

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**022200Orig1s000**

**STATISTICAL REVIEW(S)**



U.S. Department of Health and Human Services  
Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Translational Sciences  
Office of Biostatistics

# STATISTICAL REVIEW AND EVALUATION

## CLINICAL STUDIES

**NDA/Serial Number:** 022200/0

**Drug Name:** Bydureon™ (Exenatide once-weekly) injectable suspension

**Indication(s):** Treatment of type 2 diabetes mellitus

**Applicant:** Amylin Pharmaceuticals, Inc.

**Date(s):** Stamp date 7/18/11  
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Response from Amylin to Complete Response Letter from DMEP dated October 18, 2010

**Review Priority:** Standard

**Date of this review:** 9/6/11

**Biometrics Division:** Division of Biometrics 2

**Statistical Reviewer:** Janice Derr, Ph.D.

**Concurring Reviewers:** J. Todd Sahlroot, Team Leader and Deputy Division Director  
Thomas Permutt, Division Director

**Medical Division:** Division of Metabolism and Endocrinology Products

**Clinical Team:** Valerie Pratt, M.D., Medical Reviewer  
Ilan Irony, M.D., Medical Team Leader  
Mary H. Parks, M.D., Division Director

**Project Manager:** Pooja Daria, Pharm.D.

**Keywords:** clinical studies, NDA review

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## 1. EXECUTIVE SUMMARY

### 1.1 Conclusions and Recommendations

**Efficacy Conclusions:** The efficacy of Exenatide QW (2 mg SC injection once weekly) was supported by a non-inferiority comparison to Byetta® (Exenatide 10 mcg SC injection twice a day) for change in HbA1c at week 24 compared to baseline (TABLE 1). The results from study BCB108 support the conclusion that the efficacy of Exenatide QW is superior to Byetta with respect to the HbA1c endpoint at week 24. These results are fairly similar to those from Study 105, which had a similar design and was reviewed as part of the original submission of this NDA (see the statistical review of NDA 022200/0 dated 1/4/10). The key difference between the studies is that Study BCB108 was conducted with the commercial source of Exenatide QW and not the investigational source, which was used in Study 105. The effectiveness of the commercial source was an issue of concern, and was one of the issues in the Division's Complete Response to the original NDA submission. The results from Study BCB108 support the efficacy of the commercial source of Exenatide QW.

TABLE 1 Study BCB108 and Study 105; Primary HbA1c endpoint

	N	Baseline mean HbA1c ± SE	Adjusted mean change from baseline at Week 24 ± SE <sup>1</sup>	Exenatide QW – Byetta Difference in adjusted mean change (95% CI) <sup>1</sup>	P-value
<b>Study BCB108: HbA1c at week 24 as a change from baseline</b>					
All subjects (ITT/LOCF)					
Exenatide QW	123	8.5 ± 0.1	-1.6 ± 0.1	-0.7 (-0.9, -0.4)	<0.001
Byetta	129	8.4 ± 0.1	-0.9 ± 0.1		
<b>Study 105: HbA1c at week 30 as a change from baseline</b>					
All subjects (ITT/LOCF)					
Exenatide LAR	148	8.3 ± 0.1	-1.9 ± 0.1	-0.3 (-0.5, -0.1)	0.002
Byetta	147	8.3 ± 0.1	-1.5 ± 0.1		

Sources: Study BCB108 report, Table 7; Study 105 report, Table 8

The average HbA1c response in the two arms was fairly similar across gender, age (< 65, ≥65 years), and race (Caucasian, Hispanic) subgroups. In addition, the average HbA1c response in the two arms was fairly similar by baseline HbA1c (< 9.0% and ≥ 9.0%) and sulfonylurea use at screening (yes, no). These factors were used to stratify the randomization. The subgroup of subjects with baseline BMI < 30 kg/m<sup>2</sup> had a larger mean difference between Exenatide QW and Byetta in the HbA1c response at week 24 compared to the subgroup of subjects with baseline BMI ≥ 30 kg/m<sup>2</sup> (p=0.025). These findings are fairly similar to those from Study 105. The treatment interaction with baseline BMI was not significant in Study 105, but the means of the two subgroups were in approximately the same relationship.

Results from three key secondary endpoints supported the superior efficacy of Exenatide QW compared to Byetta: (1) the proportion of subjects achieving HbA1c target value of < 7%; (2) the change from baseline in fasting plasma glucose (FPG) concentration; and (3) the proportion of subjects achieving a FPG concentration target value of  $\leq 126$  mg/dL, all evaluated at week 24. In addition, both groups showed a small average weight loss at week 24 compared to baseline. The Exenatide QW arm had a somewhat greater weight loss than the Byetta arm by about 1 kg.

**Recommendations:** This review includes recommendations for Part 14 (Clinical Studies) of the labeling text. See Part 5.3 of this review for these recommendations.

## 1.2 Overview / Background

This submission from the applicant to NDA 022200/0 is in response to a Complete Response letter issued by the Division of Metabolism and Endocrinology Products (DMEP) on October 18, 2010. This statistical review covers the efficacy and safety data from Study BCB108, in which Exenatide 2 mg SC once weekly (QW; manufactured by Amylin) was compared to Byetta 5 mcg SC twice daily for 4 weeks followed by Byetta 10 mcg SC BID for 20 weeks. Eligible subjects had type 2 diabetes, and had been treated with diet and exercise alone or with a stable regimen of metformin, sulfonylurea (SU), thiazolidinediones or a combination of up to two of these oral antidiabetic medications for a minimum of two months prior to screening. The study had 252 subjects in the intention-to-treat data base.

The submission of information from Study BCB108 is in response to a concern from the review of Study 2993 LAR-105<sup>1</sup>. This concern involved the source of manufactured Exenatide QW for the 30-week assessment period of Study 105. Study 105 used an investigational source of Exenatide QW that was different from the commercial source. Because the bioequivalence of the two sources had not been established at the outset of Study 105, a sub-study was conducted, comparing the two sources, in the weeks after the primary endpoint had been determined. The commercial source resulted in a less favorable average change in HbA1c by 0.2 (95% confidence interval 0.0, 0.3), compared to the investigational source. Reducing the average effect of Exenatide QW on HbA1c by 0.3 (using the upper CI bound) would not affect the non-inferiority conclusion from Study 105. This is because the effect of Exenatide QW on HbA1c compared to Byetta was -0.3 (05% CI -0.5, -0.1) in the direction of superiority. However, the mean baseline for the start of the sub-study was low (6.8) compared to the mean baseline at the start of the main study (8.3). For this reason, the Division remained concerned about how the change in source would affect a target population with a higher baseline HbA1c.

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<sup>1</sup> I will use the term "Study 105" to refer to Study 2993 LAR-105. For the statistical review of Study 105, see NDA 022200/0 dated 1/5/10.

Study BCB108 was conducted with the commercial source of Exenatide QW. For this reason, the Division requested that the results of this study be submitted for review as part of the Complete Response letter dated October 18, 2010.

## 2. INTRODUCTION

### 2.1 Overview

Exenatide extended release formulation is an extension of the already-approved Exenatide immediate release formulation (Byetta®). Byetta injection is approved in the United States as monotherapy or as adjunctive therapy for adult subjects with type 2 diabetes mellitus treated with metformin, a sulfonylurea, a thiazolidinedione, a combination of metformin and a sulfonylurea, or a combination of metformin and a thiazolidinedione, who have not achieved adequate glycemic control (approved under NDA 021773). Exenatide is an incretin mimetic agent that stimulates glucose-dependent insulin secretion. Endogenous incretins, such as glucagon-like peptide-1 (GLP-1) enhance glucose-dependent insulin secretion and exhibit other antihyperglycemic actions following their release into circulation from the gut in response to food intake. Byetta is administered within the 60-minute period before the morning and evening meals and primarily exerts its pharmacodynamic effects on glucose concentrations during the postprandial period of those meals. Bydureon is the extended release formulation of Exenatide, described in this submission, and is a once weekly injection.<sup>2</sup>

### 2.2 Data Sources

Submissions and data that I reviewed for this NDA are summarized in TABLE 2.

TABLE 2 Data sources for this review of NDA 022200 Bydureon (Exenatide QW)

Number	Date	Description
\\cdesub1\evsprod\IND 067092\		
0139	1/9/2009	Amendment 1 of the protocol for Study BCB108 which revised the design from a comparison between the commercial and investigational sources of Exenatide QW to a comparison between Exenatide QW (commercial source) and Byetta.
0263	5/20/2011	Study report for Study BCB108 and associated data files
\\cdesub1\evsprod\NDA 022200\		
0034	7/28/11	Draft package insert Study report for Study BCB108 and associated data files (repeated from the IND submission)
0043	8/15/11	Response to FDA information request concerning subjects who withdrew due to loss of glucose control (among other topics)

<sup>2</sup> The source of this paragraph is Section 2.2 Introduction (paraphrased) of NDA 022200/0

### 3. STATISTICAL EVALUATION

#### 3.1 Data and Analysis Quality

I did not have review concerns about data and analysis quality in the parts of the submission that I reviewed.

#### 3.2 Evaluation of Efficacy

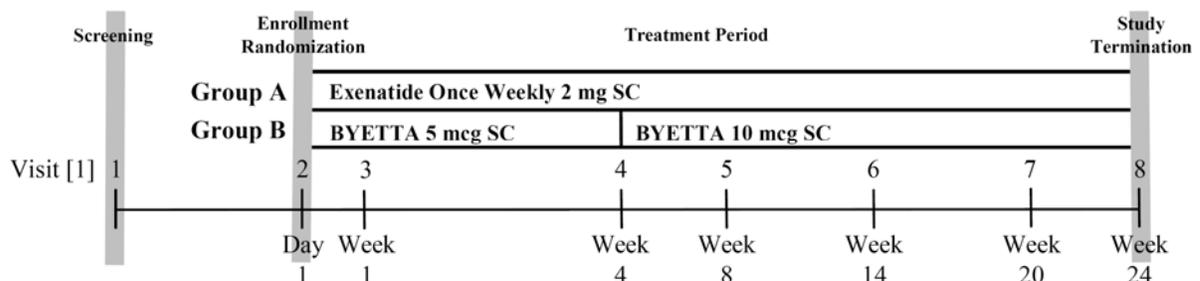
##### 3.2.1. Study design and endpoints

This review is a statistical evaluation of Study BCB108. Study BCB108 was designed as a non-inferiority comparison of Exenatide once weekly to Byetta twice daily. The study was multi-center, randomized and open label. Subjects randomized to the Exenatide arm received Exenatide 2 mg SC once weekly (QW). Subjects randomized to the Byetta arm received Byetta 5 mcg SC BID for 4 weeks followed by Byetta 10 mcg SC BID for 20 weeks for a total treatment period of 24 weeks. The study was conducted at 43 study sites in 254 subjects. All sites were in the U.S. The study was conducted from March 23 2009 (first subject dosed in the lead-in period) to October 27, 2009 (last subject’s week 52 visit).

Eligible subjects had type 2 diabetes, with a stable background therapy that could consist of metformin, a sulfonylurea (SU), a thiazolidinedione, or a combination of up to 2 of these oral antidiabetic medications and/or diet modification and exercise. Additional eligibility criteria included a screening HbA1c of 7.1% to 11.0% and body mass index of 25 – 45 kg/m<sup>2</sup>.

Subjects were randomized to in the proportion of 1:1 across treatment groups with additional stratification by screening HbA1c value (< 9.0% or ≥ 9.0%) and by whether or not a subject was taking concomitant SU agent at screening. The study design is depicted in FIGURE 1:

FIGURE 1 Design of Study BCB108



Source: Study BCB108 clinical report, Figure 1

The applicant noted that based on results from previous studies in the Exenatide once-weekly development program (including Study 105), there was no lead-in period prior to the first dose of Exenatide once weekly. Because the study was open-label, subjects, the study-site staff, the investigator, and the applicant were not blinded to the identity of the treatment assignments. However, the applicant noted that personnel remained blinded to efficacy endpoint data throughout the 24-week assessment period.

The applicant calculated the sample size for Study BCB108, approximately 250 subjects total to be randomized, with a 1:1 allocation to the Exenatide QW and Byetta arms, with the following assumptions and criteria:

- a standard deviation of the primary endpoint (change in HbA1c between week 30 and baseline) of 1.1, based on the clinical data from Study 105
- a non-inferiority margin of 0.4, based on input from the Division
- a greater reduction in HbA1c (by 0.1) for Exenatide QW than Byetta, based on previous clinical data, including the results from Study 105
- a two-tailed  $\alpha$  of 0.05
- at least 90% power

In my review of Study 105 (NDA 022200/0 dated 1/5/10), I showed that the margin of 0.4% was acceptable from the statistical perspective, based on the results from three placebo-controlled studies that are described in the original statistical review for Byetta. The Biometrics review team and the applicant agreed to the noninferiority margin of 0.4% (see the review of the statistical analysis plan submitted under IND 67092/0056 dated 6/15/07). A noninferiority margin of 0.3% or 0.4% is typically acceptable for HbA1c provided this is not greater than a “suitably conservative estimate of the magnitude of the treatment effect of the active control in previous placebo-controlled studies.”<sup>3</sup>

The primary efficacy endpoint was the change in HbA1c from baseline to week 24/study termination. Secondary endpoints included the following, all of which reference week 24/study termination and a change from baseline where appropriate:

- The proportion of subjects achieving HbA1c target value of <7%
- Change in fasting glucose concentration
- The proportion of subjects achieving a fasting plasma glucose concentration target value of  $\leq 126$  mg/dL
- The proportion of subjects achieving HbA1c target value of  $\leq 6.5\%$
- Change in body weight
- Change in systolic blood pressure and diastolic blood pressure
- Change in fasting lipid concentrations

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<sup>3</sup> See Part 5.G.1. of the February 2008 draft guidance, *Diabetes Mellitus: Developing Drugs and Therapeutic Biologics for Treatment and Prevention*.

The first three secondary endpoints listed above were identified as key endpoints, and Type I error associated with hypothesis testing was controlled with a multiple comparison procedure (see Part 3.2.3).

### 3.2.2. Subject disposition, demographic and baseline characteristics

Study BCB108 had approximately 80% retention at week 24 of the 254 subjects who were enrolled and randomized to a treatment group (TABLE 3). A somewhat larger percentage withdrew in the Byetta arm compared to the Exenatide QW arm. This appears to be due mainly to a larger percentage of subjects who withdrew consent in the Byetta arm (TABLE 3). The time course of study retention suggests that the difference between the two arms in the percentage of withdrawals is established fairly early in the study, by week 8 if not earlier (FIGURE 2). A low percentage in each arm (2-3%) withdrew due to a loss of glucose control.

The study protocol described the loss of glucose control as “Investigator believes it is in the subject’s best interest to terminate participation due to a meaningful deterioration in glycemic control.” In response to the Division’s inquiry about the 7 subjects who were withdrawn from the study due to loss of glucose control, the applicant responded (8/12/11) “At any time during the study, subjects were to be withdrawn if their blood glucose concentrations were unacceptable in the opinion of the investigator ... Rescue therapy upon discontinuation was not specified in the protocol and was left to the discretion of the investigator.”

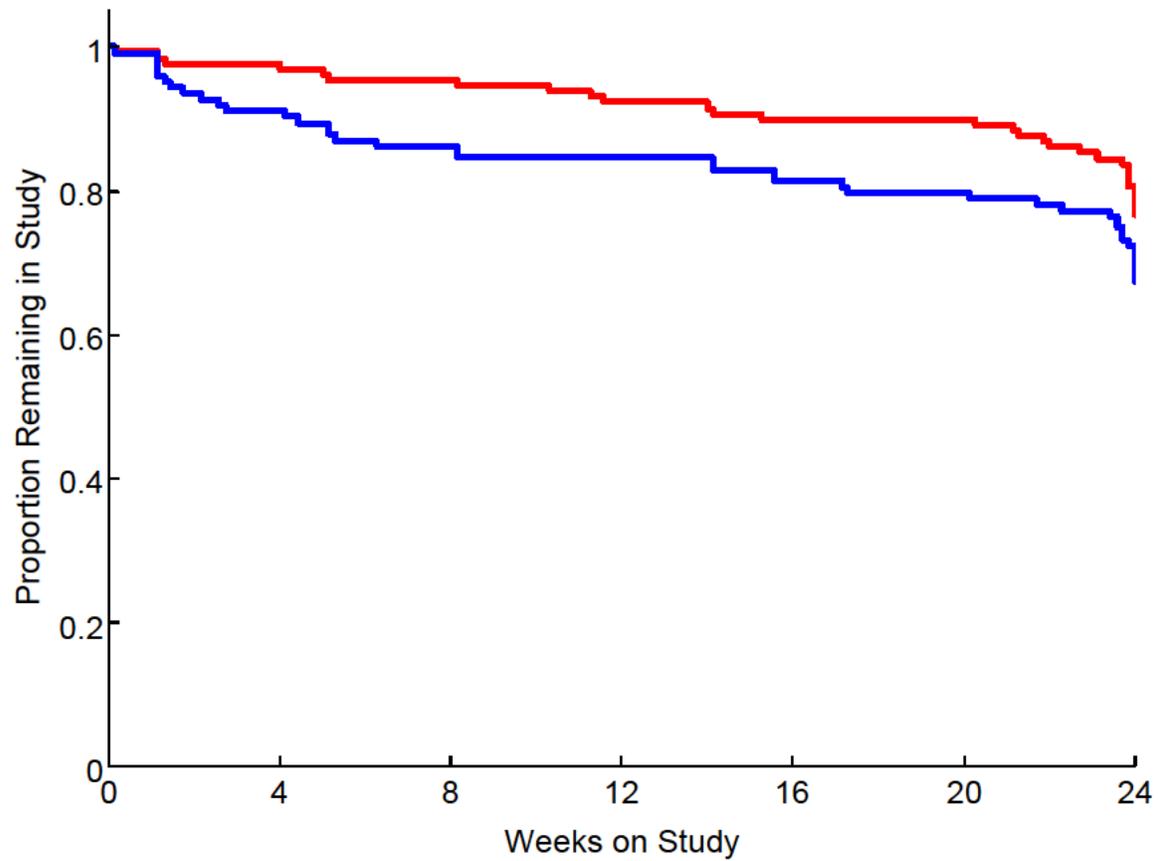
The enrolled population was fairly equally distributed between males and females (TABLE 4). The majority was white, and the next most common race/ethnicity reported was Hispanic. The average duration of diabetes was 7.0 years. Most of the subjects (75%) were being treated with metformin alone or in combination, and 27% were being treated with a sulfonylurea alone or in combination (TABLE 5).

TABLE 3 Study BCB108; Subject disposition by treatment

	Treatment		
	Byetta (n=125)	Exenatide QW (n=129)	All subjects (n=254)
Completed 24-week treatment period	95 (76.0%)	109 (84.5%)	204 (80.3%)
Withdrew during 24-week treatment period	30 (24.0%)	20 (15.5%)	50 (19.7%)
Loss of glucose control	4 (3.2%)	3 (2.3%)	7 (2.8%)
Withdrawal of consent	12 (9.6%)	6 (4.7%)	18 (7.1%)
Lost to follow-up	5 (4.0%)	5 (3.9%)	10 (3.9%)
Adverse event	6 (4.8%)	6 (4.7%)	12 (4.7%)
Investigator decision	2 (1.6%)	0 (0.0%)	2 (0.8%)
Protocol violation	1 (0.8%)	0 (0.0%)	1 (0.4%)
Administrative	0 (0.0%)	0 (0.0%)	0 (0.0%)

Source: Study BCB108 clinical report, Table 2

FIGURE 2 Study BCB108; Disposition of subjects



Treatment Arm:  
— Exenatide QW  
— Byetta BID

Source: Analysis by this reviewer

TABLE 4 Study BCB108; Demographic and baseline characteristics by treatment, ITT population

	Treatment		
	Byetta (n=123)	Exenatide QW (n=129)	All subjects (n=252)
Gender			
Male	68 (55.3%)	77 (59.7%)	145 (57.5%)
Female	55 (44.7%)	52 (40.3%)	107 (42.5%)
Age at Consent (years)			
Mean (SD)	55.2 (10.3)	56.1 (11.1)	55.7 (10.7)
Minimum, maximum	23, 79	23, 83	23, 83
≥65 years	22 (17.9%)	26 (20.2%)	48 (19.0%)
Race/Ethnicity			
Caucasian	68 (55.3)	81 (62.8%)	149 (59.1%)
Black	9 (7.3%)	6 (4.7%)	15 (6.0%)
Asian	5 (4.1%)	5 (3.9%)	10 (4.0%)
Hispanic	41 (33.3%)	37 (28.7%)	78 (31.0%)
Weight (kg)			
Mean (SD)	94.3 (18.9)	97.0 (20.7)	95.7 (19.8)
BMI (kg/m <sup>2</sup> )			
Mean (SD)	33.0 (5.3)	33.6 (5.5)	33.3 (5.4)
BMI < 30 kg/m <sup>2</sup>	45 (36.6%)	40 (31.0%)	85 (33.7%)
BMI ≥ 30 kg/m <sup>2</sup>	78 (63.4%)	89 (69.0%)	167 (66.3%)
HbA1c (%)			
Mean (SD)	8.4 (1.2)	8.5 (1.1)	8.4 (1.2)
HbA1c strata used in randomization <sup>1</sup>			
< 9.0%	88 (72.1%)	90 (70.3%)	178 (71.2%)
≥ 9.0%	34 (27.9%)	38 (29.7%)	72 (28.8%)
Sulfonylurea (SU) strata used in randomization			
SU used at screening	34 (27.6%)	49 (38.0%)	83 (32.9%)
SU not used at screening	89 (72.4%)	89 (62.0%)	178 (67.1%)
Fasting plasma glucose (mg/dL)			
Mean (SD)	168 (47)	173 (47)	171 (47)
Duration of diabetes at screening (yr)			
Mean (SD)	7.2 (5.4)	6.9 (5.3)	7.0 (5.3)
Renal function group at screening			
Normal	60 (48.8%)	65 (50.4%)	125 (49.6%)
Mild	55 (44.7%)	55 (42.6%)	110 (43.7%)
Moderate	10 (8.1%)	8 (6.2%)	18 (7.1%)
Severe	0 (0.0%)	1 (0.1%)	1 (0.0%)

Note: <sup>1</sup> The applicant has noted that HbA1c values from 2 ITT subjects were not reported because screening, baseline and postbaseline HbA1c were subsequently deleted because of invalid chromatograms

Source: Study BCB108 clinical report, Table 4, and additional analysis by this reviewer

TABLE 5 Study BCB108; Diabetes management method at screening by treatment, ITT population

	Treatment		
	Byetta n=123	Exenatide QW n=129	All subjects n=252
Diet and exercise alone	26 (21.1%)	21 (16.3%)	47 (18.7%)
Metformin alone	52 (42.3%)	51 (39.5%)	108 (40.9%)
Sulfonylurea alone	8 (6.5%)	1 (0.8%)	9 (3.6%)
Thiazolidinedione (TZD) alone	2 (1.6%)	4 (3.1%)	6 (2.4%)
Metformin plus sulfonylurea	25 (20.3%)	34 (26.4%)	59 (23.4%)
Metformin plus TZD	9 (7.3%)	13 (10.1%)	22 (8.7%)
Metformin, sulfonylurea and TZD	1 (0.8%)	5 (3.9%)	6 (2.4%)
Metformin alone or in combination	87 (70.7%)	108 (79.8%)	190 (75.4%)
Sulfonylurea alone or in combination	34 (27.6%)	40 (31.0%)	74 (29.4%)
TZD alone or in combination <sup>1</sup>	12 (9.8%)	22 (17.1%)	34 (13.5%)

*Note:* <sup>1</sup>The diabetes management method of metformin, sulfonylurea and TZD at screening represented a protocol deviation for 6 subjects. The subjects were allowed to continue in the study.

Source: Study BCB108 clinical report, Table 5

### 3.2.3. Statistical methodologies

#### 3.2.3.1. Analysis populations

The applicant defined the following analysis populations (TABLE 6):

*Randomized population:* The randomized population consisted of all subjects who were randomly assigned to a treatment group.

*Intent-to-Treat (ITT) population:* The ITT population consisted of all randomized subjects who received at least one injection of randomized study medication. For subjects in the ITT population who discontinued from the study prior to completing all study procedures through week 24, but had data collected for at least one visit subsequent to day 1, missing values of efficacy measures up to week 24 were imputed using the values at the last scheduled visit (including the early termination visit), using the last observation carried forward (LOCF) approach. Of the 254 subjects randomized, 252 were included in the ITT population (TABLE 6).

*Evaluable Population:* The Evaluable Population consisted of all ITT subjects who completed study procedures at visit 7 (week 20) or beyond in compliance with the protocol and who had adequate exposure to study medication. For subjects in the Evaluable Population who completed all study procedures through week 20 and discontinued from the study between week 20 and 24, the efficacy measures collected at the early termination visit or week 20, whichever was later, were used for week 24 summary and analyses.

TABLE 6 Study BCB108; Analysis populations by treatment

	Treatment		
	Byetta	Exenatide QW	All subjects
Randomized	125	129	254
Intent-to-Treat	123	129	252
Evaluable	93	111	204

Source: Study BCB108 clinical report, Table 3

### 3.2.3.2. Primary analysis

The primary endpoint was compared between Exenatide QW and Byetta from an analysis of variance model with factors for treatment group, baseline HbA1c stratum (<9.0% or ≥ 9.0%), and concomitant SU use at screening (with SU or without SU). The two-sided 95% confidence intervals for the comparison (Exenatide QW – Byetta) were constructed from the least squares (LS) means and standard errors, and compared to the non-inferiority margin of 0.4%.

### 3.2.3.3. Supportive analysis

As a supportive analysis, the change in HbA1c for the ITT population was analyzed using the mixed-effects model repeated-measure (MMRM) analysis. The model included treatment, week of visit, treatment by week interaction, concomitant SU use at screening, and baseline HbA1c stratum as fixed effects, and subject as random effects. All observed HbA1c data (without imputation) from all post-baseline scheduled visits (including early termination visits) were included in the MMRM analysis. The covariance structures to be tested in this model included compound symmetry, heterogeneous compound symmetry, unstructured, and first-order autoregressive. The best covariance structure was selected based on the Akaike's Information Criterion (AIC).

The evaluable population was also used in a supportive analysis of the primary endpoint, using the analysis of variance model described for the primary analysis.

### 3.2.3.4 Other analysis topics

Multiplicity from tests of treatment difference for the three key secondary endpoints (the proportion of subjects achieving HbA1c target value of < 7%, change in FPG concentration, and proportion of subjects achieving FPG concentration target value of ≤ 126 mg/dL) was adjusted using the Hochberg procedure to control overall Type I error rate at 5%.

## 3.2.4. Results and Conclusions

Primary endpoint: At week 24, Exenatide QW produced a statistically significant net mean reduction in HbA1c compared to Byetta, with a 95% confidence interval (-0.9, -0.4) in the

direction of superior efficacy (TABLE 7, analysis 1). I confirmed these findings. Additional analyses conducted by the applicant supported the results of the primary analysis. To these I added an analysis of covariance, consisting of the primary analysis model with baseline HbA1c added to it. This model is another possible primary analysis model that can be used in Phase 3 studies of antidiabetes products. The results from the analysis of covariance model are fairly similar to the results from the pre-specified analysis of variance (TABLE 7, analysis 2).

The longitudinal time course of the model-based mean HbA1c for each arm is depicted in FIGURE 3.

Key secondary endpoints: Results from the three key secondary endpoints: (1) the proportion of subjects achieving HbA1c target value of < 7%; (2) the change from baseline in fasting plasma glucose (FPG) concentration; and (3) the proportion of subjects achieving a FPG concentration target value of  $\leq 126$  mg/dL, all evaluated at week 24, supported the superior efficacy of Exenatide QW compared to Byetta (TABLE 8).

Post-hoc analysis of FPG: The applicant conducted an additional analysis of the FPG endpoint after unblinding the data. This analysis omitted the baseline FPG covariate from the model, so that the modified model was the same as the primary analysis of variance model for HbA1c. The applicant noted that their post-hoc analysis was motivated by observing the positive relationship between the baseline stratification HbA1c variable and baseline FPG. I have depicted this relationship, not with the stratification variable, but with the continuous HbA1c variable, measured at baseline (FIGURE 4A). I also depicted the relationship between FPG and HbA1c with both variables expressed as a change from baseline at week 24 (FIGURE 4B). The correlation between these two measures of glycemic control is 0.66 at baseline for both treatment arms, and 0.66 as a change from baseline in the Exenatide QW arm and 0.36 in the Byetta arm.

The statistical comparison between Exenatide QW and Byetta was fairly similar for the pre-specified analysis of covariance and the post-hoc analysis of variance (TABLE 8, analyses 2A and 2B). Where they differed was in the estimated mean change from baseline for each treatment arm. With the post-hoc analysis, the mean change from baseline for each arm was larger, in the direction of greater efficacy, than with the pre-specified analysis. The applicant has proposed

(b) (4)

I do not agree with the applicant's proposal

(b) (4)

My reasons are as follows:

- (1) The pre-specified analysis of covariance model for the FPG endpoint was a reasonable analysis model. The observed results for FPG do not suggest otherwise. The observed small difference in average baseline FPG for each group, and the observed positive correlation between baseline FPG and baseline HbA1c do not pose difficulties in interpreting the p-value from the comparison between Exenatide QW and Byetta in the FPG endpoint from this model.

- (2) The Type I error for three key secondary endpoints, which included the FPG endpoint, was protected by a multiplicity procedure. In my opinion, the p-value from the post-hoc analysis of FPG is not included in this pre-specified protection.
- (3) The focus of the statistical analysis is on the comparison between the two randomized treatment arms, which was not sensitive to the omission of the baseline covariate. The sensitivity lies with the separate estimates of change from baseline for each treatment arm. These estimates may be sensitive to correlations between measurements of FPG at baseline and week 24, and to the small observed difference in mean baseline between the two treatment arms. In this type of situation, Senn (1997) advocates the use of an analysis of covariance model:

“It turns out, however, that because the correlation between baseline and outcome is generally less than one, the correlation between baseline and change score is generally negative. It thus follows that an observed difference between groups at baseline is predictive not only of a difference in raw outcomes but also of a difference in change scores (albeit in the other direction). Hence, if the treatment is at an unfair disadvantage compared to placebo when its effects are measured in raw outcomes (due to an imbalance in baselines), it will have an unfair advantage if change scores are used. The solution is to use analysis of covariance. Analysis of covariance produces a measure which is adjusted by baseline in such a way that the result is uncorrelated with the baseline.”<sup>4</sup>

In my opinion, this description from Senn (1997) corresponds reasonably well to the observed results from Study BCB108. The observed correlation between FPG at baseline and week 24 was positive but less than one (FIGURE 4C), and the observed correlation between baseline and change from baseline at week 24 was negative (FIGURE 4D). I believe that an analysis of covariance model is appropriate for obtaining estimates of the mean FPG change from baseline, for each treatment arm, and between the two arms.

