medical literature supports and does not contradict the information contained in this review.

8.7 **Postmarketing Risk Management Plan**

Goals and Objectives

Based on what is currently known about exenatide treatment of patients with type 2 diabetes, the proposed exenatide Risk Management Plan will utilize both standard informational tools (i.e., professional and patient labeling and medical education) and pharmacovigilance activities

(monitoring the status of known and unknown risks that could change the safety profile or the benefit-risk balance).

The general risk management goals are as follows:

- Understand the known risks of exenatide treatment in the commercial environment.
- Understand whether there are risks in patient populations (comorbidities, medication use, age, etc.) different from those identified in the clinical program or occurring at a frequency too low to have been previously detected.
- Understand whether there are immune-related risks associated with exenatide treatment.
- Understand whether there are risks to pregnant women and fetuses who are exposed to exenatide.

These goals are served by the following specific objectives, measures of which appear below:

- Determine whether the incidence and types of adverse events observed in the postmarketing experience, including during the extended use of exenatide as monotherapy, are similar to those observed during clinical development.
- Identify potential safety signals in a timely manner.
- Extend the search for long-term consequences of anti-exenatide antibodies, including the exploration of drug rechallenge, by continued analyses of data obtained from ongoing, open-label, clinical studies.
- Determine whether any adverse events reported or observed in pregnant women or developing fetuses could be associated with the use of exenatide through a post-approval observational study.

Tools

The approach to pharmacovigilance for the known safety risks (expected adverse events) will be to employ general tools for data collection and signal detection. This section describes general risk management tools, as well as tools specific to each of the Risk Management Plan goals. The Plan begins with a foundation using the following tools: labeling, a call center, and standard safety surveillance.

A) Professional and Patient Labeling

The known safety risks of exenatide will be included in the labeling to make these risks

known to health care professionals and to patients treated with exenatide. These risks include the following:

(1) Gastrointestinal side-effects

Nausea, vomiting, diarrhea and dyspepsia were identified in clinical studies as gastrointestinal side-effects that have been experienced by patients treated with exenatide. The *USPI* addresses these side-effects, noting that adverse events, in general, were mild to moderate in intensity and did not result in discontinuation of therapy during clinical studies. The *USPI* also indicates that exenatide treatment should be initiated with the lower 5- μ g BID dose, with a possible increase to the 10- μ g BID dose after at least 1 month of therapy based on clinical benefit and whether the drug is tolerated. This two-step approach generally reduced gastrointestinal side-effects during clinical studies of exenatide. Other informational materials, including the *Information for the Patient*, explain the potential for gastrointestinal side-effects and encourage discussion between patients and their health care providers (HCPs).

(2) Hypoglycemia

The vast majority of hypoglycemic events in the exenatide clinical studies occurred using combination therapy with a sulfonylurea and were mild to moderate in intensity. In order to minimize the risk of hypoglycemia with exenatide treatment, the *USPI* highlights hypoglycemia as an adverse event and advises about the possible need to reduce the dose of concomitantly administered sulfonylurea. The *Information for the Patient* also specifically points out signs and symptoms of hypoglycemia and possible immediate treatment measures. Physicians are encouraged to discuss the possible symptoms and treatment with their patients. Launch education programs for HCPs and patients will include a description of the potential for hypoglycemic events and measures to minimize this risk.

(3) Dosing and Delivery Device Errors

Inappropriate dosing or device failures are recognized risks associated with any medication delivered via a device. Two separate pens are available, one delivering 5- μ g doses and the other 10- μ g doses. The pens are distinguishable by their unique colors and labeling. These differences in presentation will help reduce errors in dosing. The current pen-injector device has also been designed to minimize the potential for mechanical risks. To further reduce these risks, information regarding the appropriate use of the pen-injectors will be provided in the *USPI* and *Information for the Patient*, as well as in a *Pen User Manual* supplied with every exenatide pen-injector.

B) Call Center

HCPs can reach the Call Center (800-XXX-XXXX) to discuss questions regarding exenatide. Following product launch, unsolicited medical information questions, adverse events, or product complaints from HCPs or consumers will be handled by personnel with appropriate professional and product-specific training. These personnel will respond to callers verbally or in writing, as appropriate, after recording the contact details within a database. Adverse event reports will be transferred to the Amylin Global Product Safety Department for physician evaluation and follow-up by trained case managers. The Call Center phone number will be displayed on all information pieces and promotional materials.

C) Safety Surveillance Activities

Potential safety signals will be identified through the ongoing review of individual adverse event reports as well as aggregate surveillance methods.

Individual serious adverse events will be reported to the Agency on the appropriate time schedule, and Periodic Safety Updates will review the exenatide safety profile derived from the pharmacovigilance data and any post-approval clinical studies.

