Name of Sponsor/Company: Amylin Pharmaceuticals, LLC	Individual Study Table Referring to the Dossier	*(For National Authority Use Only)*
Name of Finished Product:		
Name of Active Ingredient: exenatide suspension		

SYNOPSIS

Final Clinical Study Report for Study MB001-004 / BCB120

TITLE OF STUDY: A Randomized, Long-Term, Open-Label, 3-Arm, Multicenter Study to Compare the Glycemic Effects, Safety, and Tolerability of Exenatide Once Weekly Suspension to Sitagliptin and Placebo in Subjects with Type 2 Diabetes Mellitus

INVESTIGATORS/STUDY CENTERS: The study was conducted at 81 sites in the United States.

PUBLICATIONS: None

STUDY PERIOD: Study Initiation Date: 08-Feb-2013 **CLINICAL PHASE:** 3

Study Completion Date: 04-Apr-2014

OBJECTIVES:

The primary objective of this study was to compare the effect on glycemic control (glycosylated hemoglobin [HbA1c]) of exenatide once weekly suspension (QWS) to that achieved by sitagliptin or placebo administered once daily for 28 weeks in subjects with type 2 diabetes mellitus.

The secondary objectives of this study were the following:

- To compare the safety and tolerability of exenatide QWS to that observed with sitagliptin or placebo administered once daily with 28 weeks of treatment in subjects with type 2 diabetes mellitus
- To compare the effects of exenatide QWS to that observed with sitagliptin and placebo administered once daily in subjects with type 2 diabetes mellitus on the following:
  - Parameters related to glycemic control, including proportion of subjects achieving HbA1c <7.0%, proportion of subjects achieving HbA1c ≤ 6.5%, fasting and postprandial plasma glucose and serum insulin concentrations, homeostatic model assessment (HOMA), and 6-point self-monitored blood glucose (SMBG) profiles
  - Anthropometric parameters, including body weight and waist circumference
  - Parameters related to cardiovascular health, including fasting lipid concentrations, postprandial triglyceride concentrations, cardiovascular risk markers, and blood pressure
  - Patient-reported outcomes (PROs) in terms of Diabetes Medications Satisfaction (DM-SAT) and Weight-related Quality of Life (IWQOL-Lite)
- To characterize the pharmacokinetics (PK) of exenatide suspension administered once weekly in subjects with type 2 diabetes mellitus

METHODOLOGY:

This Phase 3, randomized, open-label (oral agents blinded), long-term, multicenter, comparator- and placebo-controlled, 3-group study was designed to compare the efficacy, safety, and tolerability of exenatide QWS to sitagliptin and placebo, and characterize the PK of exenatide QWS over 28 weeks. This study was conducted in subjects with type 2 diabetes with inadequate glycemic control while taking ≥ 1500 mg metformin daily. Subjects were randomly assigned across 3 treatment groups (A: exenatide QWS 2 mg, B: sitagliptin 100 mg once daily, and C: placebo once daily) in a ratio of 3:2:1 (180 subjects in Group A, 120 subjects in Group B, and 60 subjects in

Group C), with randomization stratified by screening HbA1c stratum (< 9% or ≥ 9%). A subset of subjects in each treatment group at select study sites were enrolled in a meal test cohort and participated in a standardized meal test.

NUMBER OF SUBJECTS (Planned and Analyzed):

Approximately 360 subjects were planned to be randomized with approximately 180 subjects in Group A, 120 subjects in Group B, and 60 subjects in Group C. Approximately 100 subjects at selected sites were planned to participate in a standardized meal test assessment. A total of 365 subjects were randomized and treated and 364 subjects were included in the modified intent-to-treat (ITT) Population. The Modified ITT Population consists of all randomized subjects who received at least one dose of study drug. The Evaluable Population included 277 subjects. The Evaluable Population consists of all modified ITT subjects who completed study procedures through Week 24 or beyond in compliance with the protocol and had adequate study drug exposure. The meal test population included 121 subjects and 90 subjects (74.4%) were evaluable.