Body weight: At week 24, both groups showed a small average weight loss compared to baseline (TABLE 9). The Exenatide QW arm had a somewhat greater weight loss than the Byetta arm by about 1 kg (p=0.051).

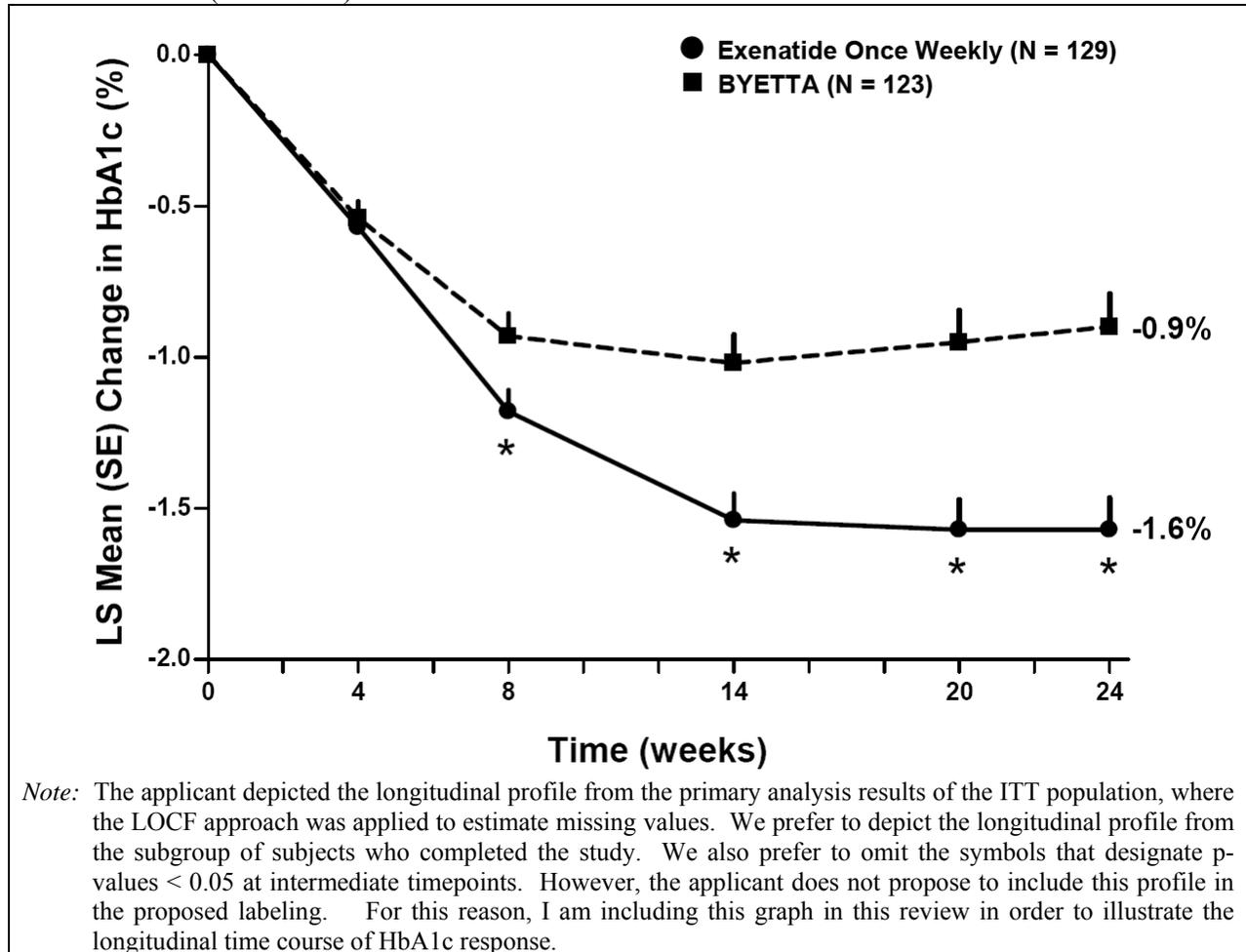
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<sup>4</sup> Senn, S., 1997. Statistical Issues in Drug Development. Chapter 7, “Baselines and covariate information,” pp. 99-100.

TABLE 7 Primary efficacy analysis: Change in HbA1c at week 24 in the ITT/LOCF population

	N	Baseline mean HbA1c ± SE	Adjusted mean change from baseline at Week 24 ± SE <sup>1</sup>	Exenatide QW – Byetta Difference in adjusted mean change (95% CI) <sup>1</sup>	P-value
<b>Primary analysis</b>					
1. ITT analysis set with LOCF, primary analysis of variance model					
Exenatide QW	128	8.5 ± 0.1	-1.6 ± 0.1	-0.7 (-0.9, -0.4)	<0.0001
Byetta	122	8.4 ± 0.1	-0.9 ± 0.1		
<b>Supportive analyses</b>					
2. ITT analysis set with LOCF, analysis of covariance model (the primary analysis of variance model with baseline HbA1c added as a covariate)					
Exenatide QW	128	8.5 ± 0.1	-1.4 ± 0.1	-0.7 (-0.9, -0.4)	<0.0001
Byetta	122	8.4 ± 0.1	-0.8 ± 0.1		
3. Evaluable population analysis set, no imputation, primary analysis of variance model					
Exenatide QW	110	8.5 ± 0.1	-1.6 ± 0.1	-0.7 (-1.0, -0.3)	<0.0001
Byetta	92	8.3 ± 0.1	-0.9 ± 0.1		
4. ITT analysis set, no imputation, mixed model repeated measures model					
Exenatide QW	129	8.5 ± 0.1	-1.5 ± 0.1	-0.7 (-1.0, -0.4)	<0.0001
Byetta	123	8.4 ± 0.1	-0.8 ± 0.1		
<i>Analysis:</i>				<i>Source:</i>	
1. The primary analysis model was an analysis of variance including treatment and the two stratification factors used in randomization: baseline HbA1c stratum, and concomitant SU use at screening.				1. Study BCB108 clinical report, Table 7	
2. The primary analysis model with baseline HbA1c added as a covariate.				2. Analysis by this reviewer	
3. The analysis model was the same as in model 1.				3. Study BCB108 clinical report, Table 7	
4. The mixed model repeated measures model included the two stratification factors used in randomization, treatment, week, interaction between treatment and week. The covariance structure was unstructured.				4. Study BCB108 clinical report, Supporting data summary 2.1.2.1.3	

FIGURE 3 Study BCB108; LS Mean (SE) change in HbA1c from baseline to week 24 by treatment (ITT/LOCF)

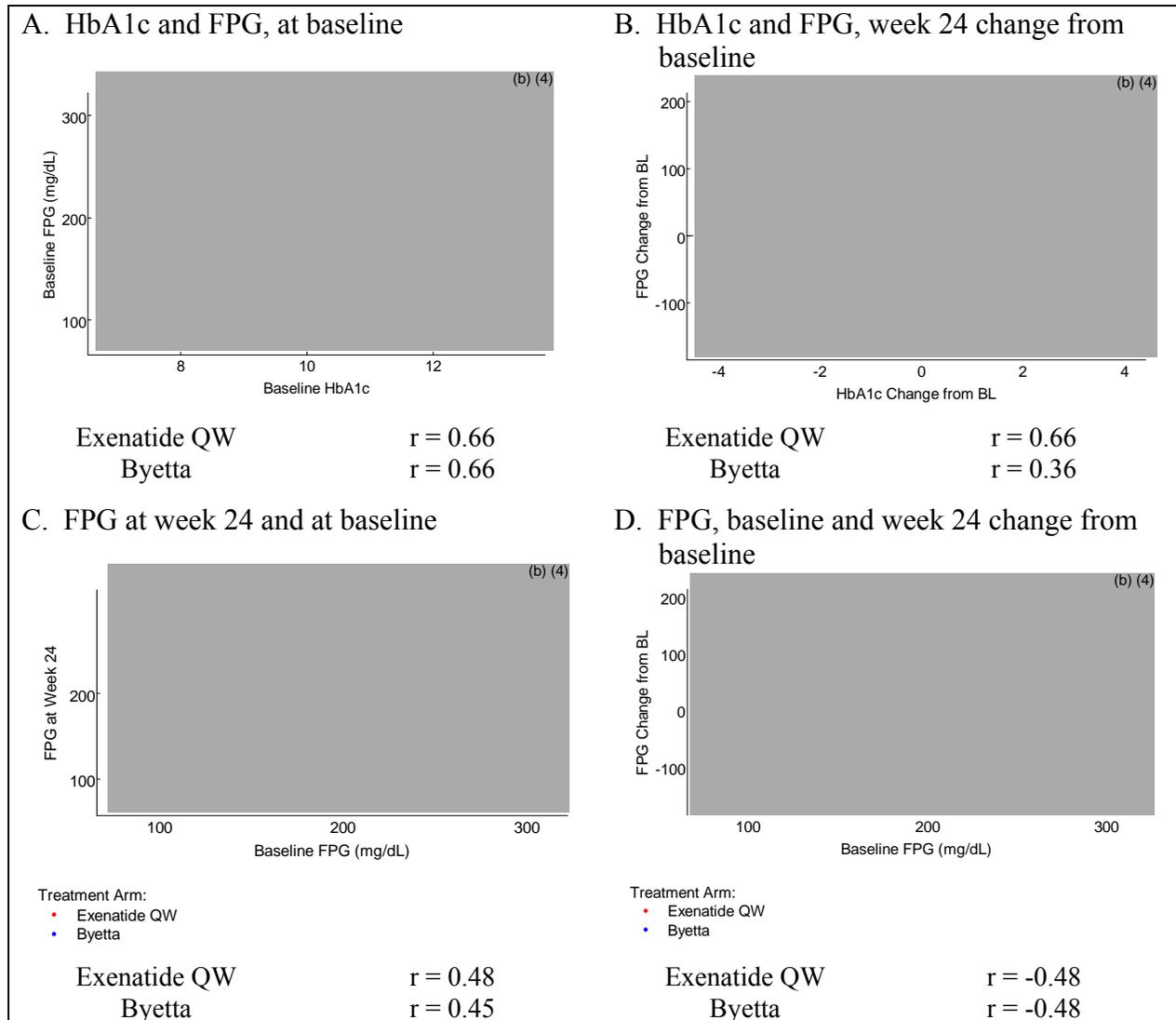


Source: Study BCB108 clinical report, Figure 3

TABLE 8 Study BCB108; Key secondary efficacy endpoints (ITT/LOCF at week 24)

1. The proportion of subjects achieving HbA1c target value of < 7%					
	n	Proportion with HbA1c < 7%	Adjusted odds ratio, each treatment arm	Exenatide QW vs Byetta Adjusted odds ratio	P-value <sup>1</sup>
Exenatide QW	129	75 (58.1%)	1.7	3.8 (2.2, 6.8)	nominal <0.0001
Byetta	123	37 (30.1%)	0.5		adjusted <0.0001
2. Change from baseline in fasting plasma glucose concentration					
A. Pre-specified analysis					
	n	Baseline mean FPG ± SE	Adjusted mean change from baseline at Week 24 ± SE <sup>1</sup>	Exenatide QW – Byetta Difference in adjusted mean change (95% CI)	P-value
Exenatide QW	129	173.3 ± 4.2	-25.1 ± 4.3	-20.4 (-31.4, -9.5)	nominal 0.0003
Byetta	123	168.1 ± 4.3	-4.6 ± 4.5		adjusted 0.0006
B. Post-hoc analysis					
Exenatide QW	129	173.3 ± 4.2	-34.6 ± 4.9	-22.4 (-35.2, -9.7)	nominal 0.0006
Byetta	123	168.1 ± 4.3	-12.1 ± 5.1		
3. The proportion of subjects achieving a FPG concentration target value of ≤ 126 mg/dL					
	n	Proportion with FPG ≤ 126 mg/dL	Adjusted odds ratio, each treatment arm	Exenatide QW vs Byetta Adjusted odds ratio	P-value
Exenatide QW	129	65 (50.4%)	1.4	2.5 (1.5, 4.2)	nominal 0.0008
Byetta	123	38 (30.9%)	0.6		adjusted 0.0008
<i>Note:</i>					
<sup>1</sup> The nominal p-values were adjusted with a multiple comparison procedure (Hochberg) that was pre-specified in the protocol in order to protect Type I error across the analyses of the three endpoints. The p-value from the post-hoc analysis in of fasting plasma glucose in 2B would not be included in this procedure.					
<i>Analysis:</i>			<i>Source:</i> Study BCB clinical report		
1. and 3. From a pre-specified Cochran-Mantel-Haenszel test adjusting for the two stratification variables used in randomization: Baseline HbA1c and concomitant SU use at screening.			1. Supporting data summary 2.1.3.1.1 and Appendix 2.3.1.7.1		
2A. From a pre-specified analysis of covariance model including treatment arm, the two stratification variables used in randomization, and baseline FPG as a covariate.			2A. Supporting data summary 2.4.2.1.1		
2B. From a post-hoc analysis of variance model including treatment arm, the two stratification variables used in randomization.			2B. Supporting data summary 2.4.2.1.2		
			3. Supporting data summary 2.4.3.1 and Appendix 2.3.4.4.1		

FIGURE 4 Study BCB108; Relationships between Fasting Plasma Glucose and HbA1c at baseline and week 24



Source: Analysis by this reviewer

TABLE 9 Study BCB108; Change in body weight (kg) at week 24 (ITT/LOCF)

	N	Baseline mean Body weight (kg) ± SE	Adjusted mean change from baseline at Week 24 ± SE <sup>1</sup>	Exenatide QW – Byetta Difference in adjusted mean change (95% CI) <sup>1</sup>	P- value
<b>All subjects (ITT/LOCF)</b>					
Exenatide QW	129	97.0 ± 1.8	-2.3 ± 0.4	-1.0 (-1.9, 0.01)	0.051
Byetta	123	94.3 ± 1.7	-1.4 ± 0.4		
<i>Note:</i>					
<sup>1</sup> The adjusted mean change from baseline at week 24 and the difference in the adjusted mean change were estimated from an analysis of covariance model including treatment, baseline HbA <sub>1c</sub> stratum, concomitant SU use at screening, and baseline value of weight.					
<i>Source:</i> Study BCB108 clinical report, Table 8, and Appendix 2.3.2.1.1					

### 3.3 Evaluation of Safety

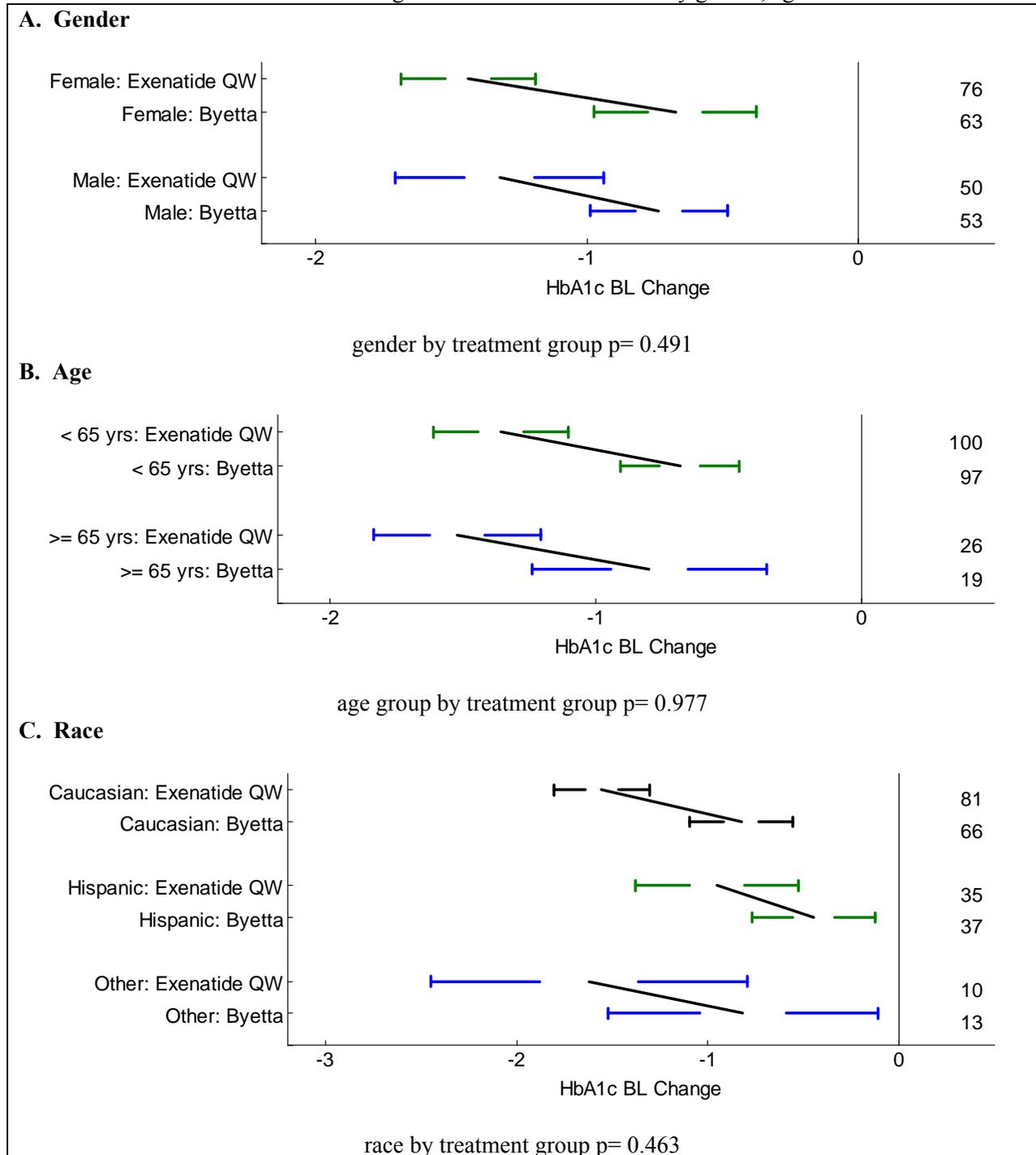
An evaluation of safety is included in the FDA clinical review by Dr. Valerie Pratt.

## 4. FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

### 4.1 Gender, Race, Age and Geographic Region

The average HbA<sub>1c</sub> response to Exenatide QW compared to Byetta at week 24 was fairly similar in males compared to females, and in the younger age group compared to the older age group, and in Caucasians and Hispanic racial subgroups (FIGURE 5A, B and C). These findings are similar to those in Study 105 at week 30 (see the statistical review of NDA 022200/0 dated 1/4/10; Figure 8). Study BCB108 was conducted entirely within the U.S. For this reason, I did not explore the effect of geographic region.

FIGURE 5 The mean HbA1c change from baseline to week 24 by gender, age and race



**Notes:**

Shown on the graphs are the t-intervals (mean and 95% confidence interval) for HbA1c change from baseline for each subgroup category. The p-values are from the analysis of variance model with the following general form: baseline HbA1c stratification level ( $< 9.0$ ,  $\geq 9$ ), baseline SU status (Yes, No), treatment group, subgroup and subgroup by treatment group interaction. For race, categories of “black,” “Asian,” “Native American” and “other” were combined into “other.” An  $\alpha$  of 0.1 was used to screen the subgroup by treatment interactions.

*Source: Analysis by this reviewer*

## 4.2 Other Special/Subgroup Populations

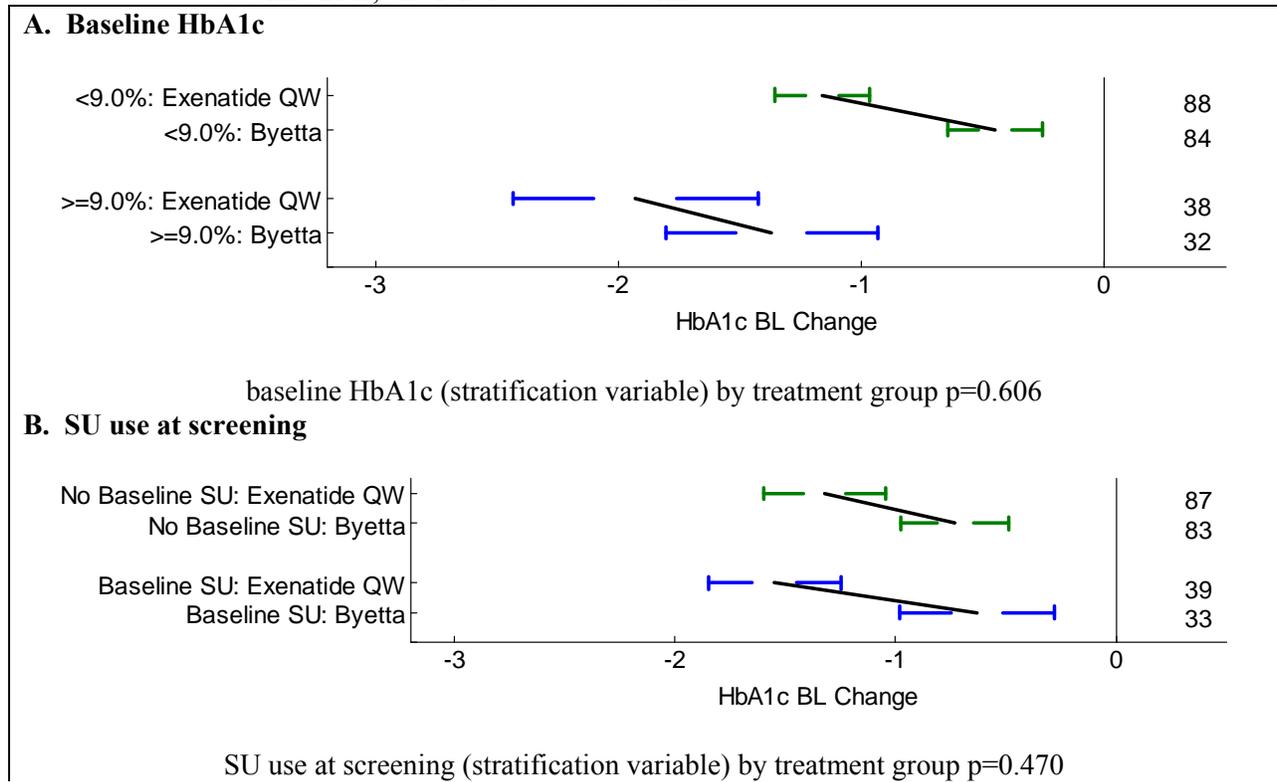
**Baseline HbA1c:** The average HbA1c response to Exenatide QW compared to Byetta at week 24 was fairly similar in the two stratified levels of baseline HbA1c ( $< 9.0$  and  $\geq 9.0$ ; FIGURE 5A). This finding is different from the results from Study 105 at week 30; where the average HbA1c response to in subjects with baseline HbA1c  $< 9.0$  was fairly similar in the Exenatide QW and Byetta arms, while subjects with baseline HbA1c  $\geq 9.0$  on average had a greater reduction in HbA1c in the Exenatide QW group than in the Byetta group (see the statistical review of NDA 022200/0 dated 1/4/10; Figure 9).

**SU use at screening:** The subgroup of subjects treated with SU were fairly similar to the subgroup of subjects not treated with SU with respect to the comparison between Exenatide QW and Byetta in the average HbA1c response at week 30 (FIGURE 5B).

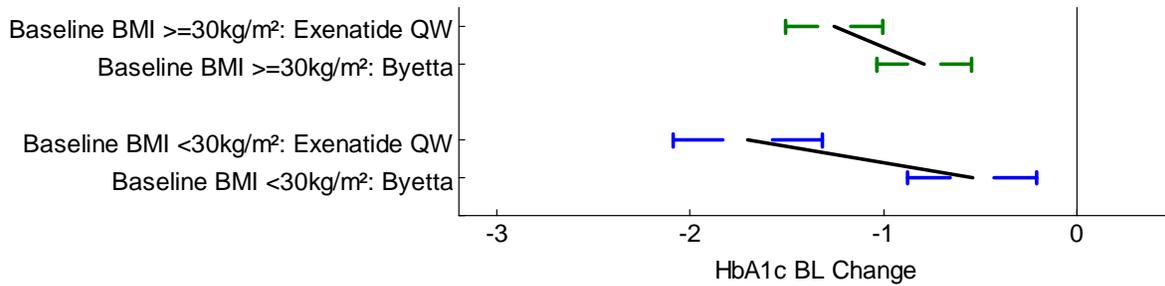
**Baseline BMI:** The subgroup of subjects with baseline BMI  $< 30$  kg/m<sup>2</sup> had a larger mean difference between Exenatide QW and Byetta in the HbA1c response at week 24 compared to the subgroup of subjects with baseline BMI  $\geq 30$  kg/m<sup>2</sup> (FIGURE 5C; TABLE 10). The treatment arm by BMI subgroup interaction had a p-value of 0.025. This interaction was not significant in Study 105 (p=0.124) although the means of the two subgroups were in approximately the same relationship (see the statistical review of NDA 022200/0 dated 1/4/10; Figure 13).

**Baseline renal status:** The subgroups of subjects defined by renal status at baseline had a fairly similar contrast between Exenatide QW and Byetta at week 24 for the average effect of HbA1c (FIGURE 5D). This interaction was not evaluated in Study 105.

FIGURE 6 Mean HbA1c change from baseline to week 24 by baseline HbA1c, SU use at screening, baseline BMI, and renal status at baseline

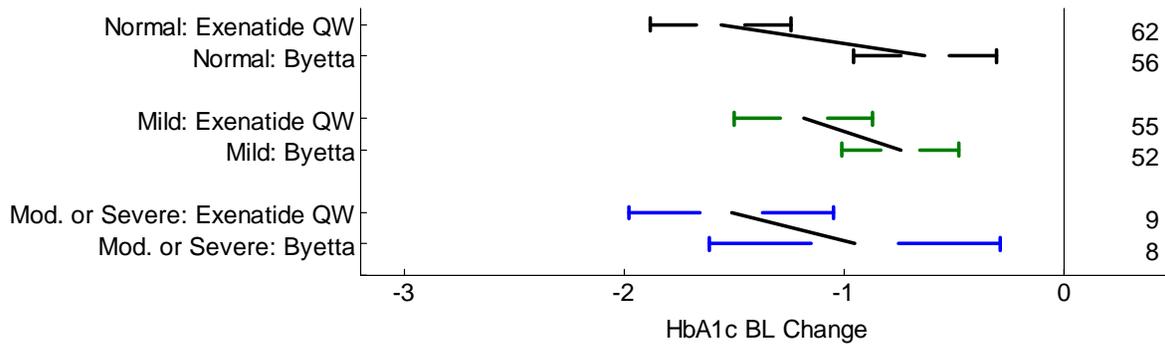


**Baseline BMI**



baseline BMI by treatment group  $p=0.025$

**D. Baseline renal status**



baseline renal status by treatment group  $p=0.577$

*Notes:*

Shown on the graphs are the t-intervals (mean and 95% confidence interval) for HbA1c change from baseline for each subgroup category. The p-values are from the analysis of variance model with the following general form: baseline HbA1c stratification level ( $< 9.0$ ,  $\geq 9$ ), baseline SU status (Yes, No), treatment group, subgroup and subgroup by treatment group interaction. For baseline renal status, the categories of “moderate” and “severe” were combined. An  $\alpha$  of 0.1 was used to screen the subgroup by treatment interactions.

*Source: Analysis by this reviewer*

TABLE 10 HbA1c results by baseline BMI subgroup (< 30 kg/m<sup>2</sup>, ≥ 30 kg/m<sup>2</sup>)

	N	Baseline mean HbA1c ± SE	Adjusted mean change from baseline at Week 30 ± SE <sup>1</sup>	Exenatide QW – Byetta Difference in adjusted mean change (95% CI) <sup>1</sup>	P-value
<b>All subjects (ITT/LOCF), primary analysis model</b>					
Exenatide QW	128	8.5 ± 0.1	-1.6 ± 0.1	-0.7 (-0.9, -0.4)	<0.0001
Byetta	122	8.4 ± 0.1	-0.9 ± 0.1		
<b>Subjects with baseline BMI &lt; 30 kg/m<sup>2</sup></b>					
Exenatide QW	38	8.7 ± 0.2	-1.8 ± 0.2	-1.1 (-1.6, -0.6)	<0.0001
Byetta	41	8.5 ± 0.2	-0.7 ± 0.2		
<b>Subjects with baseline BMI ≥ 30 kg/m<sup>2</sup></b>					
Exenatide QW	88	8.4 ± 0.1	-1.4 ± 0.1	-0.5 (-0.8, -0.1)	0.007
Byetta	75	8.3 ± 0.1	-1.0 ± 0.1		
<i>Note:</i> The adjusted mean change from baseline at week 24 and the difference in the adjusted mean change were estimated from the primary analysis of variance model, with terms added to represent the baseline BMI subgroups.					
<i>Sources:</i> Study BCB108 clinical report, Table 7, and additional analysis by this reviewer.					

## 5. SUMMARY AND CONCLUSIONS

### 5.1 Statistical Issues and Collective Evidence

I evaluated the evidence in support of the efficacy of Exenatide QW (2 mg SC once weekly) from the results of Study BCB108. I confirmed the primary efficacy result for HbA1c at week 24, expressed as a change from baseline. I concurred with the pre-specified statistical methodology used in evaluating the primary endpoint. Results from the primary and secondary analyses supported the non-inferiority of Exenatide QW compared to Byetta (10 mcg SC twice a day).

### 5.2 Conclusions

In my opinion, the efficacy results from Study BCB108, conducted with the commercial source of Exenatide QW, are similar to those from Study 105, which was conducted with the investigational source of Exenatide QW (see the statistical review of NDA 022200/0 dated 1/4/10). The results from Study BCB108 support the efficacy of the commercial source of Exenatide QW. This addresses an issue of concern that was part of the Complete Response to the original NDA submission.

