CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-919

STATISTICAL REVIEW(S)

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

CLINICAL STUDIES

NDA/Serial Number:	21-919
Drug Name:	exendin-4 (Byetta) Subcutaneous Injection 250mcg/mL
Indication(s):	As adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus
Applicant:	Amylin
Date(s):	Submitted March 19, 2008
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1. EXECUTIVE SUMMARY

Byetta (Exenatide) (NDA 21-773) was approved on April 28, 2005 for use in combination with metformin, a sulfonylurea, or a combination of metformin and a sulfonylurea in the treatment of adult patients with type 2 diabetes to improve glycemic control. In addition, Amylin received an Approvable Letter for the use of Byetta (NDA 21-919) as monotherapy in patients with type 2 diabetes mellitus based on data from two 28-day studies. For approval of the monotherapy indication, the Agency requested "data from at least one adequate and well-controlled trial of sufficient duration to assess the efficacy (i.e., HbA_{1c} lowering) and safety of exenatide monotherapy in patients with type 2 diabetes mellitus." In response to the Approvable Letter, Amylin submitted data from Study GWBJ as a Complete Response to support the use of exenatide as monotherapy to improve glycemic control in adults with type 2 diabetes mellitus who were on diet and exercise.

1.1 Conclusions and Recommendations

Both exenatide 5 mcg and 10 mcg BID were statistically significantly better than placebo in HbA1c change from baseline to Week 24 or endpoint. The least squared mean difference from the primary efficacy analysis using LOCF data was -0.5% for the 5 mcg treatment group and -0.7% for the 10 mcg treatment group from a mean baseline HbA1c of approximately 8% (Table 1).

Table 1 ANCOVA results for HbA1c from baseline – ITT, LOCF

	Placebo n=75	EX 5mcg n=76	EX 10mcg n=76
Baseline (SE)	7.93 (0.07)	7.95 (0.07)	7.92 (0.07)
Endpoint (SE)	7.72 (0.14)	7.21 (0.14)	7.05 (0.14)
Change from baseline	-0.20 (0.13)	-0.73 (0.12)	-0.87 (0.12)
Difference from placebo		-0.53 [-0.87, -0.18]	-0.67 [-1.01, -0.32]
p-value		p=0.01	p<0.01

ANCOVA model included treatment and screening HbA1c stratum (≤8% and >8%) as fixed effect and baseline HbA1c as covariate.

For a secondary efficacy analysis, the protocol specified a Mixed Model Repeated Measure (MMRM) ANCOVA under an assumption of a compound symmetry as the covariance structure for HbA1c change from baseline. LSM differences from the MMRM ANCOVA were similar to the primary analysis using LOCF data. The standard error, however, was less for the MMRM model (0.14) than the ANCOVA model (0.18). Therefore, the confidence intervals were narrower and p values more significant for the secondary analysis than the primary analysis (Table 6).

2. INTRODUCTION

2.1 Overview

Study GWBJ was a multicenter, randomized, double-blind, placebo-controlled, parallel-group safety and efficacy study of exenatide monotherapy in patients with type 2 diabetes mellitus. The study was conducted at 23 study centers in 4 countries.

The primary objective was to demonstrate superiority of exenatide to placebo in HbA1c change from baseline to endpoint after 24 weeks of treatment in patients with type 2 diabetes who are experiencing inadequate glycemic control on diet and exercise.

2.2 Data Sources

The study report and electronic datasets for the monotherapy study are located at the following link:

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The statistical analysis plan (SAP) which supersedes the statistical plans in protocol was not in the submission. The 5.3.5.1.12 Statistical Methods Interim Analysis Plan was a 2-page documentation of statistical methods (16.1.9) and errors in the locked database (16.1.13).

3. STATISTICAL EVALUATION

3.1 Evaluation of Efficacy

Study Design and Endpoints

Study H8O-MC-GWBJ was a randomized, double-blind, placebo-controlled, three-arm, parallel-group, multicenter study in type 2 diabetes mellitus patients with inadequate glycemic control by diet and exercise. The 2-week, single-blind placebo lead-in period was followed by randomization of patients in 2:2:1:1 ratio to exenatide 5 mcg, exenatide 10 mcg, placebo equivalent of 5 mcg exenatide and placebo equivalent of 10 mcg. The two placebo groups were combined into one group for analysis. Patients were stratified by screening HbA_{1c} subgroups of ≤8.0% or >8.0%. During the 4-week treatment initiation period, all patients were given 5 mcg of exenatide or the equivalent volume of placebo, BID. Following completion of the 4-week initiation period, patients were administered the randomized dose of exenatide (5 mcg or 10 mcg BID) or the equivalent volume of placebo, BID, for the remaining 20-week.

