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

SYNOPSIS

Final Clinical Study Report for Study MB001088 (BCB111)

TITLE OF STUDY: A Randomized, Multi-dose, Controlled Trial Investigating the Efficacy, Safety and Tolerability, and Pharmacokinetics of Exenatide Once Monthly Suspension

INVESTIGATORS/STUDY CENTERS:

PUBLICATIONS: None

STUDY PERIOD: Study Initiation Date: 22 May 2010 **CLINICAL PHASE:** 2

Study Completion Date: 27 Dec 2010

OBJECTIVES:

Primary:

- To examine the effect of exenatide once monthly suspension on glycemic control (HbA1c) in subjects with type 2 diabetes
- To assess the safety and tolerability of exenatide once monthly suspension in subjects with type 2 diabetes

Secondary:

- To examine the effect of exenatide once monthly suspension in subjects with type 2 diabetes on the following:
  - Fasting plasma glucose
  - Body weight
- To assess the pharmacokinetics of exenatide once monthly suspension in subjects with type 2 diabetes

METHODOLOGY:

Study BCB111 (MB001088) was a Phase 2, randomized, multi-dose, single-blind (subject and investigator blinded to exenatide once monthly suspension dose), multicenter, controlled trial conducted in subjects with type 2 diabetes inadequately treated with diet modification and exercise, metformin, pioglitazone, or a combination of metformin and pioglitazone. This study evaluated the pharmacokinetics (PK), efficacy, and safety and tolerability of exenatide once monthly suspension (EQMS; 5, 8, and 11 mg, subcutaneous [SC]) and exenatide once weekly (EQW;BYDUREON®; aqueous diluent, 2 mg SC) as a reference arm.

Subjects were randomly assigned in a ratio of 1:1:1:1 across 4 treatment groups:

- Group A: 2 mg EQW (aqueous diluent) SC
- Group B: 5 mg EQMS SC
- Group C: 8 mg EQMS SC
- Group D: 11 mg EQMS SC

The study began with Visit 1 (Screening); eligible subjects were invited to return to the study site within 14 days of screening for Visit 2 (Day 1), when subjects were enrolled, randomized, and began treatment with study medication. Subjects received 5 EQMS injections or 20 weekly EQW injections. Subjects returned to the study site at 2-week intervals (± 2 days) through Visit 6 (Week 8). Visit 7 could occur on any day between Weeks 9 and 11. Visits 8 through 12 occurred weekly (± 1 day), relative to Visit 2 (Day 1). Visit 13 occurred on any day between Weeks 17 and 19. Visit 14 occurred at Week 20 (± 2 days), relative to Visit 2 (Day 1). Exenatide once weekly was administered by study-site personnel at Visit 2 (Day 1), and self-administered weekly from Week 1 through Week 19. Exenatide once monthly suspension was administered by study-site personnel at specified visits (Day1 to Week 20; last dose on Week 16). Study Termination procedures occurred at Visit 15 (Week 24/Study Termination).

Subjects fasted overnight for at least 8 hours prior to all visits. Subjects delayed administering their oral antidiabetic medications (if applicable) and EQW (Group A) on the morning of study-site visits, where medications were administered as directed by study-site personnel. Subjects who withdrew from the study were asked to return to the study site to complete early termination procedures.

NUMBER OF SUBJECTS (Planned and Analyzed):

Approximately 120