The Sponsor will collaborate on the use of surveillance data mining tools and/or customized surveillance reports to proactively identify and evaluate any potential safety signals or trends relative to patient exposure and epidemiological data available. Targeted surveillance terms are specific adverse event terms that have been identified for ongoing targeted follow-up of spontaneously reported adverse events. Specifically designed follow-up questionnaires would be used to collect high-quality medical data for scientific evaluation. The set of targeted surveillance terms for exenatide includes both general targeted surveillance terms (events requiring special attention regardless of the product involved) and some exenatide-specific terms. The latter were identified on the basis of preclinical and clinical trial experience with the product. Targeted surveillance terms may also be identified post-launch through spontaneous adverse event reports.

D) Drug Delivery Device Adverse Event/Product Complaint Surveillance

The sponsor has specific procedures in place to monitor drug delivery system-associated adverse events on an ongoing basis. These procedures search for clustering of adverse event reports that may be indicative of device over- or under-delivery or injection-site-related events, such as pain or bruising. Such procedures help coordinate evaluation of adverse event reports with product complaint data and may trigger a manufacturing investigation or device design review.

E) Tools Specific to Immunogenicity

Clinical Studies 2993-117 and 2993-119 are currently active for the long-term evaluation of subjects treated with exenatide. Both of these studies will provide additional data regarding characteristics of the anti-exenatide antibody response and the safety profile of exenatide over an extended timeframe.

Adverse event information will be collected in an ongoing manner per the protocols. Laboratory data obtained at regular follow-up visits will include HbA_{1c} levels and antiexenatide antibody titers. This will provide additional data regarding the durability of the efficacy of exenatide treatment, characteristics of the anti-exenatide antibody response, and the safety profile of exenatide over a multi-year period.

With approximately 350 patients expected to complete a 24-month period of exenatide treatment, the likelihood of detecting an adverse event that occurs at a rate of 1 per 1000 patients is estimated to be 29.5% based on the binomial distribution. The antibody data being collected will significantly improve the ability to detect an immunogenicity-related adverse event due to exenatide. Depending on the outcome of the data analysis, this study may be terminated at the time of product launch.

F) Tools Specific to Pregnancy

There are several factors that point to the need to learn more about exenatide treatment in the setting of pregnancy:

- Pregnancy was an exclusion criterion in the exenatide clinical studies.
- Exenatide is the first in a new class of drugs, so there is no other experience with this type of agent during pregnancy.
- Exenatide is anticipated to be administered to a large number of women of childbearing potential.
- At exposures far in excess of those recommended for humans (>36- to >200-fold), exenatide has been shown to cause diminished fetal growth and development in animal reproductive toxicology studies.

To address this need, the Sponsor will implement a pregnancy observational study to determine if there is any exenatide treatment-related risk to pregnant women or their developing fetuses. Initially, the overall objective of this observational study would be safety surveillance. Although many specific details of the observational study are yet to be determined, it is anticipated that the conduct of this study would be managed by a contract research organization. Major medical centers seeing large numbers of type 2 diabetic and/or obstetrical patients would be targeted for participation in this study.

The hypothesis being tested is that the difference in proportions of spontaneous abortions and pregnancy outcomes other than live birth, between pregnant women with type 2 diabetes who are treated with exenatide and those who are not treated with exenatide, would not be greater than 15% (80% power, alpha = 0.05). This assumes that the incidence of such adverse pregnancies is 40% in case-matched controls (based on the published literature) and that there would be only a small number of patients that can be recruited into this study given that exenatide is a new agent lacking fully-developed safety information for pregnancy. As information about outcomes accumulates, the objective may shift to encompass testing of one or more other hypotheses.

Based on the primary objective of safety surveillance of exenatide use during pregnancy, the plan for this study would be to enroll 150 pregnant women, who have previously received or are receiving exenatide, with a focus on obtaining delivery outcome data. A case-matched control group of 300 pregnant women with type 2 diabetes, who have not been exposed to exenatide, would be enrolled for comparison to assess potential safety signals. It is anticipated that the patients using exenatide in this observational study will be representative of pregnant women who use exenatide in the postlaunch environment. In addition, it is expected that the greatest exposure to exenatide in this study will occur in the first trimester of pregnancy, with some patients choosing an alternative antidiabetic therapy after learning of their pregnancies. Patients who become pregnant while taking exenatide and who discontinue this agent in favor of an alternate therapy would be allowed to enroll in the study. Exposure information for all concomitant medications would be collected to aid in data analysis.

All enrolled patients would be followed until the pregnancy outcome is known. If initial analyses of data suggest that one or more specific hypotheses should be tested, enrollment may be extended beyond the numbers indicated above in order to meet the new needs.