The primary efficacy variable was HbA_{1c} change from baseline to endpoint. The analysis of covariance model included treatment and screening HbA_{1c} subgroup as fixed effects and baseline HbA_{1c} as covariate.

For the primary efficacy analysis, the protocol specified Fisher Least Significant Difference Testing procedure for multiple comparisons. The two exenatide doses vs. placebo were tested each at the 5% level of significance only when an overall F-test of all three treatment groups was significant at 5% level of significance.

The 3 key secondary efficacy variables are percentage of patients achieving $HbA_{1c} \leq 7\%$ and $\leq 6.5\%$, fasting serum glucose (FSG), and body weight.

A total of 337 patients were screened and 233 patients were randomized at 23 investigator sites in 5 countries. The only patient (exenatide 5 mcg) from Puerto Rico was combined with patients in the U.S. One placebo patient discontinued before taking study drug leaving 232 patients in the ITT population which was defined as all randomized patients who received at least one dose of study medication.

Table 2 displays the number and percent of patients by country and investigator sites for the 3 treatment groups. The country with the greatest percentage of patients was Romania (52%). The country with the smallest percentage of patients was the US (8%). Appendix 1 presents efficacy analyses for the two larger sites, #101 and #103 in Romania.

Table 2 Number of randomized patients by country and investigator

Country	Inv	Placebo (n = 78)	EX 5mcg (n = 77)	EX 10mcg (n = 78)	Total (n = 233)	Percent
India	300	2	6	1	9	3.9%
	303	4	6	3	13	5.6%
	304	4	0	5	9	3.9%
	306	1	3	3	7	3.0%
	308	1	0	0	1	0.4%
	309	7	5	3	15	6.4%
	310	3	2	3	8	3.4%
Subtotal		**22**	**22**	**18**	**62**	**26.6%**
Romania	100	1	2	0	3	1.3%
	101	21	21	23	65	27.9%
	102	0	3	3	6	2.6%
	103	12	9	9	30	12.9%
	104	3	2	1	6	2.6%
	105	3	2	6	11	4.7%
Subtotal		**40**	**39**	**42**	**121**	**51.9%**
Russia	200	2	1	1	4	1.7%
	202	2	4	5	11	4.7%
	204	0	0	2	2	0.9%
	205	3	4	2	9	3.9%
	206	2	1	2	5	2.1%
Subtotal		**9**	**10**	**12**	**31**	**13.3%**
United States	1	4	1	4	9	3.9%
	2	1	0	1	2	0.9%
	3	2	4	1	7	3.0%
	4	0	1	0	1	0.4%

Country	Inv	Placebo (n = 78)	EX 5mcg (n = 77)	EX 10mcg (n = 78)	Total (n = 233)	Percent
Subtotal		**7**	**6**	**6**	**19**	**8.2%**
Overall		78	77	78	233	100.0%

Patient Disposition, Demographic and Baseline Characteristics

Approximately 88% of the patients completed the study (Table 3). The discontinuation rate for patients due to loss of glucose control was 5% for both placebo and exenatide. The 2 AEs leading to discontinuations in the exenatide 10 mcg group were headache and nausea.

Table 3 Patient Disposition

	Placebo		EX 5mcg		EX 10mcg		Total
	n	(%)	n	(%)	n	(%)	
Screened							337
Randomized	78		77	(100%)	78	(100%)	233
ITT	77	(100%)	77	(100%)	78	(100%)	232 (100%)
Completed	69	(89.6%)	66	(85.7%)	68	(87.2%)	203(87.5%)
Withdrawn	8	(10.4%)	11	(14.3%)	10	(12.8%)	29 (12.5%)
Adverse Event	0	(0.0%)	0	(0.0%)	2	(2.6%)	2 (0.9%)
Loss of Glucose Control	4	(5.2%)	3	(3.9%)	5	(6.4%)	12 (5.2%)
Lost to follow up	1	(1.3%)	1	(1.3%)	1	(1.3%)	3 (1.3%)
Physician Decision	0	(0.0%)	2	(2.6%)	0	(0.0%)	2 (0.9%)
Sponsor Decision	0	(0.0%)	1	(1.3%)	0	(0.0%)	1 (0.4%)
Subject Decision	3	(3.9%)	4	(5.2%)	2	(2.6%)	9 (3.9%)

Table 4 displays demographic characteristics at baseline by treatment group.