DIAGNOSIS AND MAIN CRITERIA FOR INCLUSION:

- Male and nonpregnant female subjects, at least 18 years of age with type 2 diabetes mellitus treated with a stable regimen of ≥ 1500 mg/day metformin for a minimum of 2 months before Screening
- HbA1c of 7.1% to 11.0%, inclusive
- Body mass index ≤ 45 kg/m^2
- Fasting plasma glucose concentration < 280 mg/dL (15.5 mmol/L)

TEST PRODUCT, DOSE AND MODE OF ADMINISTRATION, DURATION OF TREATMENT, BATCH NUMBERS:

Exenatide 2 mg QWS was self-administered by subcutaneous (SC) injection using an autoinjector. Duration of treatment was 28 weeks. The exenatide QWS formulation (AC2993-F37) was entrapped in microspheres (5% exenatide in a matrix of poly[D,L-lactide-co-glycolide]) and suspended in a medium chain triglyceride (MCT) diluent. Batch numbers were AVLC02-120965 and AVMB02-130486.

REFERENCE THERAPY, DOSE AND MODE OF ADMINISTRATION, DURATION OF TREATMENT, BATCH NUMBERS:

Sitagliptin and placebo were taken orally once daily for 28 weeks. Sitagliptin was commercially acquired and overencapsulated to maintain the blinding of oral medication. Two 50-mg sitagliptin tablets were encapsulated in an opaque, snap-lock, hard gelatin AA-sized capsule filled with microcrystalline cellulose (MCC). Batch numbers were C12135 and A12296. The placebo (batch number B12135) contained MCC filler, lactose, and magnesium stearate in the same capsule used for overencapsulation of sitagliptin.

CRITERIA FOR EVALUATION:

Efficacy: Glycemic control was evaluated based on HbA1c change from baseline, proportion of subjects achieving target values, and change from baseline in fasting and 2-hour postprandial glucose concentration. Other efficacy evaluations included change from baseline in body weight and waist circumference, change from baseline in fasting insulin concentration, fasting lipid concentration, HOMA, six-point self monitored blood glucose concentration, postprandial insulin and triglyceride concentration, blood pressure, cardiovascular risk markers, and patient-reported outcomes.**Safety:** Safety was evaluated based on adverse events, clinical laboratory tests (including calcitonin), physical examination findings, concomitant medications, vital signs, and antibodies to exenatide.

Pharmacokinetics: Exenatide steady state concentration (Css) was evaluated.

Pharmacodynamics: The pharmacodynamic parameters area under the concentration-time curve (AUC), time-weighted average concentration (Cave), peak concentration (Cmax), and the time of peak concentration (Tmax) were evaluated for postprandial insulin, glucose or triglycerides. **STATISTICAL CONSIDERATIONS:**

The primary efficacy endpoint was assessed by a mixed-effect model with repeated measures (MMRM) as the primary analysis. The MMRM model included the change in HbA1c as the dependent variable, treatment, week of visit, treatment by week interaction and baseline HbA1c stratum (< 9% or ≥ 9%) as fixed factors, and subject as random effect. Baseline HbA1c, baseline HbA1c by week interaction, and baseline HbA1c stratum by week interaction were also included as covariates. All observed HbA1c data from post-baseline scheduled visits (including

Early Termination visits but excluding those collected after subject initiates glycemic rescue therapy or post-treatment follow-up) were included in the MMRM analysis. In addition, if a subject's last available measurement during the 28-week assessment period was from an unscheduled visit or Early Termination visit, the value was programmatically mapped to the next closest scheduled visit and included in the MMRM analysis. No other imputation for missing or post-rescue therapy data was performed. Hypothesis testing on the primary efficacy endpoint followed a serial gated procedure with all tests carried out at a 2-sided significance level of 0.05 to protect the family-wise error rate. Three tests were conducted sequentially with each test being the gatekeeper of the later tests. A serial gatekeeping procedure was also applied to control the family-wise error rate at 0.05 for all secondary endpoints.

Safety data collected prior to and after subjects initiated glycemic rescue therapy were summarized together. Treatment-emergent AEs are defined as those occurring during or after the first dose of randomized study drug on Day 1, or existing prior to the time of and worsening after the time of the first dose of randomized study drug through Study Termination or Early Termination. AEs were also determined to be treatment emergent if they were reported after Study Termination but considered by the investigator as clinically significant and as related to study drug; or a serious adverse event (SAE) reported within 90 days of the last administration of study drug.

SUMMARY OF RESULTS:

Disposition and Baseline/Demographic Characteristics: A total of 365 subjects were randomized and treated: 182 to exenatide QWS 2 mg, 122 to sitagliptin 100 mg daily, and 61 to placebo once daily (Table 1).