Evaluation

Process metrics is the way in which implementation of the exenatide Risk Management Plan would be documented. Table 31 describes process metrics for the Risk Management Plan's foundational and objective-specific tools.

Table 31: Process Metrics

Tool	Metrics	Documentation of Compliance With Target
Labeling	Wording on gastrointestinal side-effects, hypoglycemia, the pen-injector device, immunogenicity, and the lack of full study	Final <i>USPI</i>

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	during pregnancy will be included in the <i>USPI</i> .	
Call Center	At launch, Call Center personnel will have been trained on product information for exenatide, including targeted surveillance terms. At launch, a toll-free telephone number will be operational. This number will be provided on all product labeling.	Training documentation (maintained by Call Center) Summary report demonstrating that toll-free numbers are operational
Safety surveillance activities	Individual serious adverse reports, periodic safety updates, and aggregate safety data reports will be submitted in compliance with regulatory obligations.	Regulatory submissions
Studies 2993-117 and 2993-119	Clinical Study Reports 2993-117 and 2993-119 completed.	Safety update reports on a periodic basis and Clinical Study Reports 2993-117 and 2993-119
Pregnancy observational study	Clinical Study Report completed within 6 months of the last patient visit.	Clinical Study Report

Follow-up

There will be a review of the Risk Management Plan activities in the annual safety report. Outcomes of this review will drive consideration of whether changes to the Risk Management Plan are needed for the following year. The Agency will be notified of any change through an amendment to the Plan.

8.8 Other Relevant Materials

9 OVERALL ASSESSMENT

The pathogenesis of type 2 diabetes is characterized by peripheral insulin resistance and progressive failure of pancreatic β -cell function, ultimately resulting in deficient insulin secretion. Furthermore, an excessive glucagon secretion and an impaired incretin response to meals contribute to the metabolic derangement of the disease. Control of circulating glucose levels is rarely optimal, and many currently available therapies also have unfavorable side effects and restrictions, limiting the extent of their use. This emphasizes the need for novel antidiabetic agents.

Exenatide is the first drug candidate in the new class of agents known as incretin mimetics. The cumulative efficacy and safety experience of exenatide was gained through 27 completed

clinical trials and over 1800 exenatide-treated subjects. Phase 3 trials (2993-112, 2993-113, and 2993-115), each conducted over a long-term (7-month) period, account for over half of the subjects within the New Drug Application database.

Data from the clinical development program show that patients with type 2 diabetes who receive treatment with exenatide BID subcutaneously (SC) may experience sustained reductions in HbA_{1c}, lower fasting and postprandial plasma glucose concentrations, improvements in pancreatic beta-cell function, and reduced body weight.

Exenatide treatment may increase the risk of gastrointestinal side-effects (including nausea and vomiting). When exenatide is used together with a sulfonylurea, it may increase the incidence of hypoglycemia. These reported side-effects have generally been tolerated and have been more prevalent during treatment initiation. Forty-four percent of patients treated with exenatide develop anti-exenatide antibodies, but the number of antibody-positive subjects and their titer generally decrease as the length of exposure increases. Patients who developed anti-exenatide antibodies had similar rates and types of adverse events as those with no anti-exenatide antibodies. The presence of anti-exenatide antibodies at a high antibody titer may be associated with failure to further improve glycemic control.

9.1 Conclusions

Overall, this NDA substantiates the sponsor's claims of exenatide

1. mechanism of action,
2. rationale for clinical development
3. supportive clinical pharmacology data
4. proposed dosage and administration
5. effectiveness in type 2 diabetes when used as an add-on to sulfonylurea and/or metformin
6. safety in type 2 diabetes when used as an add-on to sulfonylurea and/or metformin

However, the evidence is not adequate to support the sponsor's claim of exenatide method of use and effectiveness when used as a monotherapy in type 2 diabetes.

Exenatide use has been evaluated in subjects with type 2 diabetes in combination with oral antidiabetic agents. Many patients treated with exenatide at the recommended dosages in long-term, controlled studies experienced a robust and durable improvement in glycemic control and achieved desired glycemic targets as assessed by HbA_{1c} values $\leq 7\%$. This improvement was at the expense of nausea (for roughly half of treated patients) and an increased risk of hypoglycemia if the patient was also using a sulfonylurea.

The combined benefit and safety profile supports a view that the benefits of using exenatide in treating patients with type 2 diabetes outweigh the risks. The benefits that exenatide provides address unmet needs within the type 2 diabetes population, and the unique combination of benefits makes exenatide an attractive treatment option.