Table 4 Demographic characteristics at baseline

			Placebo	**EX 5 mcg**	**EX 10 mcg**
Age (yr)		Mean	53.3	53.7	55.2
		Std Dev	9.2	10.1	9.9
		Maximum	73.0	71.5	77.4
		Minimum	25.6	28.0	33.4
Gender	**F**	n	35	37	30
		%	45.5	48.1	38.5
	M	n	42	40	48
		%	54.6	52.0	61.5
Race					

			Placebo	EX 5 mcg	EX 10 mcg
African		n	3	0	3
		%	3.9	0.0	3.9
Caucasian		n	51	50	56
		%	66.2	64.9	71.8
East Asian		n	1	0	0
		%	1.3	0.0	0.0
Hispanic		n	2	5	1
		%	2.6	6.5	1.3
West Asian		n	20	22	18
		%	26.0	28.6	23.1
HbA1c (%)	Mean		7.8	7.9	7.8
	Std Dev		0.9	1.0	1.0
	Maximum		9.9	10.0	11.0
	Minimum		6.4	6.3	6.1
Diabetes	Mean		1.3	2.4	2.0
Duration (yr)	Std Dev		1.7	3.4	2.8
	Maximum		7.0	18.0	12.0
	Minimum		0.1	0.0	0.0
Weight (kg)	Mean		85.9	85.1	85.9
	Std Dev		15.8	15.2	15.7
	Maximum		143.2	147.2	140.0
	Minimum		50.0	57.0	51.3

The primary efficacy variable was HbA1c change from baseline to endpoint. The primary analysis was based on the analysis of covariance (ANCOVA) model in the intent-to-treat (ITT) population with last observation carried forward (LOCF) data. The fixed effects in the model were treatment and screening HbA1c subgroup (≤8% and >8%) and the covariate was the screening HbA1c. The overall test for significant differences among treatments preceded the pairwise comparisons between each exenatide treatment and placebo.

The sample sizes for patients with a baseline HbA1c value and at least one follow up HbA1c value were 75, 76 and 76 for placebo, exenatide 5 mcg and exenatide 10 mcg, respectively.

Table 5 summarizes the ANCOVA results in HbA1c changes from baseline to endpoint for the ITT population. Baseline HbA1c values were approximately 7.9% for the 3 treatment groups. The overall p-value from the F test was <0.01. The pairwise comparisons versus placebo were statistically significant at the 5% level of significance. Figure 1 displays HbA1c mean changes from baseline over time for the completers population. Figure 2 displays the cumulative distribution functions for HbA1c changes from baseline in the ITT population with LOCF data.

Table 5 ANCOVA results in HbA1c (%) Change from baseline to endpoint -ITT

	Placebo n=75	EX 5 mcg n=76	EX 10 mcg n=76
Baseline (SE)	7.93 (0.1)	7.95 (0.1)	7.92 (0.1)
Endpoint	7.72	7.21	7.05
Change from baseline (SE)	-0.20 (0.13)	-0.73 (0.12)	-0.87 (0.12)
*LSM Difference (SE) from placebo		-0.53 (0.15)	-0.67 (0.15)
95% Confidence Interval		[-0.87, -0.18]	[-1.01, -0.32]
p-value		<0.01	<0.01

* LSM=least squares mean

Figure 1 HbA_{1c} (%) Mean change from baseline over time - completers

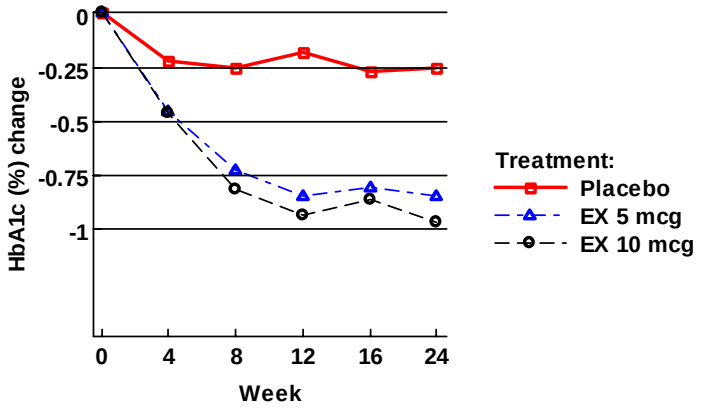
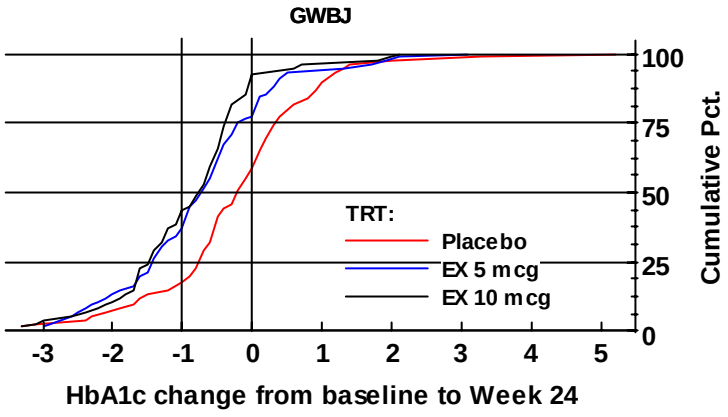