Eighty-five percent of subjects in the exenatide QWS group, 89% of subjects in the sitagliptin group, and 77% of subjects in the placebo group completed the 28-week treatment period. The most common reason for withdrawal was decision by the subject, followed by lost to follow-up, and adverse events.

Table 1: Subject Disposition

	Exenatide QWS 2 mg	**Sitagliptin 100 mg**	**Placebo**
No. of Subjects Randomized	182	122	61
No. of Subjects Completed 28-week	155 (85.2%)	109 (89.3%)	47 (77.0%)
No. of Subjects Discontinued	27	13	14
Withdrawal by Subject	14 (7.7%)	7 (5.7%)	7 (11.5%)
Adverse Event	4 (2.2%)	0	3 (4.9%)
Investigator Decision	1 (0.5%)	0	1 (1.6%)
Protocol Violation	1 (0.5%)	0	0
Lost to Follow-up	7 (3.8%)	6 (4.9%)	3 (4.9%)
Administrative	1 (0.5%)	0	0

One subject in the exenatide QWS group was randomized at 2 different sites. For this subject, the reason for withdrawal was coded as 'Lost to Follow-up' for the first randomization and 'Protocol Violation' for the later randomization.

The demographic and baseline characteristics were generally balanced across the randomized treatment groups (Table 2).

Table 2: Baseline and Demographic Characteristics

All Modified ITT Subjects

	Exenatide QWS 2 mg N=181	Sitagliptin 100 mg N=122	Placebo N=61
Sex, N (%)			
Male	89 (49.2)	66 (54.1)	37 (60.7)
Female	92 (50.8)	56 (45.9)	24 (39.3)
Age, year			
Mean (SD)	53.4 (9.82)	54.3 (9.01)	53.4 (9.48)
Race, N (%)			
White	148 (81.8)	98 (80.3)	50 (82.0)
Black or African American	24 (13.3)	18 (14.8)	7 (11.5)
Asian	9 (5.0)	2 (1.6)	3 (4.9)
American Indian or Alaska Native	0	2 (1.6)	1 (1.6)
Other	0	1 (0.8)	0
Native Hawaiian or Other Pacific Islander	0	1 (0.8)	0
Weight, kg			
Mean (SD)	88 (22)	87 (20)	87 (19)
BMI, kg/m2			
Mean (SD)	32.1 (5.4)	31.6 (5.8)	31.5 (5.1)
Duration of Diabetes, years			
Mean (SD)	8.5 (6.3)	7.9 (4.6)	8.7 (5.8)
HbA1c (%)			
Mean (SD)	8.42 (1.0)	8.50 (1.0)	8.50 (1.0)

Efficacy Results: The reduction in HbA1c from baseline to Week 28, the primary efficacy endpoint, was statistically significantly greater in the exenatide QWS group compared with the sitagliptin and placebo groups (Table 3).

A statistically significantly higher proportion of subjects in the exenatide QWS group achieved HbA1c < 7% at Week 28 than in the sitagliptin group. There was a larger reduction in fasting plasma glucose in the exenatide QWS group than in the sitagliptin group, but this difference did not reach the statistical significance level. There was a mean reduction in body weight in all treatment groups, but the difference between the exenatide QWS and the sitagliptin group was not statistically significant. There was a larger reduction from baseline to Week 16 in 2-hour postprandial glucose concentration in the exenatide QWS group than in the sitagliptin group.

Table 3: Primary and Secondary Efficacy Endpoints - Change from Baseline to Week 28

All Modified ITT Subjects* or Meal Test Evaluable Subjects#

Parameter **Statistics**	**Exenatide QWS 2 mg N=181**	**Sitagliptin 100 mg N=122**	**Placebo N=61**
HbA1c (%)*			
N	141	98	38
LS Mean (SE)	-1.13 (0.1093)	-0.75 (0.1324)	-0.40 (0.1945)
LS Mean Difference (SE) vs sita.	-0.38 (0.1638)		
95% CI for LS Mean Difference	-0.70, -0.06		
P-value	0.0209		
LS Mean Difference (SE) vs pla.	-0.72 (0.2167)	-0.34 (0.2278)	
95% CI for LS Mean Difference	-1.15, -0.30	-0.79, 0.11	
P-value	0.0010	0.1347	