9.2 Recommendation on Regulatory Action

This Reviewer recommends the approval of exenatide as an adjunctive therapy to metformin, a sulfonylurea, or a combination of metformin and a sulfonylurea when they fail to achieve adequate glycemic control.

The one short-term controlled trial #2993-120 to support the use of exenatide as a monotherapy does not suffice as a proof of efficacy. This Reviewer recommends an action of "approvable" of exenatide as a monotherapy for the treatment of type 2 diabetes, pending evidence from at least one adequately controlled Phase III trial to support its use as a monotherapy in type 2 diabetes.

9.3 Recommendation on Postmarketing Actions

9.3.1 Risk Management Activity

The Risk Management Plan proposed by the Sponsor is acceptable to this reviewer.

Identified Risks

Exenatide treatment is associated with gastrointestinal side-effects (nausea in 44%, vomiting in 13%, Diarrhea in 13% and dyspepsia in 6% of the treated subjects). Exenatide delays gastric emptying and may delay or decrease the absorption of concomitant drugs administered orally. When exenatide is used together with a sulfonylurea (SFU), it may increase the risk of SFU-induced hypoglycemia. Exenatide therapy is not associated with increased risk of hypoglycemia when used alone or in combination with only metformin. Forty-four percent of patients treated with exenatide develop anti-exenatide antibodies, but both the number of antibody-positive subjects and the titers of the antibodies in individual patients generally decrease as the length of exposure increases. Patients who developed anti-exenatide antibodies had similar rates and types of adverse events as those with no anti-exenatide antibodies. However, for the 14% of anti-exenatide-positive subjects (6% of the total exenatide-treated subjects) with higher antibody titers (1/625 to 1/15,625) still present at Week 30, glycemic responses were diminished for about half of the subjects while the rest had no apparent decrease in efficacy. Patients with diminished glycemic response to exenatide may therefore be patients with high anti-exenatide antibody titers.

Proposed Risk Management Activity

In addition to dealing with potential risks by using the appropriate language in the US Package Insert (USPI) and in the content of medical education instructional programs, a three-component risk management program will be established with:

- (1) Pharmacovigilance and signal detection to monitor and assess the post-launch safety profile of exenatide, with particular attention to adverse events where hypoglycemia is suspected, to certain disease states, and to concomitant medication use.
- (2) Clinical studies (currently ongoing), to evaluate whether there are long-term consequences related to the presence of anti-exenatide antibodies in treated patients.
- (3) An observational study of pregnancy, to monitor whether any safety issues emerge from exposure of pregnant women and developing fetuses to exenatide.

9.3.2 Required Phase 4 Commitments

All applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred. The sponsor requests a waiver for pediatric studies in patients' ages 0 to 11 years and a deferral of pediatric studies in patients' ages 12 to 16 years for exenatide to improve glycemic control in patients with type 2 diabetes mellitus.

This Reviewer agrees that a waiver is justified for pediatric studies in patients' ages 0 to 11 years for exenatide to improve glycemic control in patients with type 2 diabetes mellitus. Pediatric studies in patients' ages 12 to 16 years for exenatide to improve glycemic control in patients with type 2 diabetes mellitus who have not achieved adequate glycemic control on metformin, a sulfonylurea, or a combination of metformin and a sulfonylurea are being deferred under 21 CFR 314.55 until December 31, 2007. In the interim, the applicant should submit its pediatric drug development plans within 120 days from the date of drug approval.

9.3.3 Other Phase 4 Requests

A single dose human in vivo drug interaction study between exenatide and a combination oral contraceptive (e.g., ethinyl estradiol plus norethindrone) in which the effect of timing of the exenatide injection relative to administration of the oral contraceptive on the bioavailability of the components of the oral contraceptive is studied.

9.3.4 Recommended Trade Name

The Sponsor requests to assign the trade name BYETTA instead of BYETTA to Exenatide. The consult from the Division of Medication Errors and Technical Support (DMETS) does not

recommend the use of the proprietary name BYETTA, because it may be confused for Diabeta tab, Viagra tab, Zyrtec tab, Zebeta tab. This is not deemed a concern sufficient to preclude use of the name BYETTA. BYETTA is an injectable drug; all others are oral tablets. The patient should know if he or she was prescribed an injection or not, and furthermore if he or she had, training on self-injection would have been given. Thus, given the fact that BYETTA would be the only one to be administered by injection, there is a very low likelihood of such medication error, if it happens, not being caught and corrected. Therefore, this reviewer recommends the approval of the proprietary name BYETTA to Exenatide instead of Byetta.

A) Labeling Review

The package insert of exenatide has been thoroughly reviewed. Comments were forwarded to the Sponsor to which a complete response was received and accepted except for the items which were resolved over a telephone conference on April 19, 2005.

B) Comments to Applicant

None.

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