Figure 2 Cumulative distribution of HbA_{1c} (%) change from baseline to endpoint – ITT (LOCF)



Secondary analysis of HbA1c change from baseline

Mixed model repeated measure (MMRM)

The protocol specified MMRM ANCOVA as a secondary analysis to support the primary analysis. The model included treatment, week of visit, treatment-by-week interaction and screening HbA1c subgroup as fixed effects and baseline HbA1c as covariate. The patient variable and residual error were chosen as random effects. The 5 measurements measured on each patient at weeks 4, 8, 12, 16 and 24 were correlated. The analysis used a compound symmetric covariance structure which assumes the variances at each time point are homogeneous and the correlation between 2 separate measurements is constant regardless of the distance between the time points. Table 6 displays the LSMs for each time point and the difference with placebo for exenatide 5 mcg and exenatide 10 mcg at Week 24. HbA1c LSM differences with placebo were similar to those using the ANCOVA, the primary efficacy analysis method. The MMRM method with the compound symmetry variance-covariance structure produced smaller p-values than ANCOVA due to smaller standard errors.

Table 6 Results of ANCOVA MMRM – ITT patients

	Placebo			**EX 5 mcg**			**EX 10 mcg**		
Week	**n**	**LSM**	**SEM**	**n**	**LSM**	**SEM**	**n**	**LSM**	**SEM**
Week 4	**75**	**-0.17**	**0.10**	**76**	**-0.34**	**0.10**	**75**	**-0.40**	**0.10**
Week 8	**75**	**-0.18**	**0.10**	**76**	**-0.62**	**0.10**	**76**	**-0.69**	**0.10**
Week 12	**71**	**-0.12**	**0.10**	**69**	**-0.72**	**0.10**	**74**	**-0.81**	**0.10**
Week 16	**70**	**-0.21**	**0.10**	**68**	**-0.68**	**0.10**	**69**	**-0.76**	**0.10**
Week 24	**69**	**-0.20**	**0.10**	**65**	**-0.74**	**0.10**	**67**	**-0.87**	**0.10**
Week 24 Difference from placebo (95% CI)					**-0.54 (-0.81, -0.27)**	**0.14**		**-0.67 (-0.95, -0.41)**	**0.14**
p-value					**0.0001**				**<0.0001**

Secondary efficacy variables:

HbA1c ≤7%

Table 7 displays percent of patients with HbA1c ≤ 7% at endpoint. The p-value from the stratified analysis (baseline HbA1c ≤8% and >8%) was not significant for exenatide 5 mcg vs. placebo (0.07). Furthermore, the results were not significant between exenatide doses and placebo in the sponsor's per protocol patients (Table GWBJ.14.12).

Table 7 Analysis of patients with HbA1c ≤ 7% at endpoint - ITT

	Placebo		EX 5 mcg		EX 10 mcg	
	n	%	n	%	n	%
Number of Patients	75		76		76	
Patients with HbA1c ≤ 7%	31	(41%)	42	(55%)	44	(58%)
Percent difference				14%		17%
Exenatide vs. placebo				(-2, 30)		(1, 32)
p-value				0.07		0.03

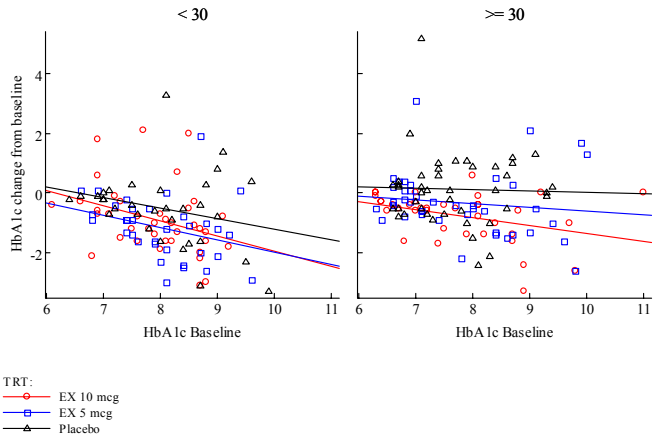
3.2 Evaluation of Safety

There were no severe hypoglycemia episodes in the study.

4. FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

The treatment-by-subgroup interactions on HbA1c change from baseline in gender, race and age group (<65 years of age versus ≥65) were not significant. The overall treatment-by-BMI group (<30 or ≥30) was significant (p=0.07) (Fig. 3). However, the significant result was driven by the 2 exenatide doses (p=0.01), not by subgroup differences between the exenatide doses and placebo. The p-value for interaction between exenatide 10 mcg vs. placebo was 0.14, and for exenatide 5 mcg vs. placebo was 0.5.

Figure 3 HbA1c change from baseline vs. baseline HbA1c by BMI group



5. Labeling Recommendations

1. Tables 5 and 6 present the efficacy results of the monotherapy study and previously submitted combination studies, respectively. The HbA1c baselines and changes from baseline are presented by treatment group. I recommend adding another row to present the differences between exenatide doses and placebo. The p-value <0.05 symbol can also be moved from the row for HbA1c change from baseline to the row for differences vs. placebo.

2. In addition to the primary efficacy variable, HbA1c, the secondary efficacy variables, Proportion (of patients) Achieving HbA1c ≤6.5%, Body Weight, FSG, and Oral Glucose Tolerance Test at 2-hr are presented. It is unnecessary to present information that is correlated with the primary efficacy variable, especially the 2-hr Oral Glucose Tolerance Test which was an exploratory variable evaluated in a subset of patients.

3. The percent of patients achieving HbA1c ≤ 6.5% is presented in Table 5 but a cutoff of ≤ 7% was presented in other tables. To be consistent in the label, the ≤7% cutoff should be presented.

4. The p-values for the secondary efficacy variables should not be presented. The sponsor did not have a pre-specified plan for type 1 error control of secondary variables.

5. Blood pressure was not a pre-specified efficacy endpoint. The ANCOVA analysis showed no significant results for systolic BP (p=0.17) or diastolic BP (p=0.23). The statement, 'Reductions from baseline in systolic and diastolic blood pressure were noted in both exenatide 5 mcg (-3.6 mmHg/-0.5 mmHg) and exenatide 10 mcg (-4.3 mmHg/2.9 mmHg) treatment groups, compared to slight increases (0.1 mmHg/0.1 mmHg) in the placebo group.', therefore, should not be presented.

6. The One-Year Clinical Results are from a cohort of 163 patients in the open label extension studies without placebo control. The change from baseline information without comparative control should not be presented.

7. The comparative statement that '… a statistically significant dose-effect was observed between 5 mcg and 10 mcg BYETTA groups for the change from baseline HbA1c at Week 30 in the three studies' is usually not a part of the label for type 2 diabetes drugs. First of all, the studies were designed to show superiority of exenatide to placebo. In addition, there was no significant difference between exenatide 5 and 10 mcg in the monotherapy trial.

6. Appendix

The Medical Officer, Valerie Pratt asked for a statistical evaluation of the largest sites in Study GWBJ, both in Romania with 41% of the total patient population in the efficacy intent-to-treat population. She asked for this evaluation in order to decide on appropriate sites for DSI inspection.

The study was conducted at 23 study centers in 4 countries (Romania, India, Russian Federation and United States). Table 8 presents the number (%) of patients in each country and Table 9 the number (%) of patients at each site by treatment groups ranked from largest to smallest sites.

Table 8 Number (%) of patients by country – ITT

	N	%
India	57	25%
Romania	120	53%
Russian federation	31	14%
United states	18	8%
Total	226	100%

Table 9 Number of patients by investigator site and treatment group - ITT

COUNTRY	INVID	EX10mcg	EX5mcg	Placebo	Total	Percent
RO	101	23	21	20	64	28%
RO	103	9	9	12	30	13%
IN	309	3	5	6	14	6%
IN	303	3	6	4	13	6%
RO	105	6	2	3	11	5%
RU	202	5	4	2	11	5%
IN	304	5	.	4	9	4%
RU	205	2	4	3	9	4%
US	1	4	1	4	9	4%
IN	300	1	5	2	8	4%
IN	306	3	3	1	7	3%
US	3	1	4	2	7	3%
RO	102	3	3	.	6	3%
RO	104	1	2	3	6	3%
IN	310	1	2	2	5	2%
RU	206	2	1	2	5	2%
RU	200	1	1	2	4	2%
RO	100	.	2	1	3	1%
RU	204	2	.	.	2	1%
US	2	1	.	1	2	1%
IN	308	.	.	1	1	0%
PR	4	.	1	.	1	0%