### 5.3 Recommendations for Labeling

Recommendations for the proposed package insert are summarized in TABLE 11:

TABLE 11 Proposed Label, Part 14 (Clinical Studies), with statistical review comments

<b>Draft Label submitted 7/18/11</b> <b>Part 14. Clinical Studies</b>	<b>Statistical review comments</b>
 <p>(b) (4)</p>	<p>The summary statistics correspond to the summaries in the clinical study report.</p>

<b>Draft Label submitted 7/18/11</b> <b>Part 14. Clinical Studies</b>	<b>Statistical review comments</b>
 (b) (4)	<p>The summary statistics reported in this table correspond to the summaries in the clinical report.</p> <p>However, the p-value used as a cut-off (referenced by symbol ¶ in the table footnotes) should be changed so that it accurately reflects the p-value for HbA1c (p=0.0023) and for FPG (p&lt;0.0001). A cut-off p-value of 0.01 would be appropriate.</p>
	<p>No statistical review comments.</p>

<b>Draft Label submitted 7/18/11</b> <b>Part 14. Clinical Studies</b>	<b>Statistical review comments</b>
 <p>(b) (4)</p>	<p>These summary statistics correspond to the summaries in the clinical report.</p> <p>The summary statistics correspond to the summaries in the clinical study report.</p>

(b) (4)	<b>Statistical review comments:</b>
	<p>Summary statistics for HbA1c are okay.</p> <p>See comments below about the cut-off p-value for the symbol ¶ Change “Proportion” to “Percentage”</p> <p>Change the summary statistics for FPG to the results from the pre-specified analysis: Change to: -25 -5 Change to: -20 [-31, -10] ¶ Change “Proportion” to “Percentage”</p> <p>Summary statistics for body weight are okay.</p> <p>Change the cut-off p-value for the symbol ¶ to <math>p &lt; 0.0005</math> or <math>p &lt; 0.001</math>. These are more standard cut-off values.</p>

	<p>(b) (4) The summary statistics correspond with the summary statistics in the clinical report.</p>
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## CHECK LIST

Number of Pivotal Studies: 1

### Trial Specification

**Protocol Number (s):** BCB108

**Phase:** 3

**Control:** Active Control (Byetta 10 mcg/day)

**Blinding:** Open-Label

**Number of Centers:** 43

**Region(s) (Country):** US only

**Duration:** 24 Weeks

**Treatment Arms:** 2 arms: Exenatide QW (once weekly injection); Byetta 10 mcg SC (twice daily injection)

**Treatment Schedule:** see above

**Randomization:** Yes

Ratio: 1:1

Method of Randomization: Stratified; From the statistical analysis plan: “Randomization was carried out centrally in a manner to achieve a balanced distribution of subjects across treatment groups according to the two stratification factors.” Study site personnel contacted an interactive

voice response system to randomly assign subjects and trigger a request to ship the appropriate study medication kit required for upcoming visits.

If stratified, then the Stratification Factors: 2 factors: (1) Baseline HbA1c ( $< 9.0\%$ ,  $\geq 9.0\%$ ), and (2) Sulfonylurea use at screening (Yes, No)

**Primary Endpoint:** HbA1c at week 24 as a change from baseline. The units are %.

**Primary Analysis Population:** ITT/LOCF

**Statistical Design:** Non-Inferiority

If non-inferiority or equivalence: Was the non-inferiority margin calculated based on historical data? Yes, and also considerations of clinical significance and typical margins of 0.3 and 0.4 as described in the diabetes guidance were considerations in the development of the margin. The combined placebo-adjusted effect of Byetta from three placebo-controlled studies was -0.99 with 95% CI of (-1.18, -0.80). The margin of -0.40 retains 50% of the most conservative (i.e., upper 95% CI bound) estimate of the placebo-adjusted effect. For more information, see the statistical review of NDA 022200/0 dated 1/4/10.

Margin = 0.4 % (i.e., % units)

%Retained = See above

Adaptive Design: No

**Primary Statistical Methodology:** Analysis of variance model with terms for the two stratification variables and the treatment arm. The dependent variable was HbA1c at week 24 expressed as a change from baseline.

**Interim Analysis:** No

**Sample Size:** Planned as 244 subjects randomized 1:3

**Sample Size Determination:** Was it calculated based on the primary endpoint variable and the analysis being used for the primary variable? Yes

**Statistic** = one-sided two-sample t-test with significance level of 0.025

**Power**= 90%

$\Delta$ = NI margin of 0.4%, assuming superiority of Bydurean (Exenatide QW) of 0.1% to Byetta and common standard deviation of 1.1%

$\alpha$  = two-sided alpha of 0.05

- Was there an **Alternative Analysis** in case of violation of assumption; e.g., Lack of normality, Proportional Hazards Assumption violation. No
- Were there any major changes, such as changing the statistical analysis methodology or changing the primary endpoint variable? No
- Were the **Covariates** pre-specified in the protocol? No covariates in the primary analysis model
- Did the Applicant perform **Sensitivity Analyses**? Yes
- How were the **Missing Data** handled? Imputation by LOCF for primary model; additional analyses of the evaluable analysis population (per protocol), and additional analysis by mixed model repeated measures method of both analysis populations.
- Was there a **Multiplicity** involved? Yes, in the three key secondary endpoints, the type I error was protected.

If yes,

Multiple Arms: No

Multiple Endpoints: Yes, three key secondary endpoints.

Which method was used to control for type I error? Hochberg procedure

- **Multiple Secondary Endpoints:** Are they being included in the label? If yes, method to control for type I error. Yes: See the above discussion of multiplicity

**Were Subgroup Analyses Performed (Yes)?** Yes

- Were there any **Discrepancies** between the protocol/statistical analysis plan vs. the study report? No
- Overall, was the study positive (Yes/No)? Yes

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U.S. Department of Health and Human Services  
Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Pharmacoepidemiology and Statistical Science  
Office of Biostatistics

# STATISTICAL SAFETY REVIEW

## CLINICAL STUDIES

**NDA/Serial Number:** N022200/0000.

**Drug Name:** Bydureon (Exenatide once weekly)

**Indication(s):** A once weekly is subcutaneous, injectable, extended release version of the approved product Byetta (Exenatide) for the treatment of type 2 diabetes. Byetta is approved as an adjunctive therapy for adults treated with metformin (met), a sulfonylurea (SU), a thiazolidinedione (TZD), a combination of met+SU, or a combination of met+TZD, who have not achieved adequate glycemic control when treated with diet and exercise alone (NDA 021773).

**Applicant:** Amylin

**Date(s):** Review: February 2, 2010  
Stamp Date: May 5, 2009  
PDUFA Goal Date: 5 March, 2009

**Review Priority:** Standard

**Biometrics Division:** Division of Biometrics 7

**Statistical Safety Reviewer:** Fiona Callaghan, Ph. D.

**Concurring Reviewer(s):** Mark Levenson, Ph. D.

**Medical Division:** Metabolism and Endocrinology Products

**Clinical Team:** Valerie Pratt, M.D., Medical Reviewer  
Ilan Irony, M.D., Medical Team Leader  
Mary Parks, M.D., Division Director

**Project Manager:** John Bishai, Ph. D.

**Keywords:** Type 2 diabetes, meta-analysis, Byetta, cardiovascular risk.

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# 1. EXECUTIVE SUMMARY

## 1.1 Conclusions and Recommendations

There is no evidence to conclude that Byetta has an increased or decreased risk of cardiovascular events compared to placebo or insulin. According to the guidelines for assessing cardiovascular risks for diabetes therapies<sup>1</sup> if the upper limit of the confidence interval for the risk ratio (RR) is above 1.3 or 1.8 further studies to assess the risk must be performed. Given that the confidence intervals were (0.3, 1.5) and (0.6, 2.3) for the SMQ MACE<sup>2</sup> and Custom MACE endpoints respectively, it is recommended that Bydureon be approved on the condition that at least one further post-marketing study is completed in order to ascertain whether the cardiovascular risk ratio is below 1.3 or not. It is also recommended that a subgroup analysis on race, gender and age be included in the post-marketing study, as per the guidance.

## 1.2 Brief Overview of Clinical Studies

For a study to be included in the sponsor's meta-analysis it had to be a placebo or insulin controlled, randomized clinical trial of Byetta of at least 12 weeks duration. All of the 12 studies that were included in the meta-analysis were designed to have parallel treatment and control arms, with the exception of study H8OMC-GWAO which has a cross-over design. There were 4 studies that have an insulin control arm and were consequently open-label. It should be noted that patients with significant history of cardiovascular disease were excluded and the cardio-vascular events were not prospectively adjudicated.

In addition to the 12 placebo or insulin controlled clinical trials, there were 5 uncontrolled, long-term studies of Byetta. There were 3 further controlled clinical trials that focus on Bydureon directly. 2993LAR-105 was a 30 week, 2 arm, parallel study comparing Bydureon with Byetta. There were 145 and 148 subjects in the Bydureon arms and Byetta arms, respectively. The second study, 2993LAR-104, was a 15 week, 3 arm study comparing Bydureon, Sitagliptin and Pioglitazone. This study had 15 subjects in each arm and no CV events were observed. The third study was BCB106, a 3 arm, 26-week study of Bydureon, Sitagliptin, and Pioglitazone, with 160, 166, and 165 patients in each arm, respectively.

## 1.3 Statistical Issues and Findings

There were several limitations to the meta-analysis.

- The studies were not designed to assess cardiovascular risk, and the cardiovascular events were not prospectively adjudicated.

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<sup>1</sup> "Guidance for Industry: Diabetes Mellitus – Evaluating Cardiovascular Risk in New Antidiabetic Therapies to Treat Type 2 Diabetes.", December 2008.

<sup>2</sup> SMQ: Standardized MedDRA Query, MACE: Major Adverse Cardiovascular Event.

- Subjects with ‘significant’ history of cardiovascular heart disease were excluded from the studies.
- There were few events, resulting in a high degree of variability in the estimates of relative risk. The study did not have sufficient power to estimate the risk of cardiovascular events with a reasonable degree of variability.

The confidence intervals of relative risk<sup>3</sup> of the 12 studies often include 1 and the upper limits of the confidence intervals frequently cross the 1.3 or 1.8 guideline thresholds given in the guidance “Guidance for Industry: Diabetes Mellitus – Evaluating Cardiovascular Risk in New Antidiabetic Therapies to Treat Type 2 Diabetes”. When the 12 studies were combined using Mantel-Haenszel techniques with no continuity correction to substitute values for the “zero-zero”<sup>4</sup> studies, the final confidence intervals were (0.56, 1.51) for the broader definition of a cardiovascular event (SMQ MACE) and (0.33, 2.31) for the narrower definition of a cardiovascular event (Custom MACE).

## 2. INTRODUCTION

Bydureon (Exenatide once weekly/Exenatide LAR) is subcutaneous, injectable, extended release version of the approved product Byetta (Exenatide). Byetta is a subcutaneous injection administered twice daily for the treatment of type 2 diabetes. It was approved as an adjunctive therapy for adults treated with metformin (met), a sulfonylurea (SU), a thiazolidinedione (TZD), a combination of met+SU, or a combination of met+TZD, who have not achieved adequate glycemic control when treated with diet and exercise alone (NDA 021773). The agency requested an evaluation of the cardiovascular (CV) risk of Bydureon on 3 November 2008. A preliminary plan to assess CV risk was sent January 15 2009. Based on discussions at an AC meeting in April 2009, the analysis of CV risk was updated. A meta-analysis of 12 placebo or insulin controlled studies of Byetta was the primary method of assessing CV risk for Bydureon. In November 2009 the FDA requested that the analysis be updated using two new definitions of the endpoints (a “narrow” and “broad” definition of a cardiovascular event) and it is on these endpoints that the following discussion is based. In addition there were 3 controlled studies of Bydureon and 5 uncontrolled, open-label studies of Byetta (4 of these were extension studies of placebo or insulin controlled, blinded studies of Byetta).

The objective of this review was to assess the validity of the meta-analysis of Byetta and the analysis of the other studies, with the goal of estimating (if possible) the cardiovascular risk of Bydureon. Each of the protocols of the 12 Byetta studies involved in the meta-analysis was reviewed in order to assess whether the studies were similar enough to be combined to form a meaningful estimate. The strengths and weaknesses of the analysis (for instance, the lack of prospective adjudication of cardiovascular events, the small number of events, the combination of risk-ratios with high variability,

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<sup>3</sup> Relative risk is defined as the proportion of events in the Byetta group divided by the proportion of events in the control group.

<sup>4</sup> Zero-zero studies are studies with zero cardiovascular events in both arms.

applicability of different analysis methods, etc.) were reviewed. To supplement the analysis provided by the sponsor, asymptotic estimates of the risk ratios for each study and an overall estimate stratified by study were calculated without using any substituted values for the zero counts of cardiovascular events. The results were then evaluated with regard to the FDA guidance on cardiovascular risk for therapies for type 2 diabetes.<sup>5</sup> A new analysis of patient-level data was not performed.

The review is based on two reports (“Exenatide Cardiovascular Risk Meta-Analysis” from 15 April 2009<sup>6</sup> and the revised report from 19 November 2009) and the protocols for the 12 studies in the meta-analysis<sup>7</sup>.

### 3. STATISTICAL EVALUATION

#### Study Design and Endpoints

The sponsor’s meta-analysis of the 12 trials used the intent-to-treat population, which was defined as all randomized subjects that received at least one dose of study medication (see Table 1 for an overview). There were two endpoints of primary interest: “SMQ MACE” and “Custom MACE”. The first endpoint (SMQ MACE) included all the preferred terms in the standardized MedDRA queries for “Myocardial Infarction” and “Central nervous system haemorrhages and cerebrovascular accidents”. The Custom MACE endpoint is based on a narrower definition of cardiovascular events and is comprised of a list of preferred terms that focus on myocardial infarction and stroke events. The definition of the Custom MACE endpoint was provided by the FDA.

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<sup>5</sup> “Guidance for Industry: Diabetes Mellitus – Evaluating Cardiovascular Risk in New Antidiabetic Therapies to Treat Type 2 Diabetes”, December 2008.

<sup>6</sup> \\Cdsub1\evsprod\NDA022200\0001\m5\53-clin-stud-rep\535-rep-effic-safety-stud\type-2-diabetes\5353-rep-analys-data-more-one-stud\cv-analysis\cv-analysis.pdf

<sup>7</sup> <\\Cdsub1\evsprod\NDA022200\0014\m5\53-clin-stud-rep\535-rep-effic-safety-stud\type-2-diabetes\5351-stud-rep-contr\2993112\2993112-protocol-02.pdf>  
<\\Cdsub1\evsprod\NDA022200\0014\m5\53-clin-stud-rep\535-rep-effic-safety-stud\type-2-diabetes\5351-stud-rep-contr\2993113\2993113-protocol-02.pdf>  
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A more detailed description of the studies can be found in Table 3 (Appendix). For a study to be included in the meta-analysis it had to be a placebo or insulin controlled, randomized clinical trial of Byetta and it had to be of at least 12 weeks duration. It should be noted that none of the three controlled studies of Bydureon had a placebo or insulin control arm and therefore were not included in this meta-analysis, but are discussed below (see also Table 14 and Table 15). All of the 12 studies that were included in the meta-analysis were designed to have parallel treatment and control arms, with the exception of study H8OMC-GWAO, which has a cross-over design. Overall, the study designs were similar with a few exceptions. There were 4 studies that have an insulin control arm and were consequently open-label. None were designed to specifically study cardiovascular risk, with the possible exception of study H8OMC-GWCD (a 12 week study with 28 and 26 patients in each arm) which was designed to investigate mean heart rate increase in patients taking Byetta compared to placebo. It is important to note that most of the studies patients with significant history of cardiovascular disease were excluded (see exclusion criteria, Table 3). The cardiovascular events were not prospectively adjudicated.

The studies were not designed to analyze cardiovascular risk and the events were rare which means that there was not enough power to accurately assess the difference in risk between the two groups. Furthermore, the sponsor's meta-analysis was comprised of studies of Byetta rather than Bydureon and therefore the meta-analysis does not account for any difference in cardiovascular risk between these two forms of the drug.

**Table 1. Summary of size and duration of trials of Byetta used in meta-analysis to assess cardiovascular risk (from p8 “Exenatide Cardiovascular Risk Meta-Analysis”, 15 April, 2009.)**

Study	Concomitant OAD	Duration (Weeks) [1]	Exenatide [2]		Comparator	
			Subjects (N)	Exposure (SY)	Subjects (N)	Exposure (SY)
<b>Placebo-Controlled Studies</b>						
2993-112	Met	30 Weeks	223	113.8	113	57.8
2993-113	SU	30 Weeks	254	123.2	123	55.1
2993-115	Met+SU	30 Weeks	486	254.9	247	122.2
H80-MC-GWAP	TZD or TZD+Met	16 Weeks	121	31.7	112	32.3
H80-MC-GWAV	SU or Met+SU	12 Weeks	111	23.9	40	9.2
H80-MC-GWBA	Met or Met+SU	16 Weeks	234	65.5	233	67.3
H80-MC-GWBJ	None (D+E Only)	24 Weeks	155	65.2	77	33.1
H80-MC-GWCD	Met and/or TZD	12 Weeks	28	5.8	26	5.7
<b>Active Comparator (Insulin)-Controlled Studies</b>						
H80-MC-GWAA	Met+SU	26 Weeks	282	122.5	267	124.6
H80-MC-GWAD	Met+SU	52 Weeks	253	220.1	248	228.6
H80-MC-GWAK	SU or Meg and/or Met	16 Weeks	33	7.7	16	5.2
H80-MC-GWAO	Met or SU	16 Weeks [3]	136	37.3	127	38.9
<b>Totals</b>	—	—	<b>2316</b>	<b>1071.6</b>	<b>1629</b>	<b>779.9</b>
<b>Placebo-Controlled</b>	—	—	1612	683.9	971	382.7
<b>Active-Controlled</b>	—	—	704	387.6	658	397.2

D+E = diet and exercise therapy; Meg = meglitinide; Met = metformin; OAD = oral antidiabetic medications; SU = sulfonylurea; SY = subject-years; TZD = thiazolidinedione.

Note: Subject number is based on the Intent-to-Treat Population.

[1] Duration of treatment with randomized study medication.

[2] Includes treatment with exenatide 2.5 mcg or 5 mcg BID for duration of study, or 4 weeks of exenatide 5 mcg BID followed by exenatide 10 mcg BID for remainder of study.

[3] Study H80-MC-GWAO had a crossover design, with 16 weeks per period (exenatide or insulin glargine).

Cross-Reference: Statistical Analysis Plan, [Appendix 2](#).

In addition to the 12 placebo or insulin controlled clinical trials, there were 5 uncontrolled, long-term studies of Byetta (see Table 2).

**Table 2. 5 open-label studies of Byetta (from p9 “Exenatide Cardiovascular Risk Meta-Analysis”, 15 April, 2009.)**

Study	Description	Subjects (N)
2993-112E	Open-label extension of Study 2993-112	225
2993-113E	Open-label extension of Study 2993-113	223
2993-115E	Open-label extension of Study 2993-115	526
2993-117	Open-label safety and efficacy study (with metformin and/or SU)	155
2993-119	Open-label extension from Studies 2993-107, -108, -116, -112E, -113E, and -115E	454
<b>Total Number of Unique Subjects</b>		<b>1271</b>

Note: Subjects transitioning into Study 2993-119 from Studies 2993-112E, -113E, and -115E are counted once in the Total.

Cross-Reference: Statistical Analysis Plan, [Appendix 2](#).

There were 3 further clinical trials that focus on Bydureon directly. 2993LAR-105 was a 30 week, 2 arm, parallel study comparing Bydureon with Byetta. There were 145 and 148 subjects in the Bydureon arms and Byetta arms, respectively. Very few events were observed in this study (see Table 14). The second study, 2993LAR-104, was a 15 week, 3 arm study comparing Bydureon, Sitagliptin and Pioglitazone. This study had 15

subjects in each arm and no CV events were observed. The third study was BCB106, a 3 arm, 26-week study of Bydureon, Sitagliptin, and Pioglitazone, with 160, 166, and 165 patients in each arm, respectively (see Table 15).

### **Patient Disposition, Demographic and Baseline Characteristics**

Summary demographic information (p11, Exenatide Cardiovascular Risk Meta-Analysis, April 2009) is given. The pooled data from the 12 main studies were summarized by the sponsor according to gender, race, age, duration of diabetes, weight/BMI, HbA1c, and renal function. The summaries were further categorized by placebo controlled studies versus insulin controlled. The main differences were:

- The comparator studies have approximately 30% more Caucasians (55.4% and 51.8% in treatment and control arms for placebo controlled studies, compared to 84.7% and 84.7% in comparator controlled studies), and lower proportion of Blacks (7.8% and 6.7% for placebo controlled compared to 1.0 and 1.1% for comparator controlled).
- The patients were, on average, approximately 2-3 years older in the comparator studies (average age in the placebo controlled studies was 55.0 and 54.8 years for treatment and control respectively, compared with 57.9 and 57.1 in the comparator controlled studies).
- Average duration of diabetes was, on average, approximately 2 years longer in the comparator controlled studies (for placebo controlled studies the average duration was 7.3 and 7.4 years for and control groups respectively, compared to 9.4 and 9.2 years for the comparator controlled studies.)

### **Statistical Methodologies**

The data from the 12 main studies was analyzed by the sponsor in several ways, and each method was repeated with the SMQ MACE and Custom MACE definitions. The primary focus of the analysis was an asymptotic Mantel-Haenszel estimate of the risk ratio stratified by study with  $\frac{1}{2}$  continuity correction for zero studies. We repeated these analyses without the continuity correction (see Table 4 through Table 7) and the results were similar, but fewer studies were included in the analysis as a result of omitting the continuity correction.

Continuity corrections are often used to fill-in values for count data when zero counts are observed. They are used for several purposes, including enabling the calculation of estimates that are otherwise impossible to calculate (e.g. the risk ratio  $p_1/p_2$  does not exist when zero events are observed in the group corresponding to the denominator), allowing the inclusion of studies in a meta-analysis that have zero events in both arms, or, more generally, providing a bias adjustment when approximating a discrete distribution with a continuous distribution. However, replacing actual values with imputed ones can lead to different estimates compared to the unimputed ones, particularly when the events are rare. Another problem was the question of which value to impute for zero – different values can lead to different results. The most common continuity correction is  $+\frac{1}{2}$ , which

may have a large impact on estimates of probability when the original counts are small (for instance, when the counts are 0, 1 or 2 as they often were in this study).

A Cox proportional hazards model was also used by the sponsor, with time-to-first-event as the outcome, with “treatment” as the only predictor, stratified by study. An Anderson-Gill model was also used to account for multiple events occurring for the same individual, also using treatment as the only predictor and stratified by study. The data was also analyzed using Shuster’s method<sup>8</sup> (a random effects meta-analysis method that stratifies by study but weights all studies equally) and a simple pooling of the data from all the studies (no stratification).

For secondary analysis, the sponsor performed an analysis on the incidence rates. A poisson regression was performed on the incidence rates, as well as point and confidence interval estimates of the incidence rates of the number of subjects experiencing an event and the incidence rate of the total number of events. The model for the poisson regression comprised the number of events as the outcome, and treatment, study, renal disease (normal, mild, moderate), BMI (BMI<30 or  $\geq 30$ ) and age (Age<65 or  $\geq 65$ ) as predictors.

In addition, the sponsor carried out a subgroup analysis on 3 risk factors: BMI, renal status and age. This was comprised of pooled 2-by-2 or 2-by-3 tables and calculating the RR and confidence interval. The sample sizes were small, and therefore stratified subgroup analysis was not feasible.

## **Results and Conclusions**

The overall results (without continuity corrections) are presented in Table 5 and Table 7, for SMQ and Custom MACE, respectively. There was great variation in the estimates for the risk ratio (RR) for each study, with estimates ranging from 0.5 to 3.6 for SMQ MACE and 0.5 to 2.9 for Custom MACE, largely due to the low frequency of events. Generally, the incidence rate ratio (IRR) was similar to the risk ratio. The overall asymptotic Mantel-Haenszel estimates of the confidence interval of the risk ratio, without continuity correction, were (0.555, 1.511) for SMQ MACE and (0.332, 2.306) for Custom MACE. The other methods (Cox, Anderson-Gill, Poisson regression) gave similar estimates. The 12 Byetta studies seemed similar enough to each other to include in a meta-analysis (see Table 3) and the sample sizes were small, so therefore a test of homogeneity or a random effects analysis would not be informative.

For the 30 week study comparing Bydureon to Byetta, there were 1 or 2 events in each arm, depending on the MACE definition (see Table 14). There were too few events to warrant estimating the confidence interval. Note that, during the lead-in period for study 2993LAR-105, there was 1 SMQ event in each arm and 1 Custom MACE event in the

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<sup>8</sup> Shuster, J.J., Jones, L.S., Salmon, D.A., Fixed vs random effects meta-analysis in rare event studies: the rosiglitazone link with myocardial infarction and cardiac death. *Statistics in Medicine*, 2007; **26**: 4375—4385.

Byetta arm. These events occurred after the first “lead-in” injection and prior to the first injection of study medication on Day 1.

For study BCB106, a 26 week study comparing Bydureon to Sitagliptin and Pioglitazone, only 2 and 0 events were observed for the SMQ and Custom MACE events respectively, compared to 2 and 1 for Sitagliptin and 4 and 1 for Pioglitazone (see Table 15).

The results for the uncontrolled studies were given as point estimates of the incidence (see Table 16). Four of the five extension studies were extensions of previous controlled studies, and the data from those studies has been added to their respective extension studies.

#### **4. FINDINGS IN SPECIAL/SUBGROUP POPULATIONS**

Subgroup analysis (not stratified by study) was based age, BMI and renal impairment and this analysis was repeated for the SMQ and Custom MACE endpoints (see Table 8 through Table 13) without using a continuity correction. The confidence intervals were wide due to the small sample sizes and some risk ratios could not be calculated due to zero counts in some cells. There were no notable results or trends in any of the subgroup analyses. It should be noted that, although in the December 2008 document “Guidance for Industry: Diabetes Mellitus – Evaluating Cardiovascular Risk in New Antidiabetic Therapies to Treat Type 2 Diabetes” it is stated that subgroup analyses of gender, race and age is required, the analyses of race and gender were not performed.

#### **5. SUMMARY AND CONCLUSIONS**

##### **5.1 Statistical Issues and Collective Evidence**

There were several limitations to the meta-analysis.

- The studies were not designed to assess cardiovascular risk, and therefore the cardiovascular events were not prospectively adjudicated. This allows for potential bias, e.g. some subgroups or treatment arms may be scrutinized more closely for cardiovascular events, information may not be collected at the time that would be important in determining if a cardiovascular event occurred, etc.
- Subjects with ‘significant’ history of cardiovascular heart disease were excluded from the studies. This means that it was not possible to assess the possible increased risk for those who already have an elevated risk for cardiovascular events. Given the correlation between diabetes and cardiovascular disease, this imposes a serious limitation on generalizing the results to the general diabetic population.
- There were few events, making estimation of risk difficult (see comments below). The study does not have sufficient power to estimate the risk of cardiovascular events with a reasonable degree of variability.

The non-significant results were due in part to the small number of events that have been observed the corresponding wide confidence bands of the relative risk (RR). Many studies have zero events in one or both arms (between 6 and 8 of the 12 studies in the meta-analysis have zero events in both arms, depending on the definition of the event) which make it impossible to estimate a RR for these studies without imputing a value for at least one of the zero counts. In addition, there was variation in the direction of the point estimate for the RR with some studies having an estimate above 1 (risk of cardiovascular event greater in the Byetta group) and some studies having an estimate below 1 (risk of cardiovascular event lower in the Byetta group). The resulting confidence intervals often include 1 and the upper limits of the confidence intervals frequently cross the 1.3 or 1.8 guideline thresholds given in the guidance “Guidance for Industry: Diabetes Mellitus – Evaluating Cardiovascular Risk in New Antidiabetic Therapies to Treat Type 2 Diabetes”. When the 12 studies were combined using Mantel-Haenszel techniques with no continuity correction to substitute values for the “zero-zero” studies, the final confidence intervals were (0.555, 1.511) for the broader definition of a cardiovascular event (SMQ MACE) and (0.332, 2.306) for the narrower definition of a cardiovascular event (Custom MACE).

## **5.2 Conclusions and Recommendations**

There is no evidence to conclude that Byetta has an increased or decreased risk of cardiovascular events compared to placebo or insulin. According to the guidelines for assessing cardiovascular risks for diabetes therapies<sup>9</sup> if the upper limit of the confidence interval for the risk ratio is above 1.3 or 1.8 further studies to assess the risk must be performed. Given that the upper limits of the confidence intervals were 1.5 and 2.3 respectively, and the limitations of the meta-analysis, the low number of events (and resulting high variability of the estimates), it is recommended that Bydureon be approved on the condition that at least one further post-marketing study is completed in order to ascertain whether cardiovascular risk ratio is below 1.3 or not. It is also recommended that a subgroup analysis on race, gender and age be included in the post-marketing study, as per the guidance.

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<sup>9</sup> “Guidance for Industry: Diabetes Mellitus – Evaluating Cardiovascular Risk in New Antidiabetic Therapies to Treat Type 2 Diabetes.”, December 2008.

## APPENDIX

**Table 3. Summary of 12 studies used in meta-analysis to assess cardiovascular risk of Byetta. No significant follow-up for cardiovascular events or other adverse events unless stated.**

Study	Control	Conco- mitant OAD <sup>10</sup>	Description	Summarized Inclusion Criteria	Summarized Exclusion Criteria
2993-112	Placebo	Met	Phase 3. Run in period with placebo 4 weeks. 4 arms: 1. 30 weeks 5mcg Exenatide BID, 2. 4 weeks 5mcg BID, 26 weeks 10mcg BID, 3.& 4. placebo arms for 1. & 2. Randomization 2:2:1:1. Stratified according to baseline HbA <sub>1c</sub> (<9% and ≥9%). Visits: week-6/screening, week -4/run-in, Day 1/baseline, Weeks 2, 4, 6, 12, 18, 24, 30. Primary efficacy measure: change in HbA <sub>1c</sub> from baseline to 30 weeks.	- 16-75 years - HbA <sub>1c</sub> between 7.1-11.0% - BMI 27-45kg/m <sup>2</sup> . - Treated with Met alone for 3 months prior to screening.	- Received exogenous insulin therapy - Other (non-Met) oral anti-diabetic agents within 3 months of screening. - Significant history of heart disease. - Hypertension. - Clinically significant history of hepatic, renal, CNS, GI, pulmonary or hematologic disease. - Acute or chronic illness.
2993-113	Placebo	SU	Phase 3. Same as 2293-112 but concomitant med is SU rather than Met.	- 16-75 years - HbA <sub>1c</sub> between 7.1-11.0% - BMI 27-45kg/m <sup>2</sup> . - Treated with SU alone for 3 months prior to screening.	- Received exogenous insulin therapy - Other (non-Met) oral anti-diabetic agents within 3 months of screening. - Significant history of heart disease. - Hypertension. - Clinically significant history of hepatic, renal, CNS, GI, pulmonary or hematologic disease. - Acute or chronic illness.
2993-115	Placebo	Met+ SU	Phase 3. Same as 2293-112 but concomitant meds are SU+Met.	- 16-75 years - HbA <sub>1c</sub> between 7.1-11.0% - BMI 27-45kg/m <sup>2</sup> . - Treated with SU alone for 3 months prior to screening.	- Received exogenous insulin therapy - Other (non-Met) oral anti-diabetic agents within 3 months of screening. - Significant history of heart disease. - Hypertension.