Table 3: Primary and Secondary Efficacy Endpoints - Change from Baseline to Week 28

All Modified ITT Subjects* or Meal Test Evaluable Subjects#

Parameter Statistics	Exenatide QWS 2 mg N=181	Sitagliptin 100 mg N=122	Placebo N=61
HbA1c < 7%*			
Baseline Yes, n (%)	6 (3.3)	2 (1.6)	2 (3.3)
Baseline No, n (%)	175 (96.7)	120 (98.4)	59 (96.7)
Week 28 Yes, n (%)	78 (43.1)	39 (32.0)	15 (24.6)
Week 28 No, n (%)	103 (56.9)	83 (68.0)	46 (75.4)
P-value vs sitagliptin	0.0489		
P-value vs.placebo	0.0103		
Fasting Plasma Glucose (mg/dL)*			
N	136	99	38
LS Mean (SE)	-21.3 (3.864)	-11.3 (4.617)	9.6 (7.097)
LS Mean Difference (SE) vs sita.	-10.1 (5.960)		
95% CI for LS Mean Difference	-21.8, 1.7		
P-value	0.0924		
LS Mean Difference (SE) vs pla.	-30.9 (8.037)		
95% CI for LS Mean Difference	-46.7, -15.1		
P-value	0.0001		
Body Weight (kg)*			
N	148	101	40
LS Mean (SE)	-1.12 (0.2592)	-1.19 (0.3134)	0.15 (0.4767)
LS Mean Difference (SE) vs sita.	0.07 (0.4058)		
95% CI for LS Mean Difference	-0.73, 0.87		
Nominal P-value	0.8625		
LS Mean Difference (SE) vs pla.	-1.27 (0.5419)		
95% CI for LS Mean Difference	-2.34, -0.20		
Nominal P-value	0.0198		
2-hour Postprandial Plasma Glucose (mg/dL)#			
N	42	27	15
LS Mean (SE)	-59.57 (10.48)	-23.61 (13.04)	-38.68 (16.98)
LS Mean Difference (SE) vs sita.	-35.96 (15.71)		
95% CI for LS Mean Difference	-67.23, -4.68		
Nominal P-value	0.0248		
LS Mean Difference (SE) vs. pla.	-20.89 (19.66)		
95% CI for LS Mean Difference	-60.02, 18.25		
Nominal P-value	0.2914		

pla=placebo, sita=sitagliptin

Safety Results: The proportions of subjects experiencing adverse events (AEs), SAEs, AEs assessed to be related to study drug, and AEs leading to withdrawal were higher in the exenatide QWS group than in the sitagliptin group (Table 4). The proportions of subjects with AEs assessed to be related to study drug were also higher in the exenatide QWS group than in the placebo group, while the proportions of subjects with AEs, SAEs, and AEs leading to withdrawal of study medication were similar in the exenatide QWS group and the placebo group. There were no deaths in this study.

In subjects treated with exenatide QWS, nausea (8.8%), injection-site nodule (7.7%), headache (4.4%), injection site induration (3.9%), and vomiting (3.3%) were the most common treatment-emergent AEs.

Table 4: Summary of Treatment-Emergent Adverse Events by Treatment, All Treated Subjects

	Exenatide QWS 2 mg N=181 n (%)	Sitagliptin 100 mg N=122 n (%)	Placebo N=61 n (%)
All adverse events	101 (55.8)	40 (32.8)	29 (47.5)
All serious adverse events	5 (2.8)	0	2 (3.3)
All adverse events related to study drug	45 (24.9)	3 (2.5)	4 (6.6)
All adverse events leading to withdrawal	3 (1.7)	0	3 (4.9)
All adverse events leading to death	0	0	0

Hypoglycemia is not included among AEs shown in Table 4. Subjects experiencing multiple episodes of a given AE are counted once in each relevant category. Includes all treatment emergent AEs (TEAEs) that occurred during the 28-week Controlled Period.

Pharmacokinetic Results: The geometric mean plasma exenatide trough concentrations remained relatively constant from Week 8 through Week 28, indicating that plasma exenatide concentrations were maintained within a therapeutic range and at steady-state from Week 8 through Week 28. No correlation was observed between the steady state exenatide plasma concentrations and treatment-emergent antibody titers.

DATE OF REPORT: 12-Nov-2014