COUNTRY INVID	EX10mcg	EX5mcg	Placebo	Total	Percent
Total	76	76	75	227	100%

The descriptive statistics of sites 101 and 103 in Romania were compared to all other sites pooled. The HbA_{1c} change from baseline means for the 3 treatment groups in site 101 and 103 were similar to the corresponding means of all other sites combined (Fig. 4). In addition the medians of HbA_{1c} change from baseline were similar for the corresponding treatment groups in sites 101, 103 and all others combined (figure 5).

Figure 4 Mean HbA1c (%) change from baseline by investigator and treatment group – ITT (LOCF)

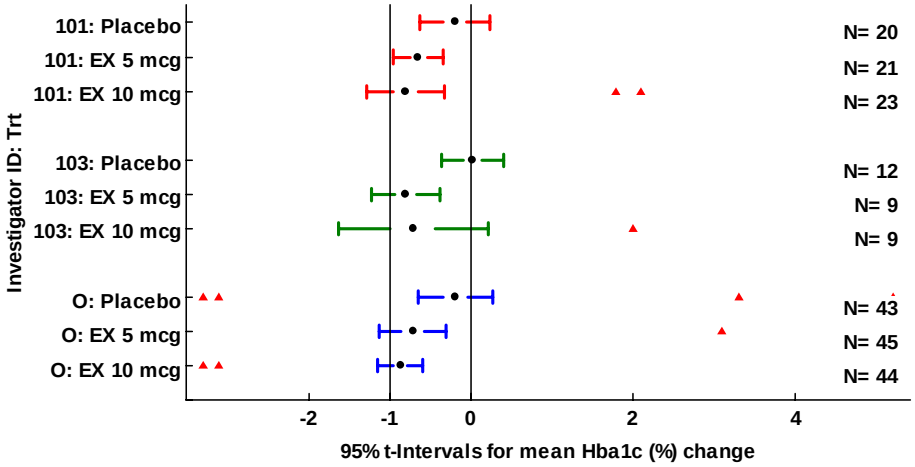
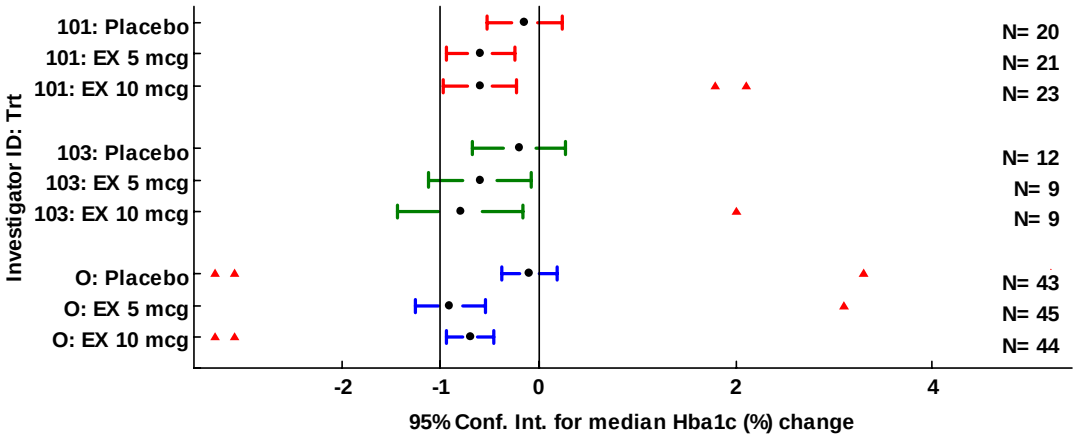


Figure 5 Median HbA1c (%) change from baseline by investigator and treatment group – ITT (LOCF)



Figures 6 and 7 display the mean and median (95% confidence intervals) for fasting serum glucose (FSG) change from baseline for investigators 101, 103 and all others pooled. For both the mean and median the dose response was not evident for the exenatide 5 mcg and 10 mcg for all 3 investigator groups.