<sup>10</sup> OAD: Oral Anti-diabetic medication

					<ul style="list-style-type: none"> <li>- Clinically significant history of hepatic, renal, CNS, GI, pulmonary or hematologic disease.</li> <li>- Acute or chronic illness.</li> </ul>
H8OJE-GWAP	Placebo	TZD or TZD+Met	Parallel, double blind study. 2 week placebo lead in. 2 arms: 1) 5mcg BID for 4weeks then 10mcg BID for 12 weeks, 2) Placebo. No follow-up for early discontinuation or after study. US, Puerto Rico.	<ul style="list-style-type: none"> <li>- 21-75 years</li> <li>- HbA<sub>1c</sub> between 7-10%</li> <li>- BMI 25-45kg/m<sup>2</sup>.</li> <li>- Treated with TZD or TZD+Met for 3 months prior to screening.</li> </ul>	<ul style="list-style-type: none"> <li>- Insulin for &gt; 1 week 3 mo prior to screening.</li> <li>- Significant history of heart disease.</li> <li>- Hypertension.</li> </ul>
H8OMC-GWAV	Placebo	SU or Met+SU	Phase 2, partial double-blind (investigators know injection volume), parallel group. 4 arms: 2.5mcg, 5mcg, 2 weeks 5mcg and 8 weeks 10mcg, and placebo BID. Japanese, dose response study where type 2 diabetes is treated with oral anti-diabetic medication but not well controlled.	<ul style="list-style-type: none"> <li>-20-75 years</li> <li>- ≥50Kg</li> </ul>	<ul style="list-style-type: none"> <li>- Hospitalization of cardiac disease within 1 year prior to study</li> </ul>
H8OMC-GWBA	Placebo	Met or Met+SU	Double-blind parallel group. 2 week placebo lead-in. 2 arms: 1). 5mcg BID 4 weeks then 10mcg for 12 weeks, 2) Placebo. China, India, Korea, Taiwan.	<ul style="list-style-type: none"> <li>- 21-75 years</li> <li>- 7.1-11% HbA<sub>1c</sub></li> <li>-BMI 21-35 kg/m<sup>2</sup></li> </ul>	<ul style="list-style-type: none"> <li>- History of cardiac disease.</li> </ul>
H8OMC-GWBJ	Placebo	D+E only	Exenatide as a monotherapy in treatment naïve patients. Double-blind, parallel, placebo controlled. 2 week lead in with placebo for both arms. 3 arms: 1)24 weeks 5mcg Exenatide BID, 2) 4 weeks 5mcgBID then 20 weeks 10 mcg BID Exenatide, 3) Placebo. US, Puerto Rico.	<ul style="list-style-type: none"> <li>- ≥18 years</li> <li>- treated with diet and exercise therapy consistent with local standards of care</li> <li>- HbA<sub>1c</sub> 6.5-10%</li> <li>- BMI 25-46 kg/m<sup>2</sup></li> </ul>	<ul style="list-style-type: none"> <li>- Treated with anti-diabetic agent</li> <li>- poorly controlled blood pressure</li> <li>- clinically significant history or presence of Class III or IV heart disease (i.e. marked limitation or inability to carry out physical activity), angioplasty or bypass surgery (in past year or expected to need during study period).</li> </ul>

H8OMC-GWCD	Placebo	Met and/or TZD	Effect on mean 24hour heart rate. GWAE and GWAQ increase heart rate was observed over 24 hours compared to placebo. This study studies HR and BP for 12 weeks. 2 arms: 1) 5mcg BID Exenatide for 4 weeks and 10mcg for 8 weeks, 2) placebo. Placebo lead-in for 1 week.	- 18-75 years - HbA <sub>1c</sub> 6.5-9.5% - BMI 25-40 kg/m <sup>2</sup> - if being treated for hypertension must have been on stable regimen for at least 6 weeks.	- clinically significant heart disease. - HR not within normal range - tachycardia, arrhythmia etc. - uncontrolled hypertension. - beta-blockers
H8OMC-GWAA	Insulin	Met+ SU	Open label comparing insulin with Exenatide (for patients already on Met+Su). 2 arms: 1)5mcg Exenatide BID for 4 weeks then 22 weeks 10mcg BID, 2) Insulin.	-30-75 years - HbA <sub>1c</sub> 7-10% - BMI 25-45 kg/m <sup>2</sup>	- Cardiac disease class III or IV (i.e. marked limitation or inability to carry out physical activity)
H8OMC-GWAD	Insulin	Met+ SU	Phase 3. Open label. Parallel. 2 arm: 1) Exenatide 5mcg BID for 4 weeks then 10mcg BID for 48 weeks, 2) Insulin.	-30-75 years - HbA <sub>1c</sub> 7-11% - BMI 25-40 kg/m <sup>2</sup>	- Cardiac disease class III or IV (i.e. marked limitation or inability to carry out physical activity)
H8OMC-GWAK	Insulin	SU or Meg and/or Met	Japanese(?) study. “Exploratory” study” substituting Exenatide for Insulin. Open label. Parallel. 2 arms: 1) 4 weeks 5mcg BID Exenatide then 12 weeks 10 mcg 2) insulin.	-30-70 years - HbA <sub>1c</sub> <10.5% - BMI 27-40 kg/m <sup>2</sup>	- Cardiac disease class III or IV (i.e. marked limitation or inability to carry out physical activity)
H8OMC-GWAO	Insulin	Met or SU	Cross-over design, 16 weeks per treatment. Open label. 2 arms: 1) Period 1 Insulin 16 weeks, Period 2 Exenatide 5mcg 4 weeks, 10mcg 12 weeks, 2) Period 1 Exenatide 5mcg 4 weeks, 10mcg 12 weeks and Period 2 Insulin 16 weeks.	- For all patients insulin would be the “next step”. - HbA <sub>1c</sub> 7.1-11% - BMI 25-40 kg/m <sup>2</sup>	- clinically significant heart disease.

**Table 4: SMQ MACE, asymptotic risk ratios and incidence rate ratios with no continuity correction (SDS 6.1, p37).<sup>11</sup>**

Study	Duration (Weeks)	Byetta		Exposure Control		Exposure		P1	P2	IR1	IR2
		events	N	(Person- Years)	events	N	(Person- Years)				
2993-112	Placebo	30	6	223	113.8	6	113	57.8	0.027	0.053	0.104
2993-113		30	15	254	123.2	2	123	55.1	0.059	0.016	0.036
2993-115		30	13	486	254.9	11	247	122.2	0.027	0.045	0.090
H8OJE-GWAV		16	3	111	31.7	1	40	32.3	0.027	0.025	0.031
H8OMC-GWAP		12	0	121	23.9	0	112	9.2	0.000	0.000	0.000
H8OMC-GWBA		16	1	234	65.5	2	233	67.3	0.004	0.009	0.030
H8OMC-GWBJ		24	0	155	65.2	0	77	33.1	0.000	0.000	0.000
H8OMC-GWCD		12	0	28	5.8	0	26	5.7	0.000	0.000	0.000
H8OMC-GWAA	Insulin	26	0	282	122.5	0	267	124.6	0.000	0.000	0.000
H8OMC-GWAD		52	3	253	220.1	2	248	228.6	0.012	0.008	0.014
H8OMC-GWAK		16	0	33	7.7	0	16	5.2	0.000	0.000	0.000
H8OMC-GWAO		16	0	136	37.3	0	127	38.9	0.000	0.000	0.000
SMQ MACE			41	2316		24	1629				

**Table 5. Mantel-Haenszel overall risk ratio with no continuity correction, for SMQ MACE:**

Study		Byetta		Control		Risk Ratio	Confidence Intervals		Mantel-Haenszel Risk Ratio	Confidence Intervals	
		events	N	events	N		Lower	Upper		Lower	Upper
2993-112	Placebo	6	223	6	113	0.507	0.167	1.536			
2993-113		15	254	2	123	3.632	0.844	15.633			
2993-115		13	486	11	247	0.601	0.273	1.321			
H8OJE-GWAV		3	111	1	40	1.081	0.116	10.096			
H8OMC-GWAP		0	121	0	112						
H8OMC-GWBA		1	234	2	233	0.498	0.045	5.453			
H8OMC-GWBJ		0	155	0	77						
H8OMC-GWCD		0	28	0	26						
H8OMC-GWAA	Active	0	282	0	267						
H8OMC-GWAD		3	253	2	248	1.470	0.248	8.725			
H8OMC-GWAK		0	33	0	16						
H8OMC-GWAO		0	136	0	127						
SMQ MACE			2316		1629				0.915	0.555	1.511

<sup>11</sup> P1: Probability of cardiovascular event in Byetta group, P2: Probability of cardiovascular event in control group, IR1: incidence rate for Byetta group (events per person-year), IR2: incidence rate for control group (events per person-year), IRR: Incidence Rate Ratio IR1/IR2.

**Table 6. CUSTOM MACE, Asymptotic risk ratios and incidence rate ratios with no continuity correction (SDS6.2, p38)**

Study	Duration (Weeks)	Byetta		Exposure Placebo		Exposure		P1	P2	IR1	IR2	
		events	N	(Person- Years)	events	N	(Person- Years)					
2993-112	Placebo	30	0	223	113.8	0	113	57.8	0.000	0.000	0.000	0.000
2993-113		30	2	254	123.2	1	123	55.1	0.008	0.008	0.016	0.018
2993-115		30	3	486	254.9	3	247	122.2	0.006	0.012	0.012	0.025
H8OJE-GWAV		16	0	111	31.7	0	40	32.3	0.000	0.000	0.000	0.000
H8OMC-GWAP		12	0	121	23.9	0	112	9.2	0.000	0.000	0.000	0.000
H8OMC-GWBA		16	1	234	65.5	2	233	67.3	0.004	0.009	0.015	0.030
H8OMC-GWBJ		24	0	155	65.2	0	77	33.1	0.000	0.000	0.000	0.000
H8OMC-GWCD		12	0	28	5.8	0	26	5.7	0.000	0.000	0.000	0.000
H8OMC-GWAA	Active	26	0	282	122.5	0	267	124.6	0.000	0.000	0.000	0.000
H8OMC-GWAD		52	3	253	220.1	1	248	228.6	0.012	0.004	0.014	0.004
H8OMC-GWAK		16	0	33	7.7	0	16	5.2	0.000	0.000	0.000	0.000
H8OMC-GWAO		16	0	136	37.3	0	127	38.9	0.000	0.000	0.000	0.000
Custom MACE				2316			1629					

**Table 7: Mantel-Haenszel overall risk ratio with no continuity correction for Custom MACE:**

Study		Byetta		Placebo		Risk Ratio	Confidence Intervals		Mantel-Haenszel Risk Ratio	Confidence Interval	
		events	N	events	N		Lower	Upper		Lower	Upper
2993-112	Placebo	0	223	0	113						
2993-113		2	254	1	123	0.969	0.089	10.578			
2993-115		3	486	3	247	0.508	0.103	2.500			
H8OJE-GWAV		0	111	0	40						
H8OMC-GWAP		0	121	0	112						
H8OMC-GWBA		1	234	2	233	0.498	0.045	5.453			
H8OMC-GWBJ		0	155	0	77						
H8OMC-GWCD		0	28	0	26						
H8OMC-GWAA	Active	0	282	0	267						
H8OMC-GWAD		3	253	1	248	2.941	0.308	28.081			
H8OMC-GWAK		0	33	0	16						
H8OMC-GWAO		0	136	0	127						
SMQ MACE			2316		1629				0.875	0.332	2.306

**Table 8: SMQ MACE by Age, risk ratios and incidence rate ratios (Table SDS 8.1.1, p46 Revised Meta Analysis)**

Age<65					Age>=65				
	Event	No Event	Total	Exposure		Event	No Event	Total	Exposure
Exenatide	37	1804	1841	851.9	Exenatide	4	471	475	219.6
Control	20	1276	1296	601.7	Control	4	329	333	178.3
Total	57	3080	3137			8	800	808	
P1	0.020		IR1	0.043	P1	0.008		IR1	0.018
P2	0.015		IR2	0.033	P2	0.012		IR2	0.022
RR	1.302		IRR	1.307	RR	0.701		IRR	0.812
95%CI RR	0.759	2.233	95%CI IRR	0.758 2.251	95%CI RR	0.177	2.783	95%CI IRR	0.203 3.247

**Table 9: Custom MACE by Age (Table SDS 8.2.1, p55 Revised Meta Analysis)**

Age<65	Event	No Event	Total	Exposure	Age>=65	Event	No Event	Total	Exposure
Exenatide	8	1833	1841	851.9	Exenatide	1	474	475	219.6
Control	5	1291	1296	601.7	Control	2	331	333	178.3
Total	13	3124	3137			3	805	808	
P1	0.004		IR1	0.009	P1	0.002		IR1	0.005
P2	0.004		IR2	0.008	P2	0.006		IR2	0.011
RR	1.126		IRR	1.130	RR	0.351		IRR	0.406
95%CI RR	0.369	3.435	95%CI IRR	0.370 3.454	95%CI RR	0.032	3.850	95%CI IRR	0.037 4.477

**Table 10: SMQ MACE by Renal Impairment (Table SDS 8.1.2 p49 Revised Meta Analysis)**

Normal	Event	No Ev.	Total	Exp.	Mild	Event	No Ev.	Total	Exp.	Moderate	Event	No Ev.	Total	Exp.
Byetta	38	1951	1989	939	Byetta	3	308	311	125.9	Byetta	0	15	15	6.4
Control	22	1374	1396	669	Control	2	220	222	106.4	Control	0	10	10	4.4
Total	60	3325	3385		Total	5	528	533		Total	0	25	25	
P1	0.019		IR1	0.040	P1	0.010		IR1	0.024	P1	0.000		IR1	0.000
P2	0.016		IR2	0.033	P2	0.009		IR2	0.019	P2	0.000		IR2	0.000
RR	1.212		IRR	1.230	RR	1.071		IRR	1.268	RR			IRR	
95%CI	0.720	2.040	95%CI	0.727 2.079	95%CI	0.180	6.355	95%CI	0.212 7.587	95%CI			95%CI	

**Table 11: Custom MACE by Renal Impairment (Table SDS 8.2.2 p58 Revised Meta Analysis)**

Normal	Event	No Ev.	Total	Exp.	Mild	Event	No Ev.	Total	Exp.	Moderate	Event	No ev.	Total	Exp.
Byetta	8	1981	1989	939.3	Byetta	1	310	311	125.9	Byetta	0	15	15	6.4
Control	6	1390	1396	668.7	Control	1	221	222	106.4	Control	0	10	10	4.4
Total	14	3371	3385		Total	2	531	533		Total	0	25	25	
P1	0.004		IR1	0.009	P1	0.003		IR1	0.008	P1	0.000		IR1	0.000
P2	0.004		IR2	0.009	P2	0.005		IR2	0.009	P2	0.000		IR2	0.000
RR	0.936		IRR	0.949	RR	0.714		IRR	0.845	RR			IRR	
95%CI	0.325	2.691	95%CI	0.329 2.736	95%CI	0.045	11.352	95%CI	0.053 13.512	95%CI			95%CI	

**Table 12: SMQ MACE by BMI (Table SDS 8.1.3 p52 Revised Meta Analysis)**

BMI<30	Event	No Ev.	Total	Exp.	BMI>=30	Event	No Ev.	Total	Exp.
Byetta	16	1012	1028	441	Byetta	25	1263	1288	630.5
Control	10	717	727	339.7	Control	14	888	902	440.2
Total	26	1729	1755			39	2151	2190	
P1	0.016		IR1	0.036	P1	0.019		IR1	0.040
P2	0.014		IR2	0.029	P2	0.016		IR2	0.032
RR	1.132		IRR	1.232	RR	1.251		IRR	1.247
95%CI RR	0.516	2.479	95%CI IRR	0.559 2.716	95%CI RR	0.654	2.392	95%CI IRR	0.648 2.398

**Table 13: Custom MACE by BMI (Table SDS 8.2.3 p61 Revised Meta Analysis)**

BMI<30	Event	No Ev.	Total	Exp.	BMI>=30	Event	No Ev.	Total	Exp.
Byetta	4	1024	1028	441	Byetta	5	1283	1288	630.5
Control	4	723	727	339.7	Control	3	899	902	440.2
Total	8	1747	1755			8	2182	2190	
P1	0.004		IR1	0.009	P1	0.004		IR1	0.008
P2	0.006		IR2	0.012	P2	0.003		IR2	0.007
RR	0.707		IRR	0.770	RR	1.167		IRR	1.164
95%CI RR	0.177	2.819	95%CI IRR	0.193 3.080	95%CI RR	0.280	4.872	95%CI IRR	0.278 4.869

**Table 14: Exenatide vs Byetta, Study 2993LAR-105, 30 week**

Endpoint	Exenatide Event	N	Byetta Event	N	P1	P1	RR
SMQ	2	148	2	145	0.0135	0.0138	0.9797
Custom	1	148	1	145	0.0068	0.0069	0.9797

**Table 15: CV events for BCB106, Exenatide LAR vs Sitagliptin and Pioglitazone, 26 week.**

Endpoint	Exenatide Event	N	Sitagliptin Event	N	Pioglitazone Event	N
SMQ	2	160	2	166	4	165
Custom	0	160	1	166	1	165

**Table 16: Incidence rates for uncontrolled studies (including events from controlled portion of study)**

	Events	N	Exposure (Years)	Incidence Rate per 1000 person-years
SMQ	98	2919	2898.7	33.808
Custom	25	2919	2993.9	8.350

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22200	ORIG-1	AMYLIN PHARMACEUTICA LS INC	EXENATIDE LAR

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/s/

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FIONA M CALLAGHAN  
02/02/2010

MARK S LEVENSON  
02/03/2010



U.S. Department of Health and Human Services  
Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Translational Sciences  
Office of Biostatistics

# STATISTICAL REVIEW AND EVALUATION

## CLINICAL STUDIES

**NDA/Serial Number:** 022200/0

**Drug Name:** Bydureon (exenatide LAR) injectable suspension

**Indication(s):** Treatment of type 2 diabetes mellitus

**Applicant:** Amylin Pharmaceuticals, Inc.

**Date(s):** Stamp date May 5, 2009  
PDUFA Goal Date March 5, 2009

**Review Priority:** Standard

**Biometrics Division:** Division of Biometrics 2

**Statistical Reviewer:** Janice Derr, Ph.D.

**Concurring Reviewers:** J. Todd Sahlroot, Team Leader and Deputy Division Director  
Thomas Permutt, Division Director

**Medical Division:** Division of Metabolism and Endocrinology Products

**Clinical Team:** Valerie Pratt, M.D., Medical Reviewer  
Hylton Joffe, M.D., Medical Team Leader  
Mary H. Parks, M.D., Division Director

**Project Manager:** John Bishai

**Keywords:** clinical studies, NDA review

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## 1. EXECUTIVE SUMMARY

### 1.1 Conclusions and Recommendations

**Efficacy Conclusions:** The efficacy of exenatide LAR (2 mg SC once weekly) was supported by a non-inferiority comparison to Byetta® (exenatide 10 mcg SC twice a day) for change in HbA1c at week 30 compared to baseline (TABLE 1). These results come from one clinical study. The majority of patients (78%) were Caucasian. The average HbA1c response in the two arms was fairly similar across gender and age groups, and for the majority of patients (73%) with baseline HbA1c < 9.0. In patients with baseline HbA1c ≥ 9.0, the average reduction in HbA1c in the exenatide LAR group was greater than in the Byetta group (p = 0.001).

TABLE 1 Study 105, Primary efficacy analysis: Change in HbA1c at week 30

	N	Baseline mean HbA1c ± SE	Adjusted mean change from baseline at Week 30 ± SE <sup>1</sup>	Exenatide LAR – Byetta Difference in adjusted mean change (95% CI) <sup>†</sup>	P-value
<b>All patients (ITT/LOCF)</b>					
Exenatide LAR	148	8.3 ± 0.1	-1.9 ± 0.1	-0.3 (-0.5, -0.1)	0.002
Byetta	147	8.3 ± 0.1	-1.5 ± 0.1		

Results from the analysis of secondary efficacy endpoints, including fasting plasma glucose, also supported the efficacy of exenatide LAR compared to Byetta. Both products were associated with weight loss in approximately 78% of patients, with a fairly similar average weight loss of approximately 3.7 kg at week 30 compared to baseline in both arms.

In my opinion, Study 105 had two weaknesses in design. These weaknesses did not appear to cause substantial problems. However, it may be useful to evaluate the efficacy of exenatide LAR further from the three clinical studies that were ongoing at the time that NDA 022200/0 was submitted. The two weaknesses were as follows: (1) Study 105 was open-label, and a dose adjustment in background sulfonylurea (SU) in the weeks prior to week 30 was made by clinical staff who had access to daily blood levels. This affected 37% of patients in the study. However, I did not find evidence for bias in the study results. (2) Study 105 used an investigational source of exenatide LAR that was different from the commercial source. A sub-study of Study 105, comparing the two sources, was conducted in the weeks after the primary endpoint had been determined, when the average starting baseline was 6.8. The commercial source resulted in a less favorable average change in HbA1c by 0.2 (95% confidence interval 0.0, 0.3), compared to the investigational source. Reducing the average effect of exenatide LAR on HbA1c by 0.3 (using the upper CI bound) would not affect the non-inferiority evaluation from Study 105. However, we do not know how this difference would affect a target population with a higher average baseline.

**Safety Conclusions:** Conclusions regarding the safety of exenatide LAR are addressed in the clinical review by Dr. Valerie Pratt. Dr. Fiona Callaghan, Division of Biometrics 7, is conducting a separate review of the analysis of cardiovascular endpoints from the Phase 2 and Phase 3 studies of exenatide (i.e., Byetta and exenatide LAR).

**Recommendations:**

- (1) I suggest that the Division consider the weaknesses in design of Study 105, even though these weaknesses did not cause substantial problems, in their decision about this application. It may be useful to evaluate the efficacy of exenatide LAR further from the three clinical studies that were ongoing at the time that NDA 022200/0 was submitted.
- (2) This review includes general recommendations for the labeling text in part 5.3.

## 1.2 Brief Overview of Clinical Studies

The NDA022200/0 submission includes efficacy and safety data from Study 2993LAR-105, in which exenatide 2 mg SC once weekly (LAR) was compared to Byetta 10 mcg SC twice a day. Eligible patients had type 2 diabetes, and had been treated with diet and exercise alone or with a stable regimen of metformin, sulfonylurea (SU), thiazolidinediones (TZD) or a combination of SU and TZD for a minimum of two months prior to screening. The study had 295 patients in the intention-to-treat data base. Following 30 weeks of treatment (at which time the primary efficacy endpoint was evaluated), all patients received exenatide LAR for at least 22 weeks.

At the time of the submission of this application, three additional randomized studies of exenatide LAR in patients with type 2 diabetes were ongoing, as shown in TABLE 3 in Part 2.3 of this review.

## 1.3 Statistical Issues and Findings

At week 30, exenatide LAR (2 mg SC once weekly) produced a statistically significant net mean reduction in HbA1c from baseline, compared to Byetta (10 mcg SC twice a day), with a 95% confidence interval of (-0.5, -0.1) in the direction of superior efficacy of exenatide LAR. Results from the analysis of secondary efficacy endpoints, including fasting plasma glucose, also supported the efficacy of exenatide LAR compared to Byetta. Both products were associated with weight loss in approximately 78% of patients, with a fairly similar average weight loss of approximately 3.7 kg at week 30 compared to baseline in both arms.

A review concern was the potential for bias due to an unblinded adjustment of the SU dose prior to week 30, in the subgroup of patients who had background SU therapy (37% of the randomized patients). The study was open-label, and the SU dose adjustment was made by clinical staff who

had access to daily blood glucose levels. In my opinion, the potential for bias could have resulted in a greater up-titration of the SU dose in patients in the exenatide LAR arm compared to the Byetta arm (within the SU subgroup). However, the distribution of SU dose adjustments in the two arms did not support this review concern. In fact, a larger percentage of Byetta-treated patients had increased SU doses than the exenatide LAR-treated patients, relative to their baseline dose. In addition, the comparison between exenatide LAR and Byetta was fairly similar in the SU subgroup and the non-SU subgroup. While it was medically necessary to manage the SU dose during the 30-week assessment period, I believe that the study blind could have been maintained through sham injections or through separation of function.

I believe that it may be useful to evaluate the efficacy of exenatide LAR further from the three clinical studies that were ongoing at the time of submission of NDA 022200/0 (see TABLE 3 in part 2.1). Study GWBR used the same open-label design as Study 105 (comparing an exenatide LAR arm to an insulin glargine arm, with background therapy of metformin or metformin and a sulfonylurea). Study BCB106 had a double-blind design (comparing an exenatide LAR arm, a sitagliptin arm and a pioglitazone arm, all with a background of metformin), as did Study GWCH (comparing an exenatide LAR arm, a metformin arm, a sitagliptin arm and a pioglitazone arm, all as monotherapies).

A second review concern was the source of manufactured exenatide LAR for the 30-week assessment period of Study 105. Study 105 used an investigational source of exenatide LAR that was different from the commercial source. Because the bioequivalence of the two sources had not been established at the outset of Study 105, a sub-study was conducted, comparing the two sources, in the weeks after the primary endpoint had been determined. The commercial source resulted in a lower average reduction in HbA1c by 0.2 compared to the investigational source, with a 95% confidence interval of (0.0, 0.3). While this average difference was small and had a p-value of 0.062, we do not know how this effect would translate to a target population with a higher baseline HbA1c (for example, the main study had average baseline of 8.3) than the sub-study (which had a baseline of 6.8). The manufacturing source of exenatide LAR in Studies GWBR and GWCH was not known at the time of this review.

## **2. INTRODUCTION**

### **2.1 Overview**

Exenatide extended release formulation is an extension of the already-approved exenatide immediate release formulation (Byetta®). Byetta injection is approved in the United States as monotherapy or as adjunctive therapy for adult patients with type 2 diabetes mellitus treated with metformin, a sulfonylurea, a thiazolidinedione, a combination of metformin and a sulfonylurea, or a combination of metformin and a thiazolidinedione, who have not achieved adequate glycemic control (approved under NDA 021773). Exenatide is an incretin mimetic agent that

stimulates glucose-dependent insulin secretion. Endogenous incretins, such as glucagon-like peptide-1 (GLP-1) enhance glucose-dependent insulin secretion and exhibit other antihyperglycemic actions following their release into circulation from the gut in response to food intake. Byetta is administered within the 60-minute period before the morning and evening meals and primarily exerts its pharmacodynamic effects on glucose concentrations during the postprandial period of those meals. The extended release formulation of exenatide, described in this submission, is intended as a once weekly injection.<sup>1</sup>

### **Scope of Statistical Review: Pivotal Efficacy and Safety Studies**

Study 105: This statistical review covers the report for Study 2993 LAR-105 (referred to as Study 105 in this review), that was submitted with NDA 022200/0. Study 105 was multicenter, open-label and randomized. Byetta served as the active control arm to exenatide once weekly. During a 3-day lead-in, all patients received Byetta 5 mcg SC twice a day (bid). Subsequently, patients randomized to the exenatide LAR group received exenatide LAR 2 mg SC once weekly (qw). Patients randomized to the Byetta group received Byetta 5 mcg SC *bid* for 4 weeks followed by Byetta 10 mcg SC *bid* for 26 weeks. Following 30 weeks of treatment, all patients received exenatide LAR 2 mg SC qw for at least 22 weeks (FIGURE 1). The duration of the extension study is described as open-ended, with treatment through week 52 described in the clinical report in this submission. The study was conducted from April 15, 2006 (first subject dosed in the lead-in period) to February 20, 2008 (last subject's week 52 visit).

Eligible patients had type 2 diabetes, and had been treated with diet and exercise alone or with a stable regimen of metformin, sulfonylurea (SU), thiazolidinediones (TZD) or a combination of SU and TZD for a minimum of two months prior to screening. Additional eligibility criteria included a screening HbA1c of 7.1 to 11.1, and a body mass index (BMI) from 25 to 45 kg/m<sup>2</sup>.

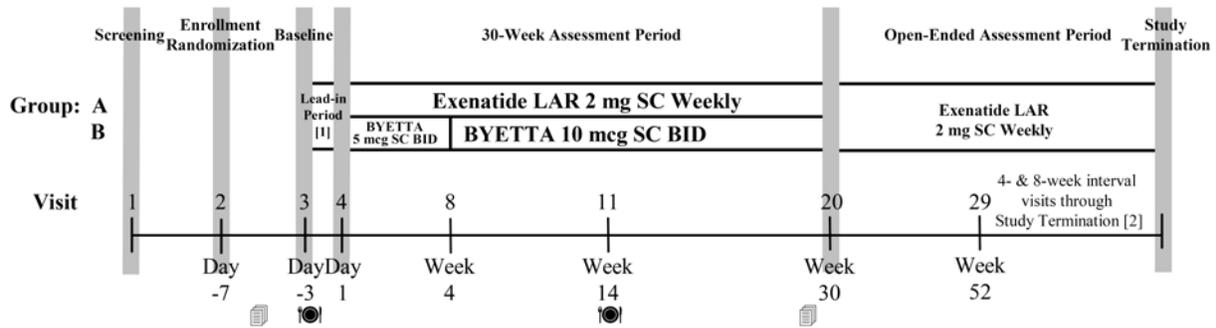
A total of 303 patients were enrolled in the study. Of these, 295 patients received at least one dose of lead-in study medication. After the 3-day lead-in period, 147 were randomized to the Byetta arm and 148 to the exenatide LAR arm. Stratification factors were baseline HbA1c stratum (<9% or ≥ 9%) and concomitant SU use at screening (yes, no).

Because the study was open-label, patients, the study-site staff, the investigator, and the sponsor were not blinded to the identity of treatment assignments. This aspect of the study design has led to review concerns about the up-titration of SU dose in the subgroup of patients with background SU therapy. I discuss these concerns in greater detail in Parts 3.1.4 and 3.1.5 of this review.

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<sup>1</sup> The source of this paragraph is Section 2.2 Introduction (paraphrased) of NDA 022200/0.

FIGURE 1 Schematic of the design of Study 105



Abbreviations: BID, twice daily; LAR, long-acting release; SC, subcutaneous.

● Indicates meal test and postprandial assessments for a subset of subjects at select sites.

☐ Indicates 7-point self-monitored blood glucose profiles performed on any three days in week prior to subsequent visit.

[1] Subjects received BYETTA 5 mcg SC BID during the lead-in period.

[2] Visit 30 (Week 56) through Visits 35 (Week 76) occur at 4-week intervals. Thereafter, all study site visits occur at 8-week intervals.

Source: Study 105 Report, Figure 1

Study 105 was conducted at 29 sites, of which 28 (288 patients) were in the US and 1 (7 patients) was in Canada.

The applicant calculated the sample size for Study 105, approximately 300 patients total to be randomized, with a 1:1 allocation to the exenatide LAR and Byetta arms, with the following assumptions and criteria:

- a standard deviation of the primary endpoint (change in HbA1c between week 30 and baseline) of 1.2
- a non-inferiority margin of 0.4
- a greater reduction in HbA1c (by 0.1) for exenatide LAR than Byetta
- a two-tailed  $\alpha$  of 0.05
- at least 90% power

I confirmed this calculation, obtaining 95% power from the above assumptions, using the statistical software package East 5.2. I note further that when, under the alternative hypothesis, the two products are assumed to have the same reduction in HbA1c, the statistical power is 82%. This is also an acceptable level of power.

The Biometrics review team and the applicant agreed to the noninferiority margin of 0.4% (see the review of the statistical analysis plan submitted under IND 67092/0056 dated 6/15/07). I note that a noninferiority margin of 0.3% or 0.4% is typically acceptable for HbA1c provided this is not greater than a “suitably conservative estimate of the magnitude of the treatment effect of the active control in previous placebo-controlled studies” (see Part 5.G.1. of the February 2008 draft guidance, *Diabetes Mellitus: Developing Drugs and Therapeutic Biologics for Treatment and Prevention*.) In addition, based on calculations from three placebo-controlled

studies that are described in the original statistical review for Byetta, the margin of 0.4% is acceptable from the statistical perspective (TABLE 2).

TABLE 2 Estimate of noninferiority margin from placebo-controlled studies of Byetta®

		Mean change from baseline in HbA1c (s.d.) after 26 weeks	Placebo-adjusted effect (95% CI)	Combined placebo-adjusted effect from Studies 1, 2 and 3 (95% CI)	NI margin calculated from 1/2 x upper 95% CI bound
Study 1 Add-on to metformin	Byetta 10mcg (n=112)	-0.84 (0.12)	-0.82 (-1.13, -0.50)	-0.99 (-1.18, -0.80)	0.4
	Placebo (n=113)	-0.02 (0.11)			
Study 2 Add-on to sulfonylurea	Byetta 10mcg (n=128)	-0.87 (0.11)	-0.96 (-1.26, -0.66)		
	Placebo (n=120)	0.09 (0.12)			
Study 3 Add-on to metformin + sulfonylurea	Byetta 10mcg (n=240)	-0.90 (0.10)	-1.09 (-1.30, -0.88)		
	Placebo (n=242)	0.19 (0.10)			
<p><i>Notes: The combined estimate of effect was obtained from a random effects meta-analysis. The upper 95% CI bound of the combined estimate serves as a conservative estimate of the placebo-adjusted effect of Byetta 10 mcg. From a statistical perspective, one-half of the upper 95% CI bound serves as an estimate of the non-inferiority margin.</i></p> <p><i>Source: Statistics review of Byetta (exenatide injection), NDA 021773; Tables 2, 3 and 4</i></p>					

Other Phase 3 studies: At the time of the submission of NDA 022200/0, three additional randomized studies of exenatide LAR in patients with type 2 diabetes were ongoing, as shown in TABLE 3. The report for Study BCB106 was submitted with the 120-day safety update. I did not evaluate Study BCB106 further in this review.

TABLE 3 Clinical studies of exenatide LAR weekly injection with a 26-week treatment period, conducted in patients with type 2 diabetes

Study identifier	No. of patients treated with Exenatide LAR	Study design	Study Status at time of submission of NDA 022200_0
BCB106	160	26-week blinded treatment period with 3 arms: exenatide LAR, sitagliptin, or pioglitazone and a subsequent open-ended, open-label treatment period in which all patients receive exenatide LAR <ul style="list-style-type: none"> <li>Extent of study blind: Double-blind, maintained by weekly placebo injections and daily placebo tablets.</li> <li>Dates of study (26-week evaluation period): February 11, 2008 to March 9, 2009</li> <li>Study population: Patients on background therapy of metformin</li> <li>Manufacturing source of exenatide LAR: investigational Alkermes source</li> </ul>	Completed (submitted with 120-day safety update on September 3, 2009)
H8O-MC-GWBR	230	26-week assessment period with exenatide once weekly or insulin glargine and an open-ended extension period with exenatide once weekly or insulin glargine expected to last at least 2.5 years <ul style="list-style-type: none"> <li>Extent of study blind: Open label</li> <li>Dates of study (26-week evaluation period): not known at the time of this review</li> <li>Study population: Patients on background therapy of metformin or metformin + sulfonylurea</li> <li>Manufacturing source of exenatide LAR: not known at the time of this review</li> </ul>	Ongoing
H8O-MC-GWCH(a)	246	26-week double-blind, assessment period with 4 arms: exenatide LAR, metformin, pioglitazone, and sitagliptin monotherapies. <ul style="list-style-type: none"> <li>Extent of study blind: Double-blind</li> <li>Dates of study (26-week evaluation period): not known at the time of this review</li> <li>Study population: Drug naïve patients</li> <li>Manufacturing source of exenatide LAR: not known at the time of this review</li> </ul>	Ongoing

## 2.2 Data Sources

The applicant submitted this NDA including the data to the FDA CDER Electronic Document Room (EDR). The submission is recorded in the EDR with the link shown in TABLE 4.

TABLE 4 Data sources for studies

Document: NDA 022200.0 CDER EDR link: <a href="#">\\CDSESUB1\N022200\</a> Company: Amylin Pharmaceuticals, Inc. Drug: Bydureon (exenatide LAR) injectable suspension;	Stamp Date: May 5, 2009
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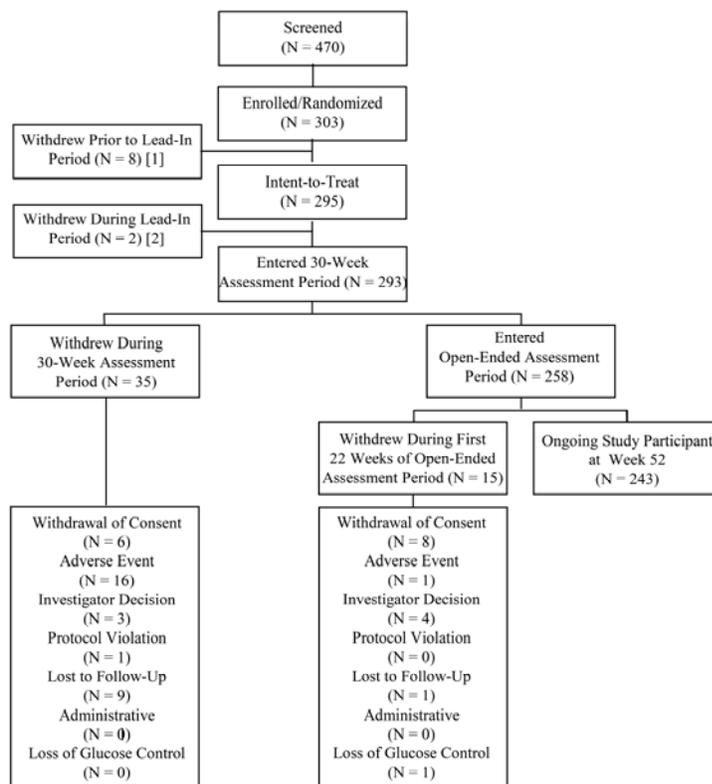
### 3. STATISTICAL EVALUATION

#### 3.1 Evaluation of Efficacy

##### 3.1.1. Subject disposition

During the 3-day lead-in period from day -3 to day 0, all patients received Byetta 5 mcg bid. Of the 295 patients who received at least one dose of lead-in study medication, only two withdrew during the 3-day lead-in period (0.7%). One withdrew consent and one withdrew because of nausea. During the 30-week assessment period, a total of 16 patients (5.4%) withdrew due to adverse events. Based on the number of patients per arm at day 0, Study 105 had greater than 80% retention of patients in both arms through the primary efficacy endpoint determination at week 30 (FIGURE 2, TABLE 5). Only one patient discontinued due to loss of glucose control.

FIGURE 2 Study 105; Subject disposition



[1] Eight subjects withdrew prior to the lead-in period due to: protocol violation (3 subjects), lost to follow-up (1 subject), withdrawal of consent (3 subjects), and investigator decision (1 subject).

[2] Two subjects in the BYETTA group withdrew during the lead in period due to withdrawal of consent (01707) and adverse event (23103 [nausea]).

Source: Study 105 report, Figure 2

TABLE 5 Study 105; Subject disposition by treatment

Disposition	Treatment		All Subjects (N = 295) n (%) [1]
	BYETTA 10 mcg BID (N = 147) n (%) [1]	Exenatide LAR 2 mg QW (N = 148) n (%) [1]	
<b>Completed 30-Week Assessment Period</b>	130 (88.4)	128 (86.5)	258 (87.5)
<b>Withdrawn During 30-Week Assessment Period [2]</b>	15 (10.2)	20 (13.5)	35 (11.9)
Withdrawal of Consent	1 (0.7)	5 (3.4)	6 (2.0)
Adverse Event	7 (4.8)	9 (6.1)	16 (5.4)
Investigator Decision	2 (1.4)	1 (0.7)	3 (1.0)
Protocol Violation	1 (0.7)	0 (0.0)	1 (0.3)
Lost to Follow-up	4 (2.7)	5 (3.4)	9 (3.1)
Administrative	0 (0.0)	0 (0.0)	0 (0.0)
Loss of Glucose Control	0 (0.0)	0 (0.0)	0 (0.0)
<b>Completed First 22 Weeks of Open-Ended Assessment Period</b>	121 (82.3)	122 (82.4)	243 (82.4)
<b>Withdrawn During First 22 Weeks of Open-Ended Assessment Period [3]</b>	9 (6.1)	6 (4.1)	15 (5.1)
Withdrawal of Consent	5 (3.4)	3 (2.0)	8 (2.7)
Adverse Event	0 (0.0)	1 (0.7)	1 (0.3)
Investigator Decision	3 (2.0)	1 (0.7)	4 (1.4)
Protocol Violation	0 (0.0)	0 (0.0)	0 (0.0)
Lost to Follow-up	0 (0.0)	1 (0.7)	1 (0.3)
Administrative	0 (0.0)	0 (0.0)	0 (0.0)
Loss of Glucose Control	1 (0.7)	0 (0.0)	1 (0.3)

Abbreviations: BID, twice daily; ITT, intent-to-treat; LAR, long-acting release; QW, once weekly.

[1] Percentages are based on the number of ITT subjects in each treatment group and overall.

[2] In addition, two subjects in the BYETTA group withdrew during the lead-in period (01707 [withdrawal of consent] and 23103 [adverse event of nausea]).

[3] During the open-ended assessment period, all subjects were treated with exenatide LAR 2 mg QW.

Source: Study 105, Table 2

### 3.1.2. Subject demographic and baseline characteristics

The distribution of subject demographic and baseline characteristics at baseline are given in TABLE 6. The concomitant use of sulfonylurea (SU) medications has a special focus in this review, because the SU dose could be adjusted in the weeks prior to the primary HbA1c endpoint, based on daily levels of blood glucose and other considerations, such as occurrences of hypoglycemia. Of 295 patients in the ITT population, 109 (37%) patients were treated with SU medications, either alone or in combination with other antidiabetic medications (metformin, a thiazolidinedione (TZD), or both; TABLE 7).

TABLE 6 Study 105; Demographic and baseline characteristics by treatment, ITT population

Baseline [1] Characteristics	Treatment		All Subjects (N = 295)
	BYETTA 10 mcg BID (N = 147)	Exenatide LAR 2 mg QW (N = 148)	
<b>Gender - n (%) [2]</b>			
Male	75 (51.0)	82 (55.4)	157 (53.2)
Female	72 (49.0)	66 (44.6)	138 (46.8)
<b>Age at Consent (years)</b>			
Mean (SD)	54.9 (9.6)	55.2 (9.7)	55.0 (9.7)
Minimum, Maximum	20, 80	19, 80	19, 80
<b>Race/Ethnicity - n (%) [2]</b>			
Caucasian	107 (72.8)	123 (83.1)	230 (78.0)
Black	19 (12.9)	9 (6.1)	28 (9.5)
Asian	1 (0.7)	0 (0.0)	1 (0.3)
Hispanic	20 (13.6)	16 (10.8)	36 (12.2)
<b>Mean (SD) Weight (kg)</b>	101.9 (21.0)	101.7 (18.8)	101.8 (19.9)
<b>Mean (SD) BMI (kg/m<sup>2</sup>)</b>	35.0 (5.1)	34.8 (5.0)	34.9 (5.0)
<b>BMI Stratum - n (%) [2]</b>			
<30 kg/m <sup>2</sup>	24 (16.3)	24 (16.2)	48 (16.3)
≥30 kg/m <sup>2</sup>	123 (83.7)	124 (83.8)	247 (83.7)
<b>Mean (SD) HbA1c (%)</b>	8.3 (1.0)	8.3 (1.0)	8.3 (1.0)
<b>HbA1c Stratum [2]</b>			
<9.0% - n (%)	107 (72.8)	109 (73.6)	216 (73.2)
≥9.0% - n (%)	40 (27.2)	39 (26.4)	79 (26.8)
<b>Mean (SD) Fasting Plasma Glucose (mg/dL)</b>	165 (41.0)	173 (44.4)	169 (42.9)
<b>Mean (SD) Duration of Diabetes at Screening (years) [3]</b>	6.4 (4.5)	7.0 (5.5)	6.7 (5.0)

Abbreviations: BID, twice daily; BMI, body mass index; LAR, long-acting release; QW, once weekly; SD, standard deviation.

[1] Baseline values were collected at Day -3. If a Day -3 value was unavailable, a value from an earlier visit (the last measurement prior to the lead-in injection) was used.

[2] Percentages are based on the number of Intent-to-Treat subjects in each treatment group and overall. Mean baseline HbA1c in the <9.0% subgroup was 7.8% in both treatment groups. Mean baseline HbA1c in the ≥9.0% subgroup was 9.7% in both treatment groups.

[3] Duration of Diabetes in years = (Date of Screening - Date of Diabetes Diagnosis + 1)/365.25.

Source: Study 105 report, Table 4

TABLE 7 Study 105; Diabetes management method at screening by treatment, ITT population

Diabetes Management Method	Treatment		All Subjects (N = 295) n (%) [1]
	BYETTA 10 mcg BID (N = 147) n (%) [1]	Exenatide LAR 2 mg QW (N = 148) n (%) [1]	
Diet and Exercise Alone	23 (15.6)	21 (14.2)	44 (14.9)
Metformin Alone	50 (34.0)	56 (37.8)	106 (35.9)
Thiazolidinedione Alone	7 (4.8)	2 (1.4)	9 (3.1)
Sulfonylurea Alone	10 (6.8)	6 (4.1)	16 (5.4)
Metformin plus Thiazolidinedione	13 (8.8)	14 (9.5)	27 (9.2)
Metformin plus Sulfonylurea	39 (26.5)	43 (29.1)	82 (27.8)
Thiazolidinedione plus Sulfonylurea	5 (3.4)	5 (3.4)	10 (3.4)
Metformin plus Thiazolidinedione plus Sulfonylurea [2]	0 (0.0)	1 (0.7)	1 (0.3)
Metformin Alone or in Combination	102 (69.4)	114 (77.0)	216 (73.2)
Sulfonylurea Alone or in Combination	54 (36.7)	55 (37.2)	109 (36.9)
Thiazolidinedione Alone or in Combination	25 (17.0)	22 (14.9)	47 (15.9)

Abbreviations: BID, twice daily; LAR, long-acting release; QW, once weekly.

Note: Subjects are included in individual categories and in the “Metformin Alone or in Combination,”

“Thiazolidinedione Alone or in Combination,” and “Sulfonylurea Alone or in Combination” categories.

[1] Percentages are based on the number of Intent-to-Treat subjects in each treatment group and overall.

[2] The diabetes management method of metformin, thiazolidinedione, and sulfonylurea at screening for Subject 09906 represented a protocol deviation (violation of Inclusion Criterion #2); the subject was allowed to remain in the study.

Source: Study 105 study report, Table 5

### 3.1.3. Analysis populations

The applicant conducted efficacy evaluations for the following analysis populations:

The intention-to-treat (ITT) population (N=295) consisted of all randomized patients who received at least one injection of study medication. Last observation carried forward (LOCF) was used to impute the endpoint levels of patients who did not complete the 30-week treatment period.

In the review of the statistical analysis plan, the Biometrics review team recommended “for data imputation using LOCF approach, data collection at early termination, not the earlier scheduled visit should be used in case the data are obtained beyond 7 days of the last dose. The 7-day requirement seems to favor the exenatide LAR treatment for some efficacy variables e.g., FPG [*fasting plasma glucose*]. Therefore, the last available data should be carried forward regardless of dosing time and should apply to all efficacy variables including HbA1c.” This recommendation is in response to the applicant’s proposal that if the data at the early termination visit were collected more than 7 days after the last dose of study medication, the data from an earlier scheduled visit would be used in imputation. The final version of the statistical analysis plan notes that data collected at the early termination visit would be used in imputation for missing data, and that this procedure was a change from the protocol.

The 30-week evaluable population consisted of all ITT patients who completed study procedures at Visit 14 (Week 26) or beyond in compliance with the protocol and received adequate study medication exposure during the 30-week assessment period. Patients who were excluded from the 30-Week Evaluable Population were those who:

- received less than 80% of planned study medication injection; or
- missed seven consecutive days of exenatide injections or more than two exenatide LAR injections during the last two months of the assessment period; or
- had less than 180 days of randomized study medication exposure (one month shorter than the expected exposure)

The 52-week evaluable population consisted of all ITT patients who completed study procedures at Visit 28 (Week 48) or beyond in compliance with the protocol and received adequate study medication exposure during the 52-week assessment period. Patients who were excluded from the 52-Week Evaluable Population were those who:

- missed more than two exenatide LAR injections during the last two months of the assessment period; or
- had less than 48 weeks of study medication exposure (about one month shorter than the expected exposure)

### 3.1.4. Primary efficacy endpoint

HbA1c at week 30 – baseline: The primary efficacy endpoint was the change in HbA1c from baseline visit 3 (day -3) to visit 20 (week 30).

Potential for bias due to unblinded adjustment of SU dose prior to week 30: A review concern was the potential for bias in estimating the primary endpoint. In my opinion, this potential for bias originates from two features of the study design:

- (1) Patients who were being treated at screening with SU medications experienced additional protocol-specified modifications to the SU dose at the lead-in period and during the 30-week assessment period. They were required to decrease their SU dose to the minimum recommended dose on day -3 to minimize the risk of hypoglycemia. From weeks 10 through 22, investigators reviewed daily finger-stick blood glucose measurements. If necessary, the SU dose was optimized to reach the target goal of fasting blood glucose  $\leq 110$  mg/dL.
- (2) Because the study was open-label, patients, the study-site staff, the investigator, and the sponsor were not blinded to the identity of treatment assignments.

In my opinion, a study investigator who has knowledge of a patient's treatment assignment and the authority to modify the dose of SU based on blood glucose measurements also has the opportunity to introduce bias into the estimate of the effect of exenatide LAR on HbA1c. I reasoned that this bias, if it existed, was likely to be in the direction of greater superiority of exenatide LAR compared to Byetta than was true in the target population. The most likely mechanism of this bias would be a greater up-titration of the SU dose in patients in the exenatide LAR arm compared to the Byetta arm (within the SU subgroup). This subgroup comprises 37% of the study population. The up-titration of the SU dose during the 30-week assessment period is reviewed in section 3.1.6.

I believe that this feature of the study design reduces the extent to which this study was adequate and well-controlled. While it was medically necessary to manage the SU dose during the 30-week assessment period, the study blind could have been maintained in one of the following ways:

- (1) Both study arms could have included sham injections so that all patients had the same schedule of injections.
- (2) The study personnel who decided about the SU dosage could have been blinded to the treatment assignment by using a separation of function approach.

Of the three other Phase 3 studies that were ongoing at the time of the NDA 022200/0 submission, study GWBR used the same open-label design as Study 105 (comparing an exenatide LAR arm to an insulin glargine arm, with background therapy of metformin or

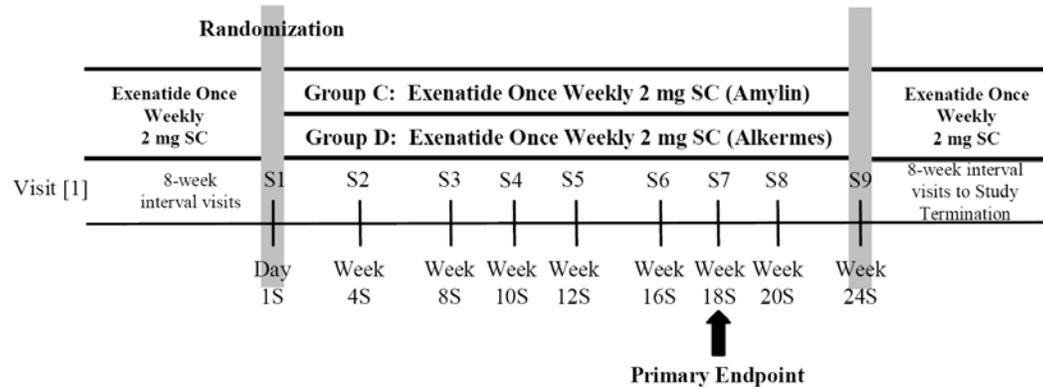
metformin and a sulfonylurea). Study BCB106 had a double-blind design (comparing an exenatide LAR arm, a sitagliptin arm and a pioglitazone arm, all with a background of metformin), as did Study GWCH (comparing an exenatide LAR arm, a metformin arm, a sitagliptin arm and a pioglitazone arm, all as monotherapies). I believe that the results from these clinical studies will provide useful information to the evaluation of the efficacy of exenatide LAR.

Change in manufacturing source: The source of exenatide LAR used for the 30-week assessment period of Study 105 was not the same as the source to be used for commercial purposes. The drug product for the 30-week assessment period was manufactured by Alkermes Inc at the (b) (4) scale. The drug product for commercial use is manufactured at Amylin Ohio LLC at the (b) (4) scale. At the time that Study 105 was conducted, the bioequivalence of these two sources had not been established. For this reason, the applicant conducted a comparability study as a sub-study during the open-ended assessment period of Study 105 (after the week 30 assessment period). This sub-study was conducted in 217 patients who were randomized to receive exenatide LAR from either Amylin or Alkermes. The start of the sub-study, designated as “Day 1S,” took place at different weeks for different patients, ranging from week 49 to week 124. Patients returned to the study site for additional visits for efficacy, pharmacodynamic, pharmacokinetic and safety assessments (FIGURE 3). The baseline level of HbA1c for the sub-study was obtained from the average of the three study visits immediately prior to Day 1S for each subject. Randomization was stratified by the average HbA1c at this baseline,  $< 6.5$  or  $\geq 6.5$ . The HbA1c at week 18 (“Week 18S”) following day 1S was the primary endpoint for comparing the two manufacturing sources.

The applicant compared the average HbA1c change from week 18S from the day 1S baseline, using the noninferiority margin of 0.4. However, the Division did not concur with the use of the non-inferiority margin to make a conclusion about the equivalence of the two manufacturing sources. At the pre-NDA meeting held on June 24, 2008, the Division noted that “The division will not necessarily be using this non-inferiority margin to assess similarity of the material from the 2 manufacturing sites. Instead, the difference between treatment groups with respect to changes from baseline in HbA1c should be presented using adjusted means with a 95% confidence interval for the treatment difference. The similarity of the data will be a review issue.” (See the minutes to the 6/24/08 pre-NDA meeting).

In my opinion, this change of source may limit the extent to which comparisons between exenatide LAR and Byetta from Study 105 can be generalized to the target population. For this reason, I evaluated the results from the comparability study of the investigational Alkermes source and the commercial Amylin source. I focused on the average HbA1c effect for each source (see part 3.1.6). A full review of the pharmacodynamic and pharmacokinetic endpoints in the comparability sub-study is included in the clinical pharmacology review by Dr. Vaidyanathan.

FIGURE 3 Study 105c; the design for the comparability sub-study, conducted during the-ended assessment period



Abbreviations: SC, subcutaneous.

Note: See Figure 1 for full study design.

[1] Visit S1 occurred at a scheduled or unscheduled study-site visit during the open-ended assessment period. Visits S2 through S9 occurred at 2- to 4-week ( $\pm 2$  days) intervals relative to Visit S1. After Visit S8, subjects returned to the site within approximately 48 to 144 hours (2 to 6 days) and prior to the next dose of exenatide once weekly for collection of an additional blood sample. Following Visit S9, subjects resumed the original visit structure, returning to the study site at 8-week intervals for study visits (approximately 8 weeks after Visit S9), and received Amylin-manufactured exenatide once weekly.

Source: Study 105 report, Figure 2

### 3.1.5. Statistical analysis methods for primary efficacy endpoint

**Primary analysis:** The hypothesis to be tested was that the change in HbA1c from baseline achieved with exenatide LAR is noninferior to that of exenatide by 0.4% at the end of 30 weeks of treatment. A two-sided 95% confidence interval was calculated for the difference in the change of HbA1c between treatment groups (exenatide LAR – Byetta). Noninferiority would be demonstrated if the upper limit of the confidence interval fell beneath 0.4%. Superiority of exenatide LAR to Byetta would be demonstrated if the same confidence interval lay entirely below zero. The confidence interval was obtained from an analysis of variance model including treatment, baseline HbA1c stratum ( $<9\%$  and  $\geq 9\%$ ), and concomitant SU use at screening (yes, no).

The primary analysis model was an analysis of variance including treatment, baseline HbA1c stratum ( $<9\%$  or  $\geq 9\%$ ), and concomitant SU use at screening.

**Supportive analyses:** Additional analyses of the primary efficacy analysis included analyses of the evaluable populations (30-week and 52-week), using the primary analysis model; an analysis

of covariance, which included baseline HbA1c as a covariate and omitted the HbA1c stratification factor; an analysis of proportions of patients achieving HbA1c target values of  $\leq 6.0\%$ ,  $\leq 6.5\%$ ,  $\leq 7.0\%$  at week 30, and descriptive summaries of the change in HbA2c from baseline to week 30, week 52 and other applicable visits. In this review I focused on results from the 30-week evaluation period.

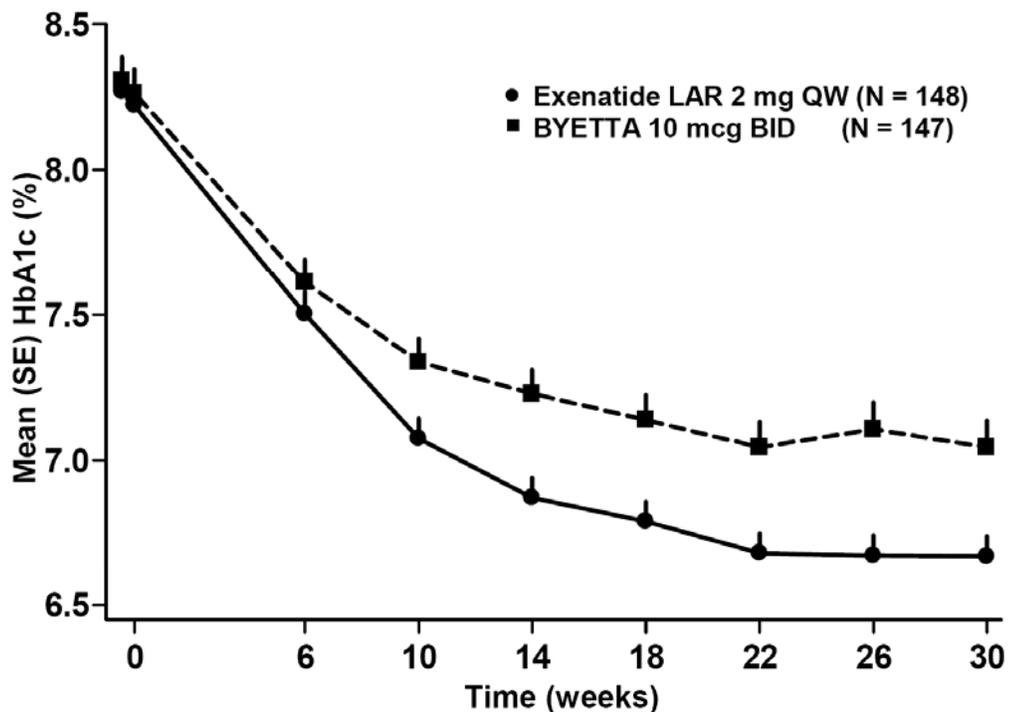
### 3.1.6. Results of the statistical analysis of efficacy

**HbA1c at week 30 – baseline:** At week 30, exenatide LAR produced a statistically significant net mean reduction in HbA1c compared to Byetta, with a 95% confidence interval of (-0.5, -0.1) in the direction of superior efficacy of exenatide LAR (TABLE 8). I confirmed these findings. The results from the primary analysis of variance model were very similar to those from the supportive analysis of covariance model, which include baseline HbA1c as a covariate. Results from the sensitivity analysis of the HbA1c endpoint, using the 30-week evaluable population, also supported the superiority of exenatide LAR in comparison to Byetta. In the 30-week evaluable population, the LS mean (SE) change in HbA1c from baseline to week 30 was -2.0 (0.1) in exenatide LAR-treated subjects and -1.6 (0.1) in Byetta-treated subjects. A 95% confidence interval of this difference (-0.6, -0.2;  $p < 0.001$ ) was in the direction of superiority of exenatide LAR to Byetta.

TABLE 8 Primary efficacy analysis: Change in HbA1c at week 30 in the ITT/LOCF population

	N	Baseline mean HbA1c $\pm$ SE	Adjusted mean change from baseline at Week 30 $\pm$ SE <sup>1</sup>	Exenatide LAR – Byetta Difference in adjusted mean change (95% CI) <sup>1</sup>	P-value
<b>All patients (ITT/LOCF)</b>					
Exenatide LAR	148	8.3 $\pm$ 0.1	-1.9 $\pm$ 0.1	-0.3 (-0.5, -0.1)	0.002
Byetta	147	8.3 $\pm$ 0.1	-1.5 $\pm$ 0.1		
<i>Note:</i>					
<sup>1</sup> The adjusted mean change from baseline at week 30 and the difference in the adjusted mean change were estimated from an analysis of variance model with treatment, baseline HbA1c stratum, and concomitant SU use at screening.					
<i>Sources:</i> Study 105 report, Table 8					

FIGURE 4 Mean (SE) HbA1c over the 30-week assessment period



Abbreviations: BID, twice daily; LAR, long-acting release; LOCF, last observation carried forward; QW, once weekly; SE, standard error.

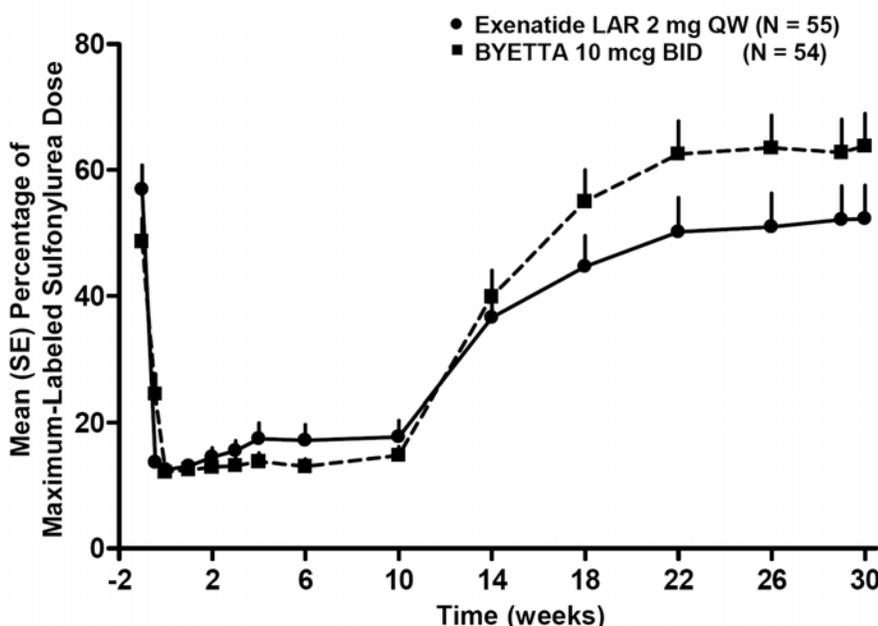
Notes: The LOCF approach was applied to estimate missing values at Day 1 through Week 30.

- Subjects treated with BYETTA initiated treatment with 5 mcg BID through Week 4.

Source: Study 105 report, Figure 5

Potential for bias due to unblinded adjustment of SU dose prior to week 30: The distribution of SU dose adjustments in the two arms did not support my review concern that the unblinded adjustment of SU dose prior to week 30 may have resulted in a larger up-titration of SU dose in the exenatide LAR arm than in the Byetta arm. In fact, a larger percentage of Byetta-treated patients had increased SU doses than the exenatide LAR-treated patients, relative to their baseline dose (FIGURE 5, TABLE 9). In addition, the comparison between exenatide LAR and Byetta in the HbA1c endpoint at week 30 was fairly similar in the SU subgroup and the non-SU subgroup (see FIGURE 11 in part 4.2 of this review).

FIGURE 5 Mean (SE) percentage of maximum-labeled SU dose by treatment



Abbreviations: BID, twice daily; LAR, long-acting release; QW, once weekly; SE, standard error.

Notes: Five subjects treated with exenatide LAR and 3 subjects treated with BYETTA increased their SU dose prior to Week 10. These changes were consistent with the general guidance in the protocol for titration of the SU dose and were not considered protocol deviations.

- Subjects treated with BYETTA initiated treatment with 5 mcg BID through Week 4.

Source: Study 105, Figure 3

TABLE 9 SU dose immediately prior to week 30, relative to SU dose at screening, in the subgroup of patients with concomitant SU use at screening

Category	Treatment	
	BYETTA 10 mcg BID (N = 54) n (%)	Exenatide LAR 2 mg QW (N = 55) n (%)
<b>Number of Subjects at Week 30 [1]</b>	50 (92.6)	49 (89.1)
<b>Sulfonylurea Dose Immediately Prior to Week 30 Relative to Sulfonylurea Dose at Screening [2]</b>		
Increased Sulfonylurea	25 (50.0)	15 (30.6)
No Change in Sulfonylurea	10 (20.0)	11 (22.4)
Decreased Sulfonylurea	15 (30.0)	22 (44.9)
Discontinued Sulfonylurea	0 (0.0)	1 (2.0)

Abbreviations: BID, twice daily; LAR, long-acting release; QW, once weekly; SU, sulfonylurea.

Notes: Subjects in the BYETTA group were required to reduce their SU dose prior to switching to exenatide LAR at Week 30, therefore the SU dose received immediately prior to the SU dose reduction is compared to that received at screening.

- Subjects treated with BYETTA initiated treatment with 5 mcg BID through Week 4.

[1] Percentages based on the number of ITT subjects in each treatment group using an SU at screening.

[2] Percentages based on the number of available subjects at Week 30 in each treatment group.

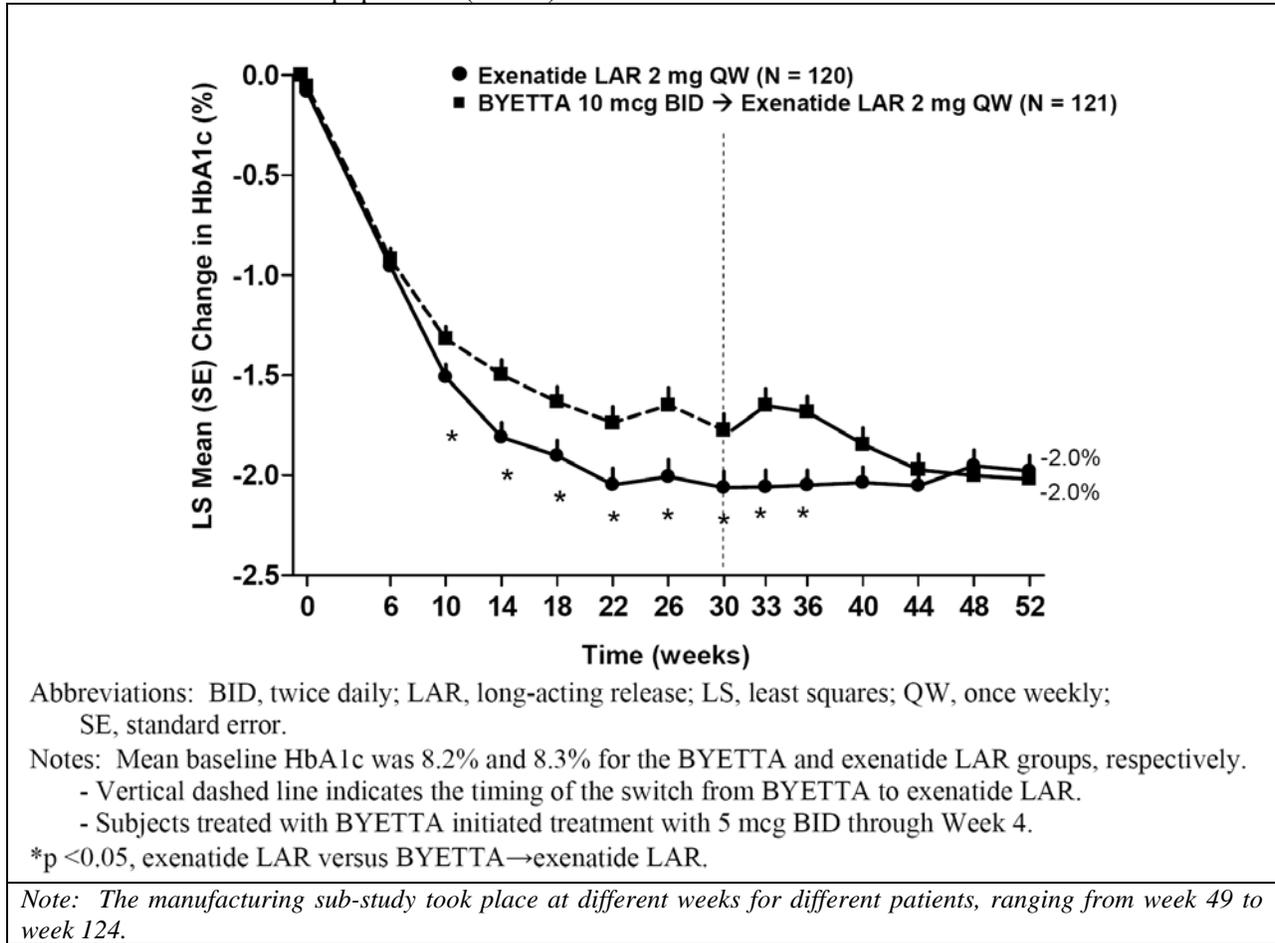
Source: Study 105 report, Table 6

Change in manufacturing source: The investigational source of exenatide LAR for the 30-week treatment endpoint resulted in a greater reduction in HbA1c than the source that will be used in the commercial manufacture of exenatide LAR (TABLE 10). The results from the evaluable population were the same as the results from the ITT/LOCF population, with both populations defined with respect to the sub-study. The average difference between the two manufacturing sources, 0.2 after 18 weeks of treatment in the comparability sub-study, was in the direction of inferiority of the commercial source to the investigational source. The 95% confidence interval of this comparison, (0.0 to 0.3) does include 0 as the lower bound. However, the average difference between the two sources raises a concern that the commercially manufactured exenatide LAR may be somewhat less effective than the product that was used in Study 105 for the primary efficacy endpoint. We do not know how this difference might affect a target population with a higher average baseline. The patient population of Study 105 had an average baseline of 8.3 at the start of the main study (TABLE 6), compared to the average of 6.8 at the start of the comparability sub-study (TABLE 10; see also FIGURE 6 for a depiction of average HbA1c levels from week 0 through week 52). For this reason, I believe it would be useful to evaluate the results from the ongoing studies GWBR and GWCH, if in fact the commercial source was used for exenatide LAR (see TABLE 3). Using the upper 95% CI bound to estimate the effect of manufacturing source, I note that a shift of 0.3 in the comparison between exenatide LAR and Byetta would not affect the non-inferiority conclusion, but it would not support a conclusion of superiority.

TABLE 10 Comparability sub-study of two sources of exenatide LAR; HbA1c endpoint after 18 weeks of treatment

	N	Day 1S baseline HbA1c ± SE	Adjusted mean change from Day 1S to Week 18S ± SE <sup>1</sup>	Amylin - Alkermes Difference in adjusted mean change (95% CI) <sup>1</sup>	P- value
<b>All patients (ITT/LOCF with respect to the comparability sub-study<sup>2</sup>)</b>					
investigational Alkermes source	109	6.8 ± 0.1	0.3 ± 0.1	0.2 (0.0, 0.3)	0.062
commercial Amylin source	108	6.7 ± 0.1	0.4 ± 0.16		
<i>Notes:</i>					
<sup>1</sup> The comparability study is described in Part 3.1.4 of this review					
<sup>2</sup> The adjusted mean change from baseline 1S at week 18S and the difference in the adjusted mean change were estimated from an analysis of variance model with treatment and baseline 1S HbA1c stratum.					
<i>Sources:</i> Study 2993 LAR-105c comparability assessment, Table 6					

FIGURE 6 LS Mean (SE) change in HbA1c from baseline by week 52 by treatment in the 52-week evaluable population (n=241).



Source: Study 105 report, Figure 7

**3.1.7. Other Efficacy Endpoints**

Fasting Plasma Glucose (FPG): The results from fasting plasma glucose at week 30 also supported the efficacy of both exenatide LAR and Byetta. On average, patients in the exenatide LAR arm experienced a greater reduction in FPG at week 30 compared to baseline than patients in the Byetta arm (TABLE 11).

TABLE 11 Change in fasting plasma glucose (FPG; mg/dL) at week 30 in the ITT/LOCF population

	N	Baseline mean FPG ± SE	Adjusted mean change from baseline at Week 30 ± SE <sup>1</sup>	Exenatide LAR – Byetta Difference in adjusted mean change (95% CI) <sup>1</sup>	P-value
<b>All patients (ITT/LOCF)</b>					
Exenatide LAR	148	173 ± 3.7	-42 ± 3.0	-16.9 (-24.4, -9.4)	< 0.001
Byetta	147	165 ± 3.4	-25 ± 2.9		

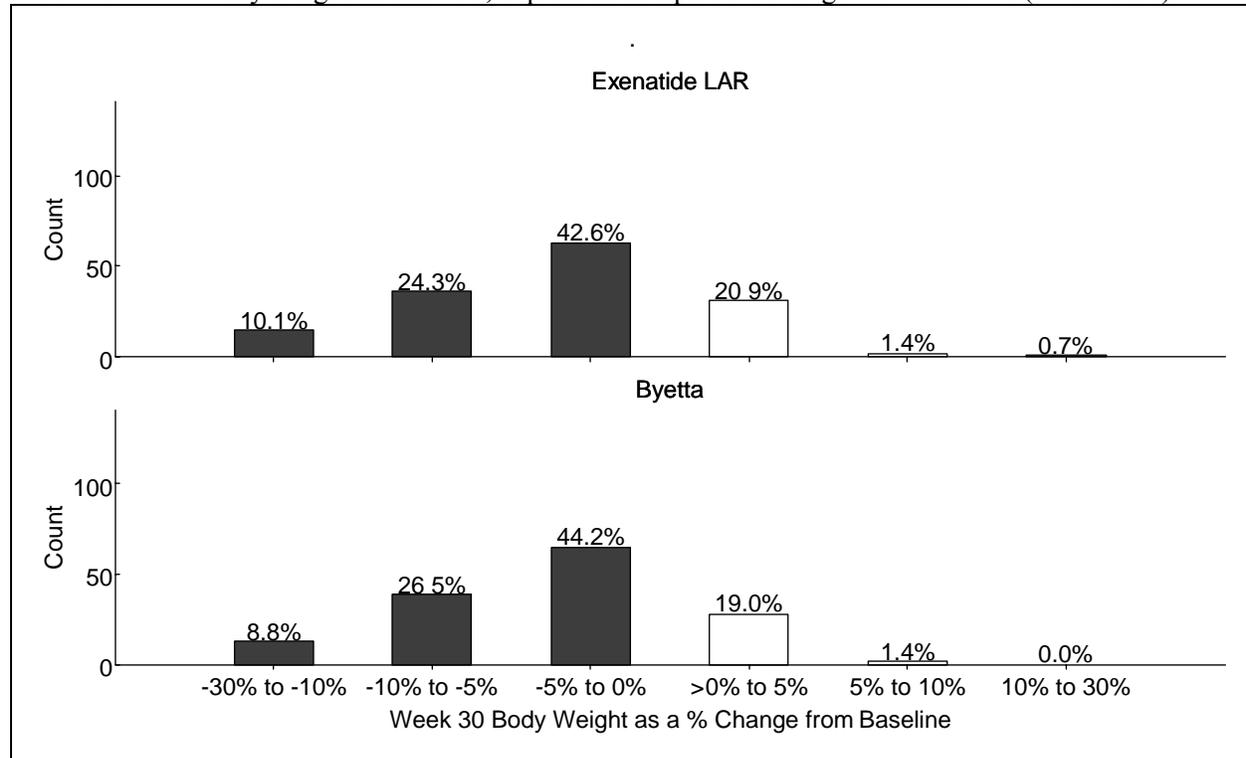
*Note:*

<sup>1</sup> The adjusted mean change from baseline at week 30 and the difference in the adjusted mean change were estimated from an analysis of covariance model with treatment, baseline HbA1c stratum, concomitant SU use at screening, and the baseline value of fasting plasma glucose.

*Sources:* Study 105 report, Table 10

**Body weight:** At week 30, the majority of patients in both arms stayed within  $\pm 5\%$  of their initial body weight (FIGURE 7). However, the trend in both arms favored weight loss, with approximately 78% of patients experiencing a weight loss at week 30 compared to baseline. The average weight loss in each arm was fairly similar, approximately 3.7 kg at week 30 (TABLE 12).

FIGURE 7 Body weight at week 30, expressed as a percent change from baseline (ITT/LOCF)



Source: Analysis by this reviewer

TABLE 12 Change in body weight (kg) at week 30 in the ITT/LOCF population

	N	Baseline mean Body weight (kg) $\pm$ SE	Adjusted mean change from baseline at Week 30 $\pm$ SE <sup>1</sup>	Exenatide LAR – Byetta Difference in adjusted mean change (95% CI) <sup>1</sup>	P-value
<b>All patients (ITT/LOCF)</b>					
Exenatide LAR	148	101.7 $\pm$ 1.5	-3.7 $\pm$ 0.5	-0.1 (-1.3, 1.1)	0.892
Byetta	147	101.9 $\pm$ 1.7	-3.6 $\pm$ 0.5		

Note:

<sup>1</sup> The adjusted mean change from baseline at week 30 and the difference in the adjusted mean change were estimated from an analysis of covariance model including treatment, baseline HbA1c stratum, concomitant SU use at screening, and baseline value of weight.

Source: Study 105 report, Supporting data summary 2.2.2.1.1

### **3.2 Evaluation of Safety**

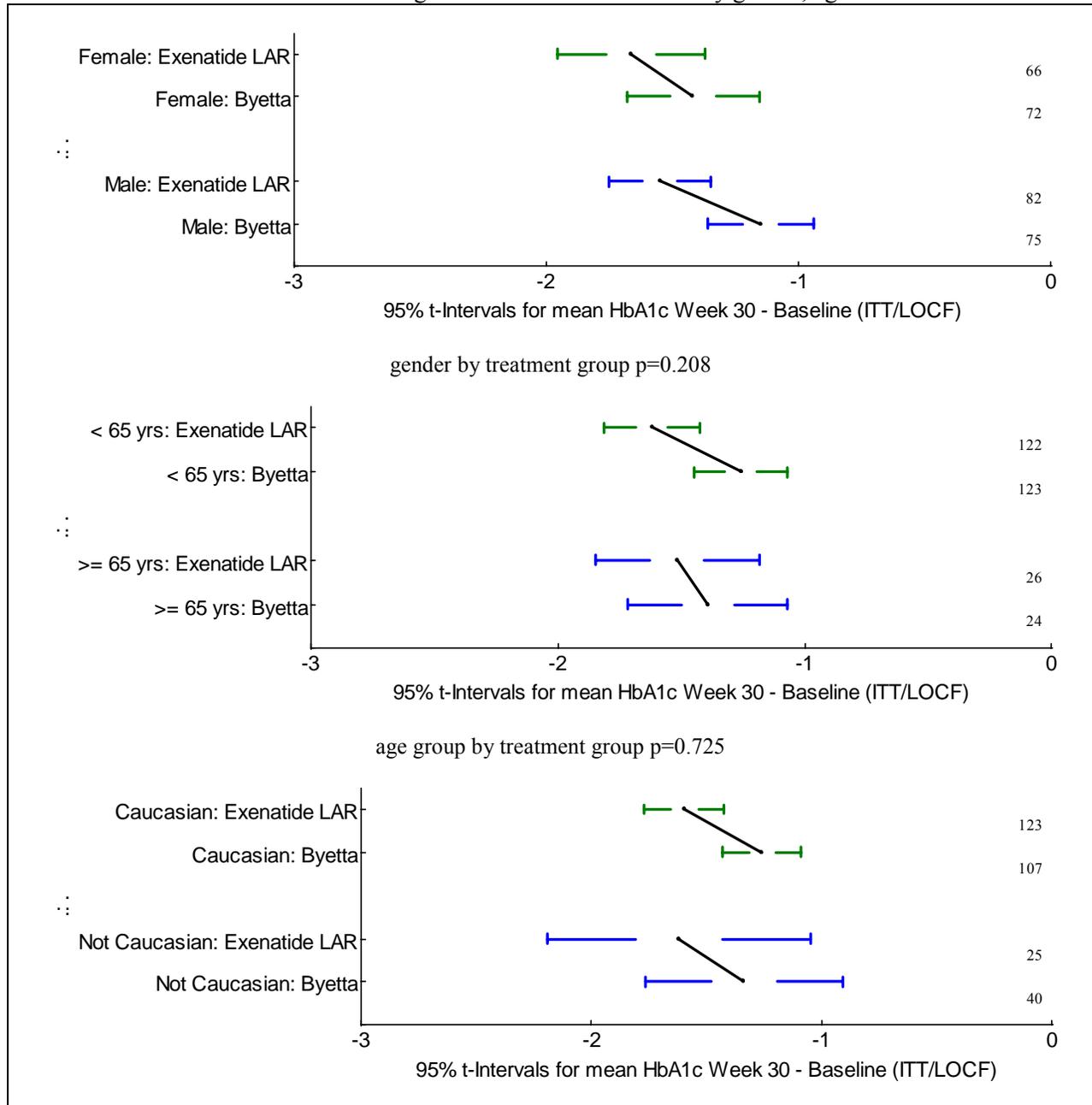
An evaluation of safety is primarily covered in the FDA clinical review by Dr. Valerie Pratt. Dr. Fiona Callaghan, Division of Biometrics 7, is conducting a separate review of the analysis of cardiovascular endpoints from the Phase 2 and Phase 3 studies of exenatide (i.e., Byetta and exenatide LAR).

## **4. FINDINGS IN SPECIAL/SUBGROUP POPULATIONS**

### **4.1 Gender, Race and Age**

The average HbA<sub>1c</sub> response to exenatide LAR compared to Byetta at week 30 was fairly similar in males compared to females, and in the younger age group compared to the older age group (< 65 and  $\geq$  65 years; FIGURE 8). I did not explore the effect of race further because the large majority (78%) of the patients were Caucasian. However, for purposes of illustration, I did combine all of the minority racial groups, designated by the applicant as Asian, Black and Hispanic, to form a comparison group (FIGURE 8).

FIGURE 8 The mean HbA1c change from baseline to week 30 by gender, age and race



*Notes:*

Shown on the graphs are the t-intervals (mean and 95% confidence interval) for HbA1c change from baseline for each subgroup category. The p-values are from the analysis of variance model with the following general form: baseline HbA1c stratification level ( $< 9.0$ ,  $\geq 9$ ), baseline SU status (Yes, No), treatment group, subgroup and subgroup by treatment group interaction. The effect of race subgroup was not evaluated because the large majority of patients (78%) were Caucasian. For purposes of illustration, the racial groups of “Asian,” “Hispanic” and “Black” were combined. An  $\alpha$  of 0.1 was used to screen the subgroup by treatment interactions.

*Source: Analysis by this reviewer*

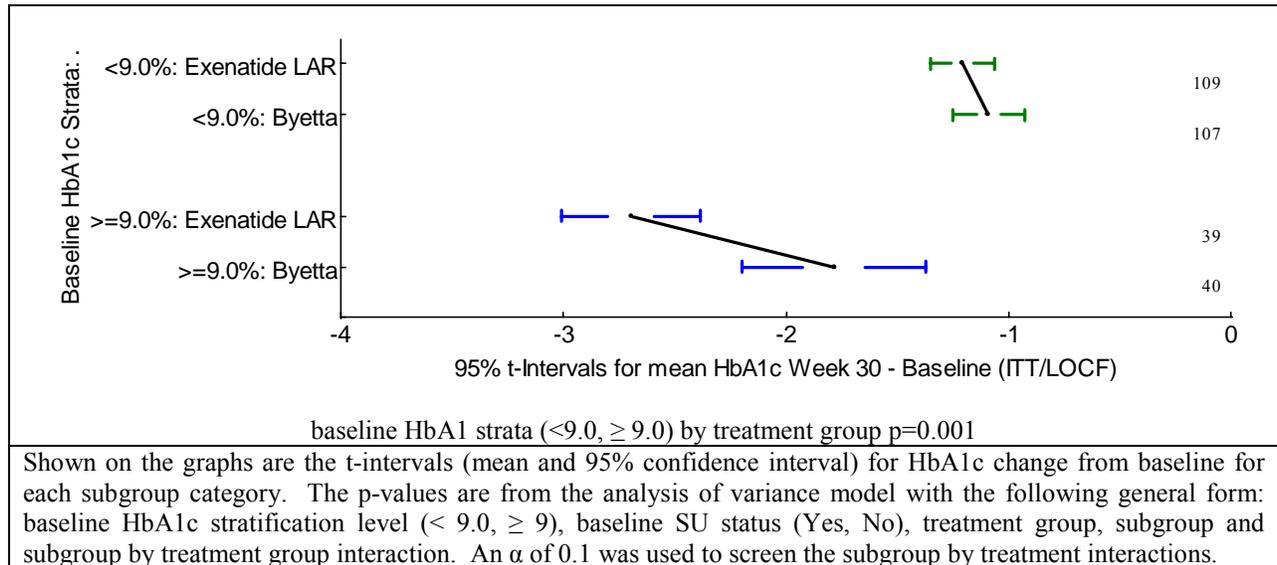
### 4.2 Other Special/Subgroup Populations

**Baseline HbA1c:** The average HbA1c response to exenatide LAR compared to Byetta at week 30 was significantly different in the two stratified levels of baseline HbA1c ( $< 9.0$  and  $\geq 9.0$ ; FIGURE 9). The average response in patients with baseline HbA1c  $< 9.0$  was relatively similar in the exenatide LAR and Byetta arms, with a 95% CI that included 0 but remained within the noninferiority margin (TABLE 13). The majority of patients in Study 105, 73%, had a baseline HbA1c  $< 9.0$ . Patients with baseline HbA1c  $\geq 9.0$  on average had a greater reduction in HbA1c in the exenatide LAR group than in the Byetta group, and this difference was statistically significant (TABLE 13).

The average change from baseline to week 30 was smaller in patients with baseline  $< 9.0$  than in patients with baseline  $\geq 9.0$  in both treatment arms. While 9.0 was used to stratify the randomization in this study, the relationship between baseline HbA1c and change from baseline at week 30 is reasonably well represented by a straight line in the range of baseline HbA1c in this study (FIGURE 10). This relationship has been observed in other anti-diabetic products. Factors that may contribute to this finding include an increased efficacy of anti-diabetic products at greater levels of baseline HbA1c, a general clinical trial effect, and a regression to the mean effect.

The greater reduction in HbA1c with exenatide LAR at higher levels of baseline HbA1c compared to Byetta is also illustrated by a steeper slope of the fitted regression line in FIGURE 10.

FIGURE 9 The mean HbA1c change from baseline to week 30 by baseline HbA1c, baseline SU use, and number of OADs at baseline



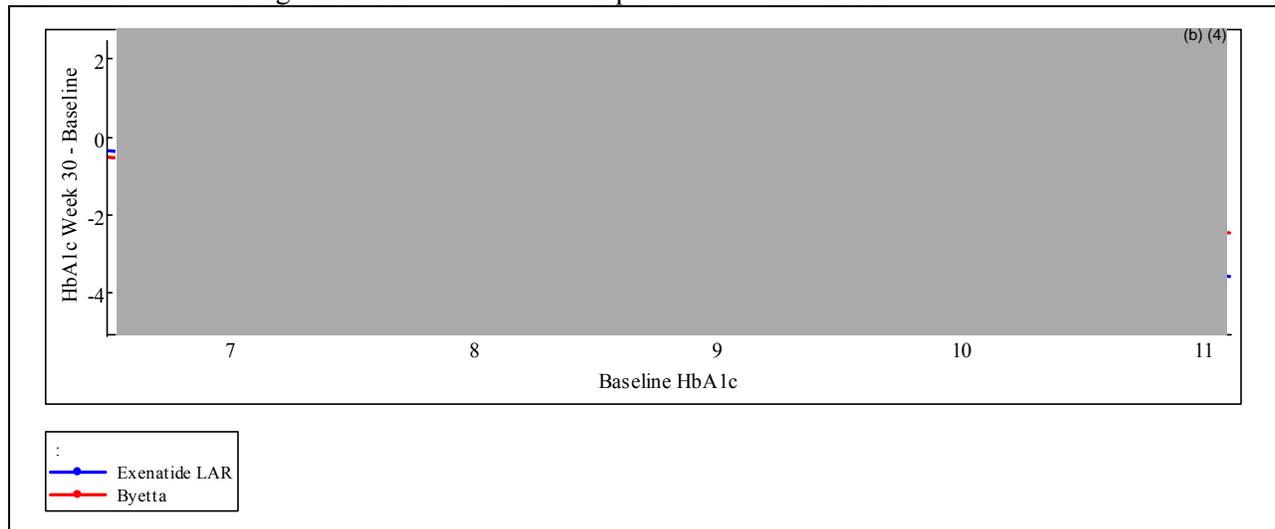
Source: Analysis by this reviewer

TABLE 13 HbA1c results by baseline HbA1c stratification level (< 0.9, ≥ 0.9)

	N	Baseline mean HbA1c ± SE	Adjusted mean change from baseline at Week 30 ± SE <sup>1</sup>	Exenatide LAR – Byetta Difference in adjusted mean change (95% CI) <sup>1</sup>	P-value
<b>All patients (ITT/LOCF)</b>					
Exenatide LAR	148	8.3 ± 0.1	-1.9 ± 0.1	-0.3 (-0.5, -0.1)	0.002
Byetta	147	8.3 ± 0.1	-1.5 ± 0.1		
<b>Patients with baseline HbA1c &lt; 9.0</b>					
Exenatide LAR	109	7.8 ± 0.1	-1.2 ± 0.1	-0.1 (-0.3, 0.1)	0.191
Byetta	107	7.8 ± 0.1	-1.1 ± 0.1		
<b>Patients with baseline HbA1c ≥ 9.0</b>					
Exenatide LAR	39	9.7 ± 0.1	-2.7 ± 0.2	-0.9 (-1.4, -0.4)	<0.001
Byetta	40	9.7 ± 0.1	-1.8 ± 0.2		

*Note:*  
<sup>1</sup> The adjusted mean change from baseline at week 26 and the difference in the adjusted mean change were estimated from the primary Analysis of Covariance model  
*Sources:* Study 105 report, Table 8 and Table 2.1.2.3.1

FIGURE 10 Change in HbA1c at week 30 compared to baseline HbA1c

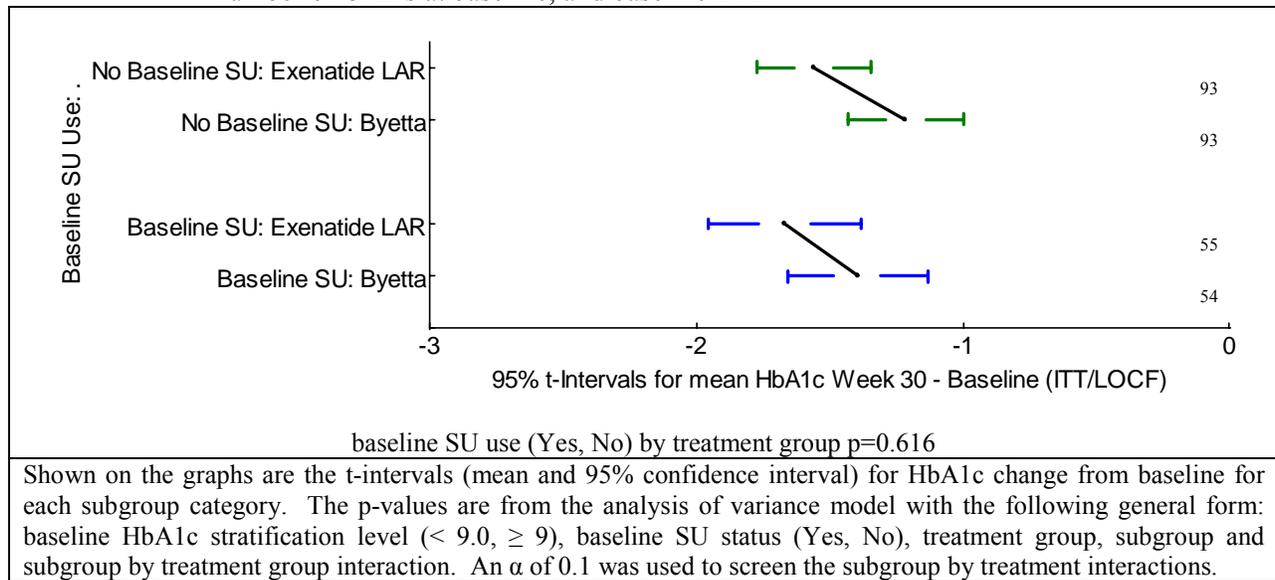


**Concomitant SU use:** Approximately 37% of the ITT population was treated with a concomitant SU at screening. Patients in this subgroup followed a protocol for adjusting their SU dose at week -3 and again at weeks 10-22, based in part on their daily blood glucose readings. The study investigator, who was not blinded to treatment assignment, was responsible for determining the dosage adjustment. In my opinion, this protocol for dosage adjustment introduced the potential

for bias in estimating the efficacy of exenatide LAR. I reasoned that the direction of this bias was likely to be in the direction of superiority of exenatide LAR compared to Byetta.

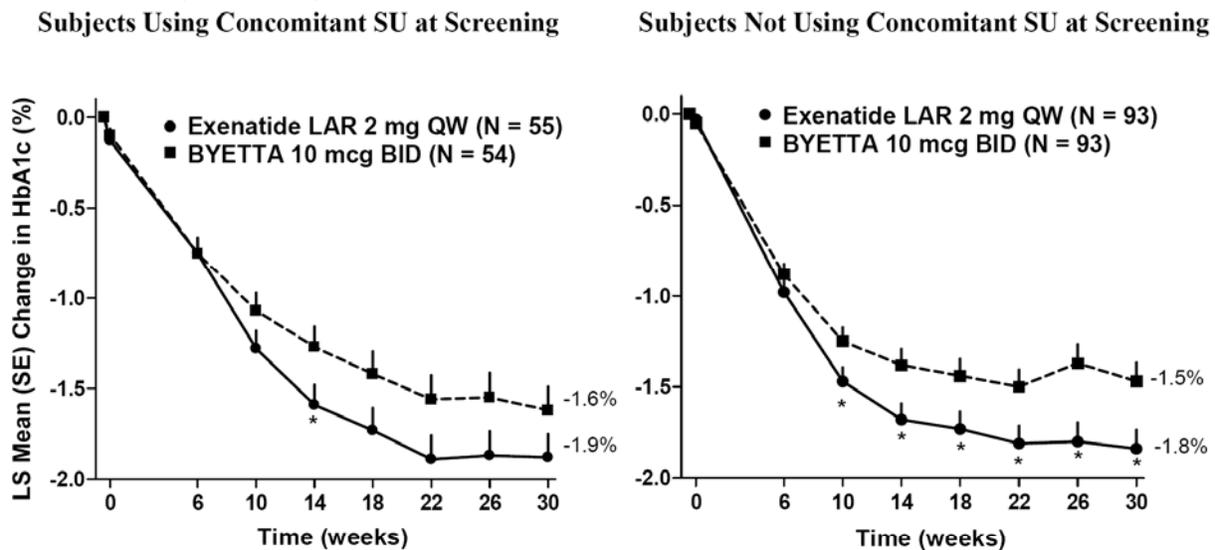
However, the subgroup of patients treated with SU were fairly similar to the subgroup of patients not treated with SU with respect to the comparison between exenatide LAR and Byetta in the average HbA1c response at week 30 (FIGURE 11, TABLE 14). In addition, the profile of the average HbA1c response up to week 30 looks fairly similar in the two subgroups (FIGURE 12). These results do not support the concern about a potential bias towards superiority of exenatide LAR compared to Byetta.

FIGURE 11 The mean HbA1c change from baseline to week 30 by baseline HbA1c, baseline SU use, number of OADs at baseline, and baseline BMI



Source: Analysis by this reviewer

FIGURE 12 Change in HbA1c from baseline to week 30 by treatment and concomitant SU use (ITT/LOCF)



Abbreviations: BID, twice daily; LAR, long-acting release; LOCF, last observation carried forward; LS, least squares; SE, standard error; SU, sulfonylurea.

Notes: Mean baseline HbA1c was 8.2% for exenatide LAR subjects not using a concomitant SU and 8.3% for all other subgroups in this analysis.

- The LOCF approach was applied to estimate missing values at Day 1 through Week 30.

- Subjects treated with BYETTA initiated treatment with 5 mcg BID through Week 4.

\*p < 0.05, exenatide LAR versus BYETTA.

Source: Study 105 report, Figure 12

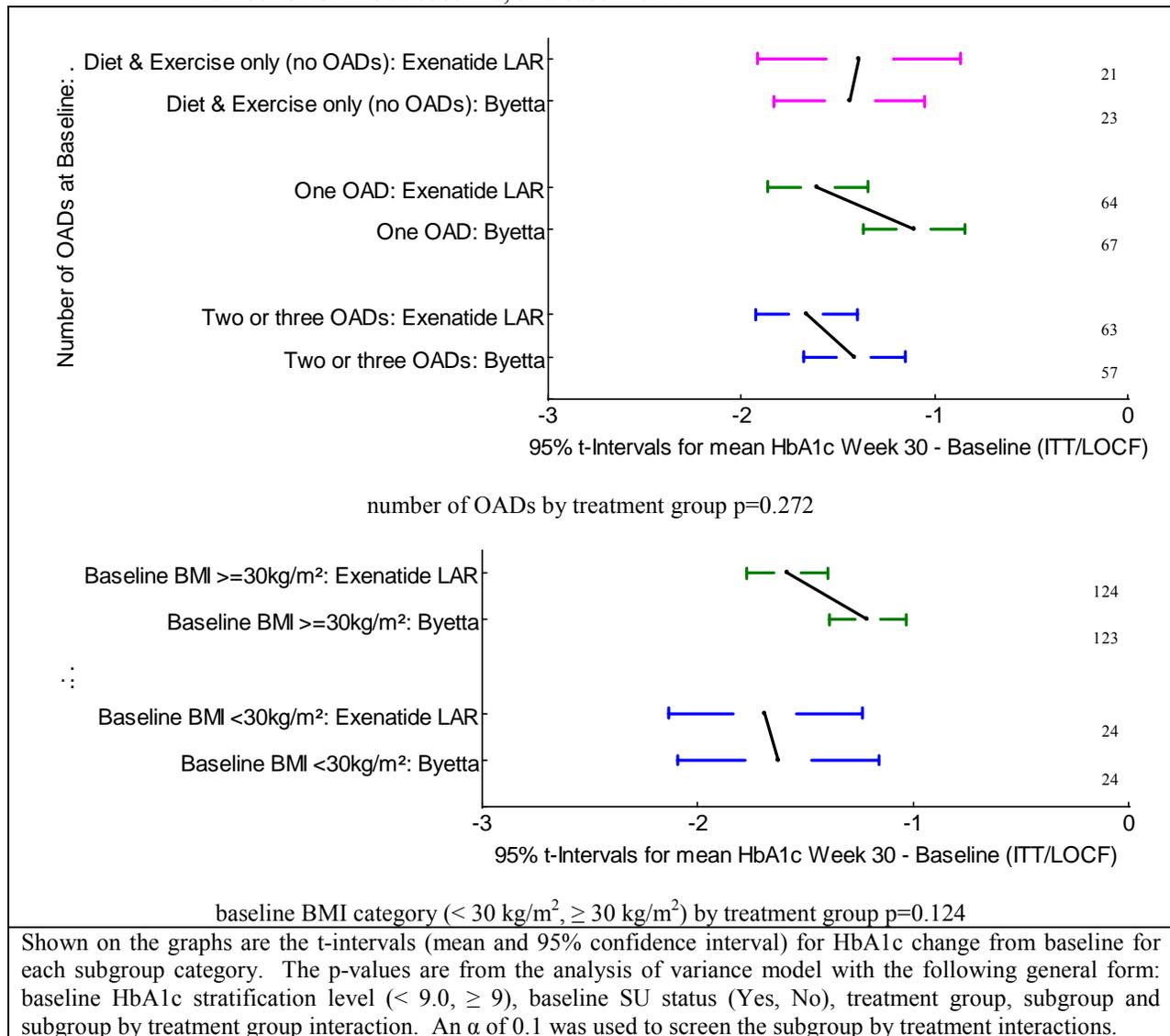
TABLE 14 HbA1c results by concomitant SU use

	N	Baseline mean HbA1c ± SE	Adjusted mean change from baseline at Week 30 ± SE <sup>1</sup>	Exenatide LAR – Byetta Difference in adjusted mean change (95% CI) <sup>1</sup>	P-value
<b>All patients (ITT/LOCF)</b>					
Exenatide LAR	148	8.3 ± 0.1	-1.9 ± 0.1	-0.3 (-0.5, -0.1)	0.002
Byetta	147	8.3 ± 0.1	-1.5 ± 0.1		
<b>Patients using concomitant SU at screening</b>					
Exenatide LAR	55	8.3 ± 0.1	-1.9 ± 0.1	-0.3 (-0.6, 0.1)	0.137
Byetta	54	8.3 ± 0.1	-1.6 ± 0.1		
<b>Patients not using concomitant SU at screening</b>					
Exenatide LAR	93	8.2 ± 0.1	-1.8 ± 0.1	-0.4 (-0.6, -0.1)	0.007
Byetta	93	8.3 ± 0.1	-1.5 ± 0.1		

Note:  
<sup>1</sup> The adjusted mean change from baseline at week 26 and the difference in the adjusted mean change were estimated from the primary Analysis of Covariance model  
 Sources: Study 105 report, Table 8 and Table 2.1.2.4.1

Other subgroups: The number of oral antidiabetic drugs (OADs) at baseline and baseline BMI did not affect the comparison between exenatide LAR and Byetta, with respect to the statistical significance of the interaction of these factors with treatment arm (FIGURE 13). Apparent trends in the plots of means of these subgroups by treatment arm may be related to an underlying relationship between baseline HbA1c and treatment group, as explored earlier. Patients with higher BMI and/or who are taking one or more OAD may also have a more advanced stage of type 2 diabetes and may be more likely to have a baseline HbA1c > 9.0. These patients may also be more likely to experience a greater reduction in HbA1c with Exenatide LAR than with Byetta.

FIGURE 13 The mean HbA1c change from baseline to week 30 by baseline HbA1c, baseline SU use, number of OADs at baseline, and baseline BMI



Source: Analysis by this reviewer

## 5. SUMMARY AND CONCLUSIONS

### 5.1 Statistical Issues and Collective Evidence

I evaluated the evidence in support of the efficacy of exenatide LAR (2 mg SC once weekly) from the results of one clinical study. I confirmed the primary efficacy result for HbA1c at week 30, expressed as a change from baseline. I concurred with the pre-specified statistical methodology used in evaluating the primary endpoint. Results from the primary and secondary analyses supported the non-inferiority of exenatide LAR compared to Byetta (10 mcg SC twice a day).

In my opinion, Study 105 had two weaknesses in design. These weaknesses did not appear to cause substantial problems. However, it may be useful to evaluate the efficacy of exenatide LAR further from the three clinical studies that were ongoing at the time that NDA 022200/0 was submitted.

### 5.2 Conclusions

**Efficacy Conclusions:** The efficacy of exenatide LAR (2 mg SC once weekly) was supported by a non-inferiority comparison to Byetta® (exenatide 10 mcg SC twice a day) for change in HbA1c at week 30 compared to baseline. Results from the analysis of secondary efficacy endpoints, including fasting plasma glucose, also supported the efficacy of exenatide LAR compared to Byetta. Both products were associated with weight loss in approximately 78% of patients, with a fairly similar average weight loss of approximately 3.7 kg at week 30 compared to baseline in both arms.

### 5.3 Recommendations for Labeling

The following recommendations for labeling pertain to Section 14.1 (“Major Effectiveness Study: DURATION-1”)

Recommendations for Table 3 (results from Study 105, also referred to as DURATION-1; see Exhibit 1):

- Omit the column of p-values. These will be replaced with 95% confidence intervals in the column for Bydureon.
- Under the results for HbA1c, include rows and results for “baseline”; “change from baseline (adjusted mean)”; and “95% confidence interval. The adjusted mean change from baseline at week 30 should be based on the primary analysis of variance model.

- Under the results for FPG and body weight, include the same rows and results as for HbA1c.
- The proportion achieving HbA1c targets at week 30 should be assessed from the full ITT population. Similarly, the proportion achieving  $\text{FPG} \leq 126 \text{ mg/dL}$  at week 30, if this result will be included in the table, should be assessed from the full ITT population.
- The inclusion of [REDACTED] (b) (4), should be decided by the Division.

Exhibit 1: Proposed Table in prescribing information for Bydureon, Part 14.1

[REDACTED] (b) (4)

Recommendations for the text in Section 14.1, pertaining to Study 105:

- The inclusion of discussion of [REDACTED] (b) (4) [REDACTED], should be decided by the Division.
- The text describes the one-year clinical results, [REDACTED] (b) (4) [REDACTED] The discussion of [REDACTED] (b) (4) [REDACTED] should be decided by the Division.
- Figure 2 (see Exhibit 2) depicts the longitudinal course of mean change in HbA1c for the completers in each arm through the 52-week period. The symbols denote results of statistical comparisons at intermediate time points, and should be omitted from this figure. The depiction of results beyond the 30-week evaluation period should be decided by the Division.



**SIGNATURE**

Janice Derr, Ph.D.  
Mathematical Statistician

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22200	ORIG-1	AMYLIN PHARMACEUTICA LS INC	EXENATIDE LAR

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JANICE A DERR  
12/29/2009

JON T SAHLROOT  
01/04/2010  
concur

THOMAS J PERMUTT  
01/05/2010  
concur



U.S. Department of Health and Human Services  
Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Translational Science  
Office of Biostatistics

## Statistical Review and Evaluation

### CARCINOGENICITY STUDIES

**IND/NDA Number:** NDA 22-200

**Drug Name:** LAR (long-acting release) AC2993-F17

**Indication(s):** 104 Week Carcinogenicity in Rats

**Applicant:** Sponsor: Amylin Pharmaceuticals, Inc., 9360 Towne Centre Drive  
San Diego, CA 92121

**Test Facility:** [REDACTED] (b) (4)

**Documents Reviewed:** Electronic submission, Dated: Sept. 3, 2009  
Electronic data submitted on Sept. 3, 2009

**Review Priority:** Standard

**Biometrics Division:** Division of Biometrics -6

**Statistical Reviewer:** Mohammad Atiar Rahman, Ph.D.

**Concurring Reviewer:** Karl Lin, Ph.D.

**Medical Division:** Division of Metabolism and Endocrinology Products

**Reviewing Pharmacologist:** Timothy Hummer, Ph.D.

**Project Manager:** John Bishai, Ph.D.

**Keywords:** Carcinogenicity, Dose response

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## 1. Background

In this submission the sponsor included a report of an animal carcinogenicity study in rats. This study was intended to assess the carcinogenic potential of AC2993 in rats when administered by subcutaneous injection biweekly at appropriate drug levels for about 104 weeks. Results of this review have been discussed with the reviewing pharmacologist Dr. Hummer.

In this review, the phrase "dose response relationship" refers to the linear component of the effect of treatment, and not necessarily to a strictly increasing or decreasing mortality or tumor rate as dose increases.

## 2. Design

Two separate experiments were conducted, one in males and one in females. In each of these two experiments there were three treated groups and two control groups. Three hundred and fifty Charles River Crl: CD®(SD) rats of each sex were randomly allocated to the treated and control groups in equal size of 70 animals. The dose levels for treated groups were 0.3, 1.0, and 3.0 mg/kg/day. In this review these dose groups were referred to as the low, medium, and high dose group, respectively. The two control groups were referred to as Control 1 and Control 2. Control 1 received diluent, while Control 2 received microspheres without the test article.

During the administration period all animals were observed twice daily for morbidity and mortality. A detailed clinical examination of each animal was performed weekly. Beginning on Week 53, a third mortality check in the evening was also conducted. Observations for clinical signs and masses were conducted weekly. Body weights were measured and recorded weekly for the first 16 weeks, and once every two weeks thereafter.

### 2.1. Sponsor's analyses

#### 2.1.1. Survival analysis

For survival data analysis the sponsor compared Control 1, Low, Medium, and High dose groups and separately compared the two control groups. The survival percentage in each group was estimated using the product-limit method. The related Kaplan-Meier plots were presented. The mortality data were evaluated for a dose-related increasing trend using the methods described in Tarone's 1975 paper. A one-sided score trend test was conducted at the 0.05 significance level. The two control groups were compared also using the Tarone's method. To compare the two controls one-sided tests for the mortality were performed for increases in Control 2 animals compared with Control 1 animals.

**Sponsor's findings:** Sponsor's analysis showed survival rates of 30%, 40%, 40%, 43%, and 30% in Control 1, Control 2, Low, Medium, and High dose groups, respectively in males and 21%, 27%, 33%, 27%, and 21% in Control 1, Control 2, Low, Medium, and High dose groups, respectively in females. Sponsor concluded that the overall survival rates in all AC2993 treated groups of both sexes were comparable to controls.

#### 2.1.2. Tumor data analysis

Similar to the survival data, for tumor data analysis the sponsor also compared Control 1, Low, Medium, and High dose groups and separately compared the two control groups. The sponsor analyzed the tumor data using the methods suggested by Peto et al. (1980). The analysis intervals for incidental neoplasms were: Weeks 0 through 52, 53 through 78, 79 through 92, and 93 through termination. The incidence rate of a

neoplasm was analyzed only if the total number of occurrences of the neoplasm in a treated group was two or more either under or over that of the control group. Peto's trend test for a positive linear trend in incidence rate was conducted at the significance levels of .025 and .005 for rare and common neoplasms. Common neoplasms are defined as those with a historical incidence in controls of more than 1% and rare neoplasms as 1% or less. Since the standard normal approximation used in the analysis of oncogenicity data may lead to artificially small p-values in the presence of low neoplasm incidence, exact permutation trend test was performed for those site/neoplasm combinations with total neoplasm incidence less than or equal to 10. Further evaluations of dose-related neoplasm incidence were carried out using Peto's trend test in the sequential fashion described in Tukey et al (1985).

**Sponsor's findings:** The sponsor's analysis showed statistically significant dose response relationships in the incidence of thyroid c-cell adenoma in both males and females. The pairwise comparisons showed that the incidence of c-cell adenomas in thyroid was statistically significantly increased at all doses in females and at 1.0 and 3.0 mg/kg in males. The sponsor's analysis also showed statistically significant dose response relationship in the incidence of c-cell carcinomas in thyroid in females. Also in females, the pairwise comparisons showed statistically significant increased incidence of c-cell carcinomas in thyroid in high dose group in females. The combined incidences of thyroid c-cell adenoma and carcinoma showed statistically significant dose response relationship in both sexes. The sponsor mentioned that the historical control data from 11 carcinogenicity studies conducted in this laboratory reported incidence for c-cell adenoma of 8.8% in males with a range of 1.9 to 15.4% while in females the incidence is 8.1% with a range of 2 to 11.4%. Also the historical control incidence for c-cell carcinoma at this laboratory is 0.6% in males with a range of 0% to 1.7% while in females the incidence is 0.6% with a range of 0% to 4.0%.

The sponsor's analysis further showed statistically significant dose response relationship in the incidence of fibroma of the subcutaneous tissue in males. Pairwise comparison with diluent control showed a statistically significant increased incidence of fibroma of the subcutaneous tissue in the high dose group in males. In female the incidence of kidneys benign lipoma also showed statistically significant dose response relationship. The sponsor mentioned that the historical control incidence at this laboratory for fibroma is 2.2% with a range of 0 to 5%. The sponsor mentioned that the historical control incidence at this laboratory for this tumor is 0.6% with a range of 0 to 3.3%.

## 2.2. Reviewer's analyses

To verify sponsor's analyses and to perform additional analysis suggested by the reviewing pharmacologist, this reviewer independently performed survival and tumor data analyses. Data used in this reviewer's analyses were provided by the sponsor electronically.

### 2.2.1. Survival analysis

The survival distributions of animals in all four treatment groups were estimated by the Kaplan-Meier product limit method. The dose response relationship was tested using the likelihood ratio test and homogeneity of survival distributions was tested using the log-rank test. The intercurrent mortality data are given in Tables 1A and 1B in the appendix for male and female rats, respectively. The Kaplan-Meier curves for survival rate are given in Figures 1A and 1B in the appendix for males and females, respectively. Results of the tests for dose response relationship and homogeneity of survivals, are given in Tables 2A and 2B in the appendix for males and females, respectively.

**Reviewer's findings:** This reviewer's analysis showed survival rates of 30%, 40%, 40%, 43%, and 32% in

Control 1, Control 2, Low, Medium, and High dose groups, respectively in males and 21%, 27%, 33%, 27%, and 21% in Control 1, Control 2, Low, Medium, and High dose groups, respectively in females. The tests showed no statistically significant dose response relationship across treatment groups or differences between either of the controls and any of the treated groups in survivals in either sex.

**Reviewer's comment:** *The sponsor's analysis showed a survival rate of 30% in the high dose group of male rats, while this reviewer's analysis showed a survival rate of 32% for this group. The reason for this difference is that, there was an animal (#1349) in the high dose group which died due to natural causes at Week 105 (terminal sacrifice week). The sponsor considered this animal as a non-survivor, while this reviewer considered it as a survivor.*

### 2.2.2. Tumor data analysis

As mentioned earlier this study had two control groups. The first control group (Control 1) received the diluent of the drug, while second control (Control 2) received microspheres without the test article. Clearly, for the determination of the carcinogenic potential of the drug as a whole (test article along with microspheres), an analysis of tumor data using Control 1 is more relevant; while for the determination of the carcinogenic potential of the compound (test article without microspheres), an analysis of tumor data using Control 2 is more relevant. A comparison of Control 1 and Control 2 would show the carcinogenic potential of microspheres only. In this review the reviewer presents all these three analyses.

The tumor data were analyzed for dose response relationships and pairwise comparisons of combined control with each of the treated. Both the dose response tests and pairwise comparisons were performed using the Poly-k method described in the paper of Bailer and Portier (1988) and Bieler and Williams (1993). In this method an animal that lives the full study period ( $w_{\max}$ ) or dies before the terminal sacrifice with a tumor gets a score of  $s_h = 1$ . An animal that dies at week  $w_h$  without a tumor before the end of the study gets a score of

$s_h = \left( \frac{w_h}{w_{\max}} \right)^k$ . The adjusted group size is calculated as  $\sum s_h$ . An animal with score  $s_h = 1$  can be interpreted as

a whole animal, while an animals with score  $s_h < 1$  can be interpreted as a partial animal. Clearly, the adjusted group size  $\sum s_h$  is equal to N (the original group size) if all animals live up to the end of the study or develops at least one tumor, otherwise the adjusted group size is less than N. These adjusted group sizes are then used for the dose response relationship and pairwise tests. One critical point for Poly-k test is the choice of the appropriate value of k. For long term 104 week standard rat and mouse studies, a value of k=3 is suggested in the literature. Hence, this reviewer used k=3 for the analysis of this data. For the calculation of p-values the exact permutation method was used. The tumor rates and the p-values of the tested tumor types are listed in Tables 3A and 3B in the appendix for males and females, respectively. The results of pairwise comparison of Control 1 and Control 2 are given in Table 4A and 4B in the appendix for males and females, respectively.

**Multiple testing adjustment:** For the adjustment of multiple testing of dose response relationship, the FDA guidance for the carcinogenicity study design and data analysis suggests the use of test levels  $\alpha=0.005$  for common tumors and  $\alpha=0.025$  for rare tumors for a submission with two species, and a significance level  $\alpha=0.01$  for common tumors and  $\alpha=0.05$  for rare tumors for a submission with one species study in order to keep the false-positive rate at the nominal level of approximately 10%. A rare tumor is defined as one in which the published spontaneous tumor rate is less than 1%. For multiple pairwise comparisons of treated group with control the FDA guidance the suggested the use of test levels  $\alpha=0.01$  for common tumors and  $\alpha=0.05$  for rare tumors, in order to keep the false-positive rate at the nominal level of approximately 10% for both

submissions with two or one submission.

It should be noted that the FDA guidance for multiple testing for dose response relationship is based on a publication by Lin and Rahman (1998). In this work the authors investigated the use of this rule for Peto analysis. However, in a later work Rahman and Lin (2008) showed that this rule for multiple testing for dose response relationship is also suitable for Poly-K tests.

**Reviewer’s findings:** Following tumor types showed p-values less than or equal to 0.05 either for dose response relationship and/or pairwise comparisons of controls and treated groups.

**Tumor Types with P-Values ≤ 0.05 for Dose Response Relationship or Pairwise Comparisons**

Organ Name	Tumor Name	0 mg Cont N=70	0.3 mg Low N=70	1.0 mg Med N=70	3.0 mg High N=70	P_Val ue Dose Response C vs. L	P_Val ue C vs. M	P_Val ue C vs. H
<u>Male Rats Using Control 1</u>								
all organs	schwannomas	0	0	1	3	0.0203*	0.5204	0.1369
parathyroid gla	adenoma, benign	0	0	3	3	0.0410*	0.1369	0.1329
skin, subcutis	fibroma, benign	0	4	2	8	0.0042*	0.0692	0.0040*
thyroid gland	adenoma, c-cell, benign	9	20	32	33	<0.001*	0.0380	<0.001*
	carcinoma, c-cell, malignant	0	2	5	3	0.1636	0.2683	0.0363*
	adenoma+carcinoma, c-cell	9	22	34	35	<0.001*	0.0185	<0.001*
<u>Male Rats Using Control 2</u>								
skin, subcutis	fibroma, benign	3	4	2	8	0.0342	0.5112	0.5188
thyroid gland	adenoma, c-cell, benign	9	20	32	33	<0.001*	0.0221	<0.001*
	adenoma+carcinoma, c-cell	10	22	34	35	<0.001*	0.0186	<0.001*
<u>Female Rats Using Control 1</u>								
kidneys	carcinoma, tubular	0	0	0	3	0.0156*	.	0.1380
thyroid gland	adenoma, c-cell, benign	5	22	19	21	0.0237	<0.001*	0.0028*
	carcinoma, c-cell, malignant	0	1	1	4	0.0139*	0.5326	0.5169
	adenoma+carcinoma, c-cell	5	23	20	25	0.0026*	<0.001*	0.0015*
<u>Female Rats Using Control 2</u>								
kidneys	carcinoma, tubular	1	0	0	3	0.0496	0.5213	0.5055
pancreas	adenoma, islet cell,	0	1	3	4	0.0284*	0.5269	0.1292
thyroid gland	adenoma, c-cell, benign	9	22	19	21	0.0723	0.0158	0.0442
	carcinoma, c-cell, malignant	1	1	1	4	0.0415	0.2749	0.2584
	adenoma+carcinoma, c-cell	10	23	20	25	0.0163	0.0187	0.0499

Based on the criteria of adjustment for multiple testing described above, the incidences of following tumor types were considered to have statistically significant dose response relationship:

Male rats

- a) Schwannomas in all organs using Control 1
- b) Benign adenoma in parathyroid gland using Control 1
- c) Benign fibroma in skin subcutis using Control 1
- d) C-cell benign adenoma in thyroid gland using both Control 1 and Control 2
- e) Combined incidences of c-cell adenoma and carcinoma in thyroid gland using both Control 1 and Control 2

Female rats

- a) Tubular cell carcinoma in kidneys using Control 1
- b) C-cell malignant carcinoma in thyroid gland using Control 1
- c) Combined incidences of c-cell adenoma and carcinoma in thyroid gland using Control 1
- d) Islet cell adenoma in pancreas using Control 2

Also all pairwise comparisons marked by the asterisks of treated groups with the controls were considered to be statistically significant for increased tumor incidence in the treated group.

The pairwise comparison of Control 1 and Control 2 did not show statistically significant difference in the incidence of any of the observed tumor type in either sex.

### 3. Summary

In this submission the sponsor included a report of an animal carcinogenicity study in rats. This study was intended to assess the carcinogenic potential of AC2993 in rats when administered by subcutaneous injection biweekly at appropriate drug levels for about 104 weeks.

In this review, the phrase "dose response relationship" refers to the linear component of the effect of treatment, and not necessarily to a strictly increasing or decreasing mortality or tumor rate as dose increases.

Two separate experiments were conducted, one in males and one in females. In each of these two experiments there were three treated groups and two control groups. Three hundred and fifty Charles River Crl: CD®(SD) rats of each sex were randomly allocated to the treated and control groups in equal size of 70 animals. The dose levels for treated groups were 0.3, 1.0, and 3.0 mg/kg/day. In this review these dose groups were referred to as the low, medium, and high dose group, respectively. The two control groups were referred to as Control 1 and Control 2. Control 1 received diluent while Control 2 received microspheres without the test article.

Clearly, for the determination of the carcinogenic potential of the drug as a whole (test article along with microspheres), an analysis of tumor data using Control 1 is more relevant; while for the determination of the carcinogenic potential of the compound (test article without microspheres), an analysis of tumor data using Control 2 is more relevant. A comparison of Control 1 and Control 2 would show the carcinogenic potential of microspheres only. In this review the reviewer presents all these three analyses.

The tests showed no statistically significant dose response relationship across treatment groups or differences between either of the controls and any of the treated groups in survivals in either sex. The tests showed statistically significant positive dose response relationship for the incidences of following tumor types:

Male rats

- a) Schwannomas in all organs using Control 1
- b) Benign adenoma in parathyroid gland using Control 1
- c) Benign fibroma in skin subcutis using Control 1
- d) C-cell benign adenoma in thyroid gland using both Control 1 and Control 2
- e) Combined incidences of c-cell adenoma and carcinoma in thyroid gland using both Control 1 and Control 2

Female rats

- a) Tubular cell carcinoma in kidneys using Control 1
- b) C-cell malignant carcinoma in thyroid gland using Control 1
- c) Combined incidences of c-cell adenoma and carcinoma in thyroid gland using Control 1
- d) Islet cell adenoma in pancreas using Control 2

The pairwise comparisons showed statistically significant for increased tumor incidence in the following tumor types:

Male rats

- a) Benign fibroma in subcutis skin in high dose group compared to Control 1
- b) C-cell benign adenoma in thyroid in medium and high dose groups compared to both Control 1 and Control 2
- c) C-cell malignant carcinoma in thyroid in medium dose group compared to Control 1
- d) Combined incidences of c-cell adenoma and carcinoma in thyroid in medium and high dose groups compared to both Control 1 and Control 2

Female rats

- a) C-cell benign adenoma in thyroid in all treated groups compared to Control 1
- b) Combined incidences of c-cell adenoma and carcinoma in thyroid in all treated groups compared to Control 1
- c) Combined incidences of c-cell adenoma and carcinoma in thyroid in high dose group compared to Control 2

The pairwise comparison of Control 1 and Control 2 did not show statistically significant difference in the incidence of any of the observed tumor type in either sex.

Mohammad Atiar Rahman, Ph.D.  
Mathematical Statistician

Concur: Karl Lin, Ph.D.  
Team Leader, Biometrics-6

cc:

Archival NDA 22-200 AC2993-F17

Dr. Hummer

Dr. Bishai

Dr. Machado

Dr. Lin

Dr. Rahman

Ms. Patrician

4. Appendix

**Table 1A: Intercurrent Mortality Rate Using All Dose Groups  
Male Rats**

Week	Control 1		Control 2		0.3 mg kg day		1.0 mg kg day		3.0 mg kg day	
	No. of Death	Cum. %								
0 - 52	4	5.71	3	4.29	4	5.71	3	4.29	5	7.14
53 - 78	13	24.29	12	21.43	10	20.00	10	18.57	7	17.14
79 - 91	15	45.71	14	41.43	16	42.86	13	37.14	14	37.14
92 - 104	17	70.00	13	60.00	12	60.00	14	57.14	22	68.57
Ter. Sac.	21	30.00	28	40.00	28	40.00	30	42.86	22	31.43

**Table 1B Intercurrent Mortality Rate Using All Dose Groups  
Female Rats**

Week	Control 1		Control 2		0.3 mg kg day		1.0 mg kg day		3.0 mg kg day	
	No. of Death	Cum. %								
0 - 52	2	2.86	7	10.00	2	2.86	5	7.14	5	7.14
53 - 78	18	28.57	15	31.43	13	21.43	13	25.71	16	30.00
79 - 91	24	62.86	13	50.00	14	41.43	18	51.43	14	50.00
92 - 104	11	78.57	16	72.86	18	67.14	15	72.86	20	78.57
Ter. Sac.	15	21.43	19	27.14	23	32.86	19	27.14	15	21.43

**Table 2A\_1: Tests for Dose-Response and Homogeneity  
Male Rats Using Control 1**

Test	Stati stic	P_Val ue
<i>ff</i>		
Dose-Response	Li kel i hood Rati o	0. 9652
Homogenei ty	Log-Rank	0. 3483

**Table 2A\_2: Tests for Dose-Response and Homogeneity  
Male Rats Using Control 2**

Test	Stati stic	P_Val ue
<i>ff</i>		
Dose-Response	Li kel i hood Rati o	0. 4793
Homogenei ty	Log-Rank	0. 6707

**Table 2B\_1: Tests for Dose-Response and Homogeneity  
Female Rats Using Control 1**

Test	Stati stic	P_Val ue
<i>ff</i>		
Dose-Response	Li kel i hood Rati o	0. 7368
Homogenei ty	Log-Rank	0. 2619

**Table 2B\_2: Tests for Dose-Response and Homogeneity  
Female Rats Using Control 2**

Test	Stati stic	P_Val ue
<i>ff</i>		
Dose-Response	Li kel i hood Rati o	0. 4130
Homogenei ty	Log-Rank	0. 5723

**Table 3A: Dose Response Relationship Test and Pairwise Comparisons  
Using Poly-3 test  
Male Rats Using Control 1**

Organ Name	Tumor Name	0 mg	0.3 mg	1.0 mg	3.0 mg	P_Val ue	P_Val ue	P_Val ue	P_Val ue
		Cont N=70	Low N=70	Med N=70	Hi gh N=70	Dose Response C			
adi pose ti ssue,	hi bernoma, mal igned	3	2	2	2	0.5931	0.5290	0.5473	0.5195
adrenal glands	adenoma, cortical, b	0	2	2	3	0.1025	0.2683	0.2733	0.1329
	osteosarcoma, mal igned	0	1	0	0	0.5075	0.5204	.	.
	pheochromocytoma, be	11	6	8	5	0.9064	0.8939	0.7593	0.9335
	pheochromocytoma, co	0	0	1	0	0.2513	.	0.5204	.
all organs	schwannomas	0	0	1	3	0.0203*	.	0.5204	0.1369
brai n	astrocytoma, mal igned	1	2	0	0	0.8985	0.5309	0.5204	0.5155
	carci noma, pars dist	0	0	1	2	0.0653	.	0.5253	0.2683
	granular cell tumor,	0	0	1	0	0.2513	.	0.5204	.
cavi ty, abdomi n	adenocarci noma, mal igned	0	0	1	0	0.2500	.	0.5253	.
	carci noma, tubular c	0	0	0	1	0.2513	.	.	0.5155
	hemangi osarcoma, mal igned	0	0	1	0	0.2513	.	0.5204	.
	lipoma, benign	0	0	1	0	0.2500	.	0.5253	.
	liposarcoma, mal igned	1	0	0	0	0.7638	0.5204	0.5204	0.5155
	mesotheli oma, mal igned	0	1	0	0	0.5075	0.5204	.	.
cavi ty, oral	carci noma, squamous	0	1	0	0	0.5075	0.5204	.	.
	carci noma, c-cell, m	0	0	1	0	0.2513	.	0.5204	.
cavi ty, thoraci	carci noma, tubular c	0	0	0	1	0.2513	.	.	0.5155
	mesotheli oma, mal igned	0	1	0	0	0.5075	0.5204	.	.
	mesotheli oma, mal igned	0	0	1	0	0.2513	.	0.5204	.
eyes	schwannoma, mal igned	0	0	0	1	0.2513	.	.	0.5155
harderian gland	adenoma, benign	1	0	0	1	0.4403	0.5204	0.5204	0.2631
head	schwannoma, mal igned	0	0	0	2	0.0622	.	.	0.2631
heart	mesotheli oma, mal igned	1	0	0	0	0.7638	0.5204	0.5204	0.5155
injection site	fi brous histi ocytoma	0	0	1	0	0.2513	.	0.5204	.
ki dneys	adenocarci noma, mal igned	0	0	1	0	0.2513	.	0.5204	.
	carci noma, tubular c	1	0	0	1	0.4403	0.5204	0.5204	0.2631
	hemangi osarcoma, mal igned	1	0	0	0	0.7638	0.5204	0.5204	0.5155
	liposarcoma, mal igned	1	1	0	1	0.5406	0.2683	0.5204	0.2631
	osteosarcoma, mal igned	0	1	0	0	0.5075	0.5204	.	.
	papill oma, transi tio	1	0	0	0	0.7638	0.5204	0.5204	0.5155
li ver	adenocarci noma, mal igned	0	0	1	0	0.2513	.	0.5204	.
	adenoma, hepatocell u	1	1	1	2	0.2672	0.2683	0.2683	0.5234
	carci noma, hepatocel	0	0	1	1	0.1916	.	0.5204	0.5155
	pheochromocytoma, ma	0	0	1	0	0.2500	.	0.5253	.
lung	adenocarci noma, mal igned	0	0	2	0	0.4384	.	0.2733	.







**Table 3A\_2: Dose Response Relationship Test and Pairwise Comparisons  
Using Poly-3 test  
Male Rats Using Control 2**

Organ Name	Tumor Name	0 mg	0.3 mg	1.0 mg	3.0 mg	P_Val ue	P_Val ue	P_Val ue	P_Val ue
		Cont N=70	Low N=70	Med N=70	Hi gh N=70	Dose Response			
Lung	pheochromocytoma, ma	0	0	1	0	0.2463	.	0.5098	.
Lymph node, hep	carci noma, tubular c	0	0	0	1	0.2475	.	.	0.5000
Lymph node, ili	hemangi osarcoma, mal	0	0	1	0	0.2475	.	0.5050	.
Lymph node, man	carci noma, squamous	0	0	0	1	0.2475	.	.	0.5000
Lymph node, med	adenocarci noma, mali	0	0	1	0	0.2463	.	0.5098	.
	carci noma, tubular c	0	0	0	1	0.2475	.	.	0.5000
Lymph node, mes	adenocarci noma, mali	0	0	2	0	0.4329	.	0.2574	.
	hemangi oma, beni gn	0	0	0	1	0.2475	.	.	0.5000
	hemangi osarcoma, mal	0	0	1	0	0.2475	.	0.5050	.
	lymphangi osarcoma, m	1	0	0	0	0.7525	0.5050	0.5050	0.5000
mammary gland	adenocarci noma, mali	0	0	1	0	0.2463	.	0.5098	.
	fi broadenoma, beni gn	2	1	0	1	0.6253	0.5075	0.7574	0.5000
multicentric ne	leukemi a, granulocyt	1	0	0	1	0.4347	0.5050	0.5050	0.7525
	leukemi a, large gran	0	0	0	1	0.2475	.	.	0.5000
	lymphoma, malignan	1	0	1	0	0.6232	0.5000	0.2524	0.4950
	sarcoma, histiocyti c	2	0	2	2	0.2905	0.7525	0.3162	0.6913
nose, level a	odontoma, malignan	0	0	0	1	0.2475	.	.	0.5000
nose, level b	adenoma, beni gn	0	1	0	0	0.5000	0.5050	.	.
	carci noma, squamous	0	0	1	0	0.2475	.	0.5050	.
pancreas	adenocarci noma, mali	0	0	1	0	0.2475	.	0.5050	.
	adenoma, islet cell, 12	12	12	3	3	0.9984	0.5706	0.9885	0.9859
	carci noma, islet cel	2	3	0	0	0.9751	0.5000	0.7525	0.7475
parathyroi d gla	adenoma, beni gn	1	0	3	3	0.0837	0.5050	0.3162	0.3087
pi tui tary gland	adenoma, pars distal	35	36	42	32	0.6432	0.4823	0.1846	0.5631
	adenoma, pars interm	1	0	0	0	0.7525	0.5050	0.5050	0.5000
	carci noma, pars dist	2	0	1	2	0.2963	0.7574	0.5149	0.3162
	pi tui cytoma, pars ne	0	1	0	0	0.5000	0.5050	.	.
	schwanna, malignan	0	0	0	1	0.2475	.	.	0.5000
prostate gland	adenoma, beni gn	1	0	0	0	0.7488	0.5000	0.5000	0.4950
semi nal vesicle	adenoma, beni gn	1	1	0	0	0.8110	0.7525	0.5000	0.4950
skel etal muscle	adenocarci noma, mali	0	0	1	0	0.2475	.	0.5050	.
	schwanna, malignan	0	0	0	1	0.2475	.	.	0.5000
ski n	adenoma, sebaceous c	0	0	2	0	0.4329	.	0.2574	.
	hai r follicle tumor,	0	1	1	0	0.4975	0.5050	0.5050	.









**Table 3B\_2: Dose Response Relationship Test and Pairwise Comparisons  
Using Poly-3 test  
Female Rats Using Control 2**

Organ Name	Tumor Name	0 mg	0.3 mg	1.0 mg	3.0 mg	P_Val ue	P_Val ue	P_Val ue	P_Val ue
		Cont N=70	Low N=70	Med N=70	Hi gh N=70	Dose Response C vs. L			
fff									
mammary gland	fibroadenoma, benign	29	24	20	25	0.5474	0.8629	0.9547	0.6898
multicentric ne	leukemia, granulocyt	1	0	0	0	0.7609	0.5269	0.5111	0.5056
	leukemia, large gran	0	0	0	1	0.2446	.	.	0.5056
	lymphoma, malignant	0	0	1	1	0.1851	.	0.5111	0.5111
	sarcoma, histiocytic	0	0	1	0	0.2446	.	0.5111	.
nose, level b	osteosarcoma, malign	0	0	0	1	0.2486	.	.	0.5111
ovaries	cystadenoma, benign	1	0	0	0	0.7609	0.5269	0.5111	0.5056
pancreas	adenoma, islet cell,	0	1	3	4	0.0284*	0.5269	0.1292	0.0639
	carcinoma, islet cel	1	1	1	0	0.7332	0.2749	0.2584	0.5056
parathyroid gla	adenoma, benign	0	0	1	1	0.1818	.	0.5111	0.5056
	carcinoma, c-cell, m	0	1	1	0	0.4918	0.5269	0.5111	.
pituitary gland	adenoma, pars distal	42	49	52	51	0.0901	0.3183	0.1318	0.1046
	carcinoma, pars dist	7	9	6	5	0.7890	0.4634	0.5165	0.6053
skel etal muscle	carcinoma, squamous	1	0	0	0	0.7609	0.5269	0.5111	0.5056
skin	carcinoma, sebaceous	0	1	0	0	0.4919	0.5319	.	.
skin, subcutis	fibrosarcoma, malign	1	0	0	0	0.7568	0.5213	0.5055	0.5000
	fibrous histiocytoma	0	0	0	1	0.2446	.	.	0.5056
	lipoma, benign	1	0	0	0	0.7568	0.5213	0.5055	0.5000
thyroid gland	adenoma, c-cell, ben	9	22	19	21	0.0723	0.0158	0.0442	0.0152
	adenoma, follicular	0	1	0	2	0.1093	0.5269	.	0.2584
	carcinoma, c-cell, m	1	1	1	4	0.0415	0.2749	0.2584	0.1874
	adenoma+carcinoma, c-cell	10	23	20	25	0.0163	0.0187	0.0499	0.0036*
urinary bladder	carcinoma, transiti o	1	0	0	0	0.7568	0.5213	0.5055	0.5000
	leiomyoma, benign	0	0	0	1	0.2446	.	.	0.5056
uterus with cer	granular cell tumor,	2	5	2	3	0.4970	0.2636	0.3166	0.5000
	leiomyosarcoma, mali	0	2	0	0	0.7432	0.2803	.	.
	polyp, stromal, beni	6	4	1	4	0.6389	0.6835	0.9481	0.6445
	sarcoma, stromal, ma	0	1	1	0	0.4891	0.5319	0.5111	.
	schwannoma, malignan	0	0	1	0	0.2446	.	0.5111	.
vagina	carcinoma, squamous	1	0	0	0	0.7609	0.5269	0.5111	0.5056
	granular cell tumor,	1	2	4	3	0.2245	0.5407	0.2017	0.3253
zymbal `s gland	carcinoma, squamous	0	0	0	1	0.2446	.	.	0.5056

**Table 4A: Pairwise Comparison of Control 1 and Control 2  
Using Poly-3 test  
Male Rat**

Organ Name	Tumor Name	Control 1	Control 2	P_Value C1 vs. c2
fff				
adipose tissue,	hibernoma, malignant	3	1	0.7140
adrenal glands	adenoma, cortical, b	0	1	0.5155
	osteosarcoma, malign	0	0	.
	pheochromocytoma, be	11	8	0.7593
	pheochromocytoma, co	0	0	.
brain	astrocytoma, maligna	1	0	0.5155
	carcinoma, pars dist	0	1	0.5155
	granular cell tumor,	0	1	0.5155
	meningioma, benign	0	1	0.5155
cavity, abdomin	adenocarcinoma, mali	0	0	.
	carcinoma, tubular c	0	0	.
	hemangiosarcoma, mal	0	0	.
	lipoma, benign	0	0	.
	liposarcoma, maligna	1	0	0.5155
	mesothelioma, malign	0	0	.
	osteosarcoma, malign	0	0	.
cavity, oral	carcinoma, squamous	0	1	0.5155
cavity, thoraci	carcinoma, c-cell, m	0	0	.
	carcinoma, tubular c	0	0	.
	mesothelioma, malign	0	0	.
	neuroendocrine tumor	0	1	0.5155
epididymides	mesothelioma, malign	0	1	0.5155
eyes	schwannoma, malignan	0	0	.
harderian gland	adenoma, benign	1	0	0.5155
head	schwannoma, malignan	0	0	.
heart	mesothelioma, malign	1	0	0.5155
injection site	fibrous histiocytoma	0	0	.
kidneys	adenocarcinoma, mali	0	0	.
	carcinoma, tubular c	1	1	0.2631
	hemangiosarcoma, mal	1	0	0.5155
	liposarcoma, maligna	1	0	0.5155
	osteosarcoma, malign	0	0	.
	papilloma, transi tio	1	0	0.5155
liver	adenocarcinoma, mali	0	0	.
	adenoma, hepatocellu	1	2	0.5309
	carcinoma, hepatocel	0	1	0.5155
	pheochromocytoma, ma	0	0	.
lung	adenocarcinoma, mali	0	0	.
	carcinoma, tubular c	0	0	.
	hibernoma, malignant	0	0	.
	osteosarcoma, malign	0	0	.
	pheochromocytoma, ma	0	0	.

**Table 4A: Pairwise Comparison of Control 1 and Control 2  
Using Poly-3 test  
Male Rat**

Organ Name	Tumor Name	Control 1	Control 2	P_Value C1 vs. c2
lymph node, hep	carci noma, tubul ar c	0	0	.
lymph node, ili	hemangi osarcoma, mal	0	0	.
lymph node, man	carci noma, squamous	0	0	.
lymph node, med	adenocarci noma, mali	0	0	.
	carci noma, tubul ar c	0	0	.
	adenocarci noma, mali	0	0	.
	hemangi oma, beni gn	0	0	.
	hemangi osarcoma, mal	1	0	0.5155
	lymphangi osarcoma, m	0	1	0.5155
mammary gland	adenocarci noma, mali	0	0	.
	adenoma, beni gn	1	0	0.5155
	fi broadenoma, beni gn	2	2	0.3323
mul ti centri c ne	leukemi a, granul ocyt	0	1	0.5155
	leukemi a, large gran	1	0	0.5155
	lymphoma, mali gnant	0	1	0.5204
	sarcoma, hi sti ocyti c	2	2	0.3401
nose, level a	carci noma, squamous	1	0	0.5155
	odontoma, mali gnant	0	0	.
nose, level b	adenoma, beni gn	0	0	.
	carci noma, squamous	1	0	0.5155
pancreas	adenocarci noma, mali	0	0	.
	adenoma, aci nar cell	1	0	0.5155
	adenoma, islet cell,	8	12	0.2747
	carci noma, aci nar ce	1	0	0.5155
	carci noma, islet cel	3	2	0.5390
parathyroid gla	adenoma, beni gn	0	1	0.5155
pi tui tary gland	adenoma, pars di stal	38	35	0.7343
	adenoma, pars interm	2	1	0.5234
	carci noma, pars di st	0	2	0.2631
	pi tui cytoma, pars ne	0	0	.
	schwannoma, mali gnant	0	0	.
prostate gland	adenoma, beni gn	1	1	0.2683
semi nal vesicle	adenoma, beni gn	1	1	0.2683
skel etal muscl e	adenocarci noma, mali	0	0	.
	schwannoma, mali gnant	0	0	.

**Table 4A: Pairwise Comparison of Control 1 and Control 2  
Using Poly-3 test  
Male Rat**

Organ Name	Tumor Name	Control 1	Control 2	P_Value C1 vs. c2
fff				
skin	adenoma, basal cell,	1	0	0.5155
	adenoma, sebaceous c	0	0	.
	carci noma, squamous	1	0	0.5155
	hair follicle tumor,	0	0	.
	keratoacanthoma, ben	3	2	0.5296
	papilloma, squamous	0	1	0.5155
skin, subcutis	fibroma, benign	0	3	0.1329
	fibrous histiocyoma	0	1	0.5155
	lipoma, benign	1	2	0.5234
	schwannoma, malignan	0	1	0.5155
small intestine	adenocarci noma, mali	0	1	0.5155
spleen	adenocarci noma, mali	0	0	.
stomach, glandu	adenocarci noma, mali	0	0	.
testes	adenoma, interstitia	4	2	0.6994
	mesothelioma, malign	0	1	0.5155
thyroid gland	adenoma, c-cell, ben	9	9	0.4719
	adenoma, follicular	1	5	0.1220
	carci noma, c-cell, m	0	1	0.5155
	carci noma, follicula	0	2	0.2683
tongue	papilloma, squamous	0	1	0.5204
uri nary bladder	papilloma, transiti o	0	0	.
zybal `s gland	carci noma, squamous	1	2	0.5234

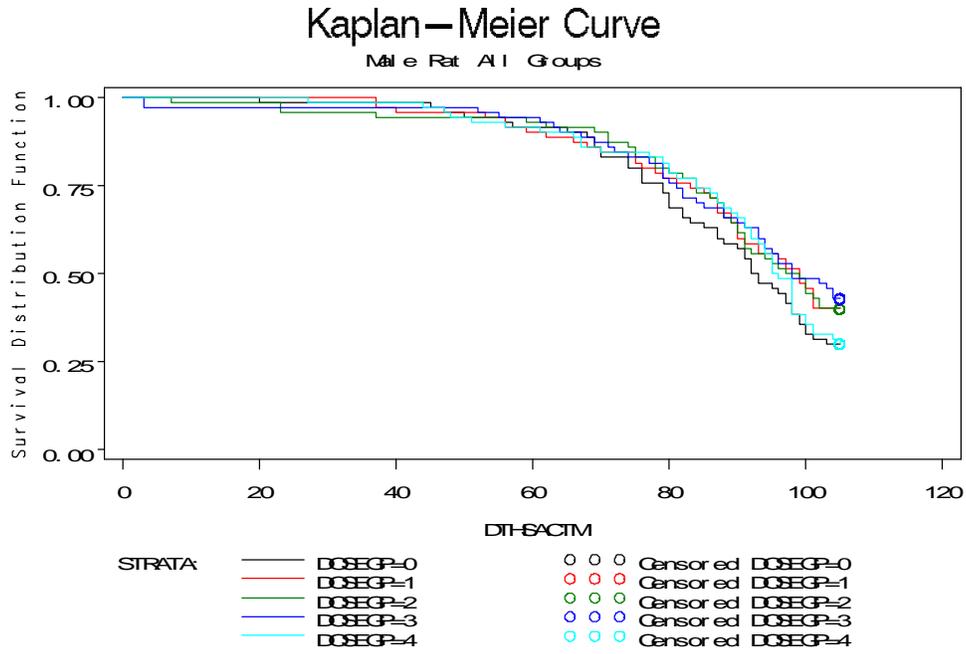
**Table 4B: Pairwise Comparison of Control 1 and Control 2  
Using Poly-3 test  
Female Rat**

Organ Name	Tumor Name	Control 1	Control 2	P_Value C1 vs. c2
fff				
adipose tissue,	hibernoma, malignant	1	2	0.5172
adrenal glands	adenoma, cortical, b	2	1	0.5172
	carcinoma, cortical,	0	1	0.5114
	pheochromocytoma, ma	2	3	0.5218
brain	astrocytoma, maligna	1	0	0.5057
	carcinoma, pars dist	7	7	0.4209
	granular cell tumor,	0	1	0.5114
cavity, abdomin	carcinoma, squamous	0	1	0.5057
	fibrosarcoma, malign	0	0	.
	schwannoma, benign	1	0	0.5057
cavity, thoraci	hemangiosarcoma, mal	0	0	.
harderian gland	adenoma, benign	0	0	.
heart	schwannoma, malignan	0	0	.
kidneys	adenocarcinoma, mali	0	1	0.5114
	adenoma, tubular cel	0	0	.
	carcinoma, tubular c	0	1	0.5114
	lipoma, benign	1	0	0.5057
	nephroblastoma, mali	0	1	0.5114
	osteosarcoma, malign	0	0	.
large intestine	fibroma, benign	0	0	.
	leiomyosarcoma, mali	1	0	0.5057
liver	adenoma, hepatocellu	0	0	.
	cholangiobroma, be	0	1	0.5057
	cholangioma, benign	1	0	0.5057
liver	hemangiosarcoma, mal	0	0	.
	pheochromocytoma, ma	1	0	0.5057
lung	adenocarcinoma, mali	0	2	0.2643
	carcinoma, bronchiol	0	0	.
	carcinoma, cortical,	0	0	.
	carcinoma, squamous	0	1	0.5057
	hemangiosarcoma, mal	0	0	.
	hibernoma, malignant	0	0	.
	osteosarcoma, malign	0	0	.
	pheochromocytoma, ma	1	2	0.5172
lymph node, man	osteosarcoma, malign	0	0	.
lymph node, med	carcinoma, bronchiol	0	0	.
lymph node, ren	carcinoma, squamous	0	1	0.5057

**Table 4B: Pairwise Comparison of Control 1 and Control 2  
Using Poly-3 test  
Female Rat**

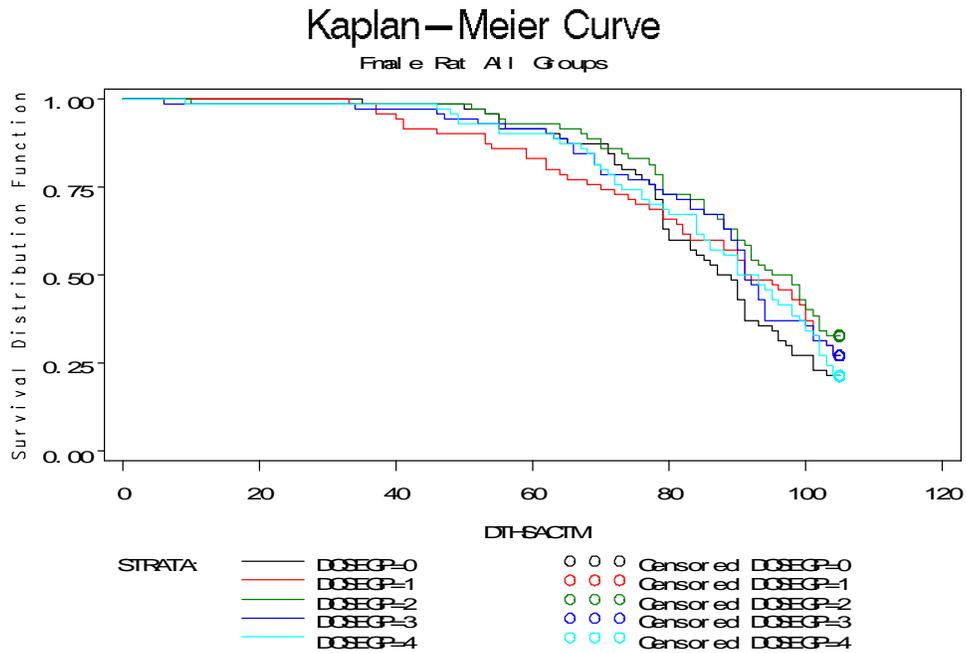
Organ Name	Tumor Name	Control 1	Control 2	P_Value C1 vs. c2
%%%				
mammary gland	adenocarcinoma, malignant	29	28	0.5729
	adenoma, benign	3	1	0.7089
	carcinoma, squamous	0	1	0.5057
	fibroadenoma, benign	21	29	0.0957
mesentery/peritoneum	lipoma, benign	1	0	0.5057
multicentric	leukemia, granulocytic	0	1	0.5057
	leukemia, large granular	0	0	.
	lymphoma, malignant	0	0	.
	sarcoma, histiocytic	2	0	0.7529
nose, level B	osteosarcoma, malignant	0	0	.
ovaries	cystadenoma, benign	0	1	0.5057
ovaries	Sertoli cell tumor,	1	0	0.5057
pancreas	adenoma, islet cell,	1	0	0.5057
	carcinoma, islet cell	0	1	0.5057
parathyroid gland	adenoma, benign	0	0	.
	carcinoma, C-cell, malignant	0	0	.
pituitary gland	adenoma, pars distalis	52	42	0.9325
	carcinoma, pars distalis	9	7	0.6446
skeletal muscle	carcinoma, squamous	0	1	0.5057
skin	carcinoma, sebaceous	0	0	.
skin, subcutis	fibrosarcoma, malignant	0	1	0.5114
	fibrous histiocytoma	0	0	.
	lipoma, benign	0	1	0.5114
thyroid gland	adenoma, C-cell, benign	5	9	0.2046
	adenoma, follicular	1	0	0.5057
	carcinoma, C-cell, malignant	0	1	0.5057
urinary bladder	carcinoma, transitional	0	1	0.5114
	leiomyoma, benign	0	0	.
	leiomyosarcoma, malignant	1	0	0.5057
uterus with cervix	fibroma, benign	1	0	0.5057
	granular cell tumor,	3	2	0.5218
	leiomyosarcoma, malignant	0	0	.
	polyp, stromal, benign	3	6	0.2536
	sarcoma, stromal, malignant	0	0	.
	Schwannoma, malignant	0	0	.
vagina	carcinoma, squamous	0	1	0.5057
	granular cell tumor,	2	1	0.5087
Zymbal's gland	carcinoma, squamous	0	0	.

Figure 1A: Kaplan-Meier Survival Functions for Male Rats



X-Axis: Weeks, Y-Axis: Survival rates

Figure 1B: Kaplan-Meier Survival Functions for Female Rats



X-Axis: Weeks, Y-Axis: Survival rates

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Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22200	ORIG-1	AMYLIN PHARMACEUTICA LS INC	EXENATIDE LAR

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12/22/2009

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12/22/2009  
Concur with review