Figure 6 Mean FSG change from baseline by site and treatment group

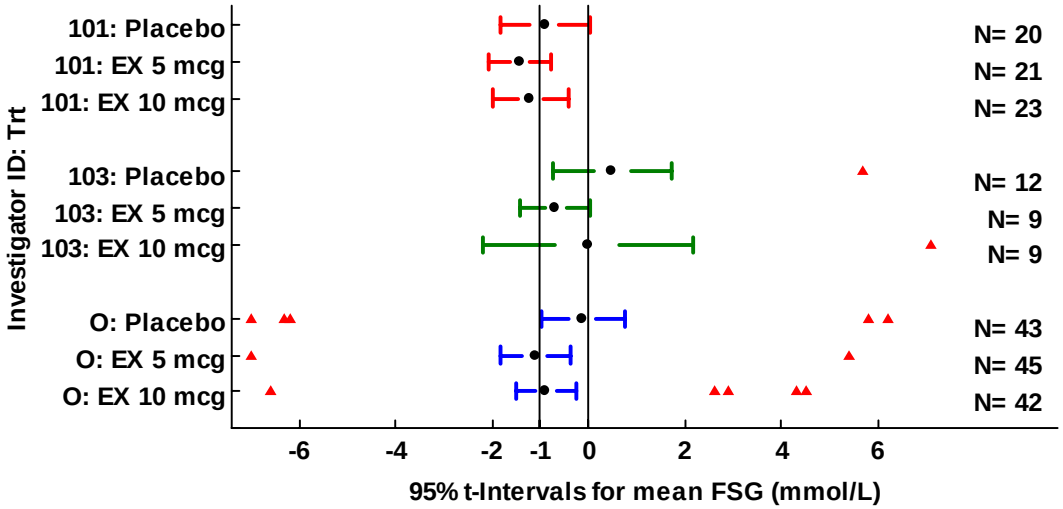
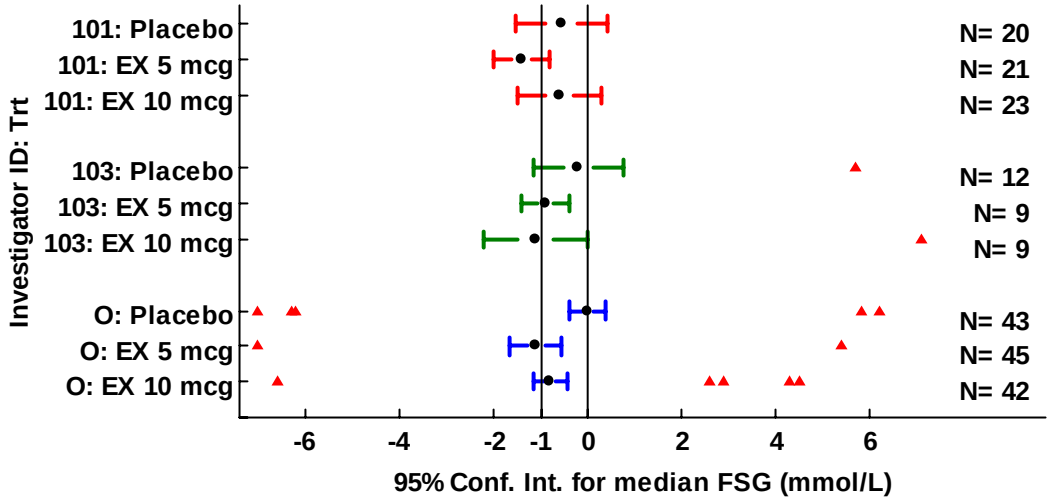


Figure 7 Median FSG change from baseline by site and treatment group



Figures 8 and 9 display the mean and median weight changes from baseline, respectively. The weight change medians for all 3 treatment groups were similar in site 101.

Figure 8 Mean weight change from baseline by treatment group

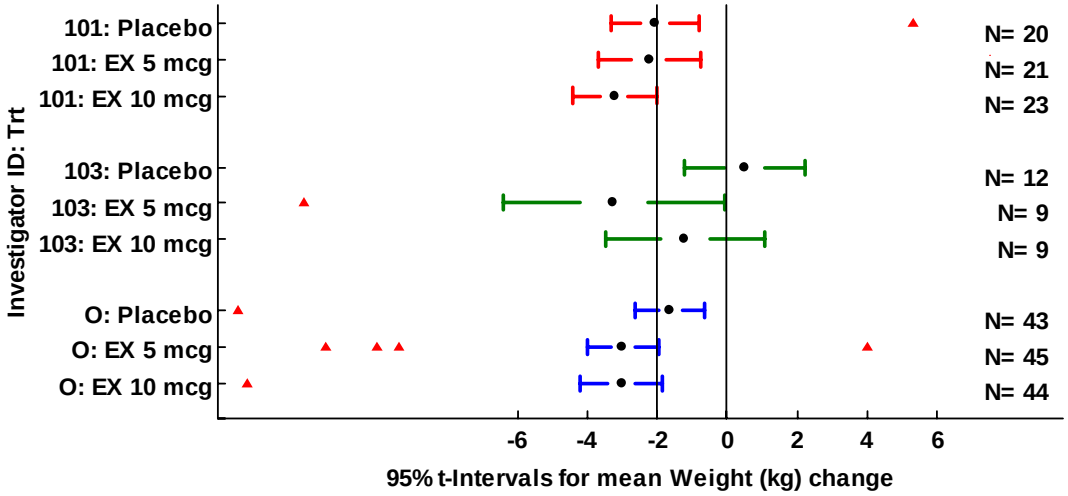
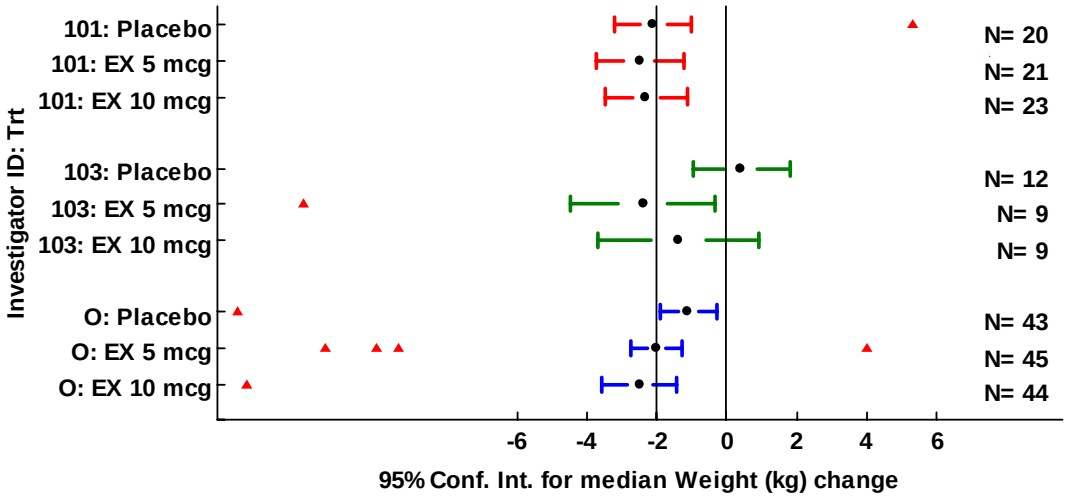


Figure 9 Median weight change from baseline by treatment group



This reviewer performed analysis of covariance (ANCOVA) in HbA_{1c} change from baseline with treatment group, screening HbA_{1c} stratum (≤8% and >8%) and investigator site (101, 103 and all others combined) as fixed effects and baseline HbA_{1c} as covariate. Investigator site 101 and site 103 were either included or excluded from the analysis.

Table 10 displays the ANCOVA results that showed the consistent significance for the overall p-value for all 3 treatment groups.

Table 10 ANCOVA results for HbA_{1c}

	Placebo	EX 5mcg	Ex 10mcg	overall P	EX 5mcg-Plb	EX10mcg-Plb
All	n=75	n=75	n=76	0.0005	-0.5	-0.7
	-0.2	-0.7	-0.8		[-0.9, -0.2]	[-1.0, -0.3]
	(0.1)	(0.1)	(0.1)			
no 101	-0.2	-0.7	-0.8	0.01	-0.5	-0.6
	(0.2)	(0.2)	(0.2)		[-1.0, -0.1]	[-1.1, -0.2]
no 101, 103	-0.3	-0.7	-0.9	0.04	-0.5	-0.7
	(0.2)	(0.2)	(0.2)		[-1.0, 0.05]	[-1.2, -0.1]
101 only	-0.1	-0.7	-0.8	0.03	-0.5	-0.7
	(0.2)	(0.2)	(0.2)		[-1.1, 0.01]	[-1.3, -0.2]
103 only	-0.05	-0.8	-0.7	0.09	-0.8	-0.6
	(0.2)	(0.3)	(0.3)		[-1.5, -0.03]	[-1.4, 0.1]

In conclusion, both the descriptive statistics and the inferential statistics in HbA_{1c} changes from baseline were consistent with or without sites 101 and site 103 in the analysis. The overall p values were all statistically significant with or without sites 101 and 103.

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/s/

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8/26/2008 04:26:31 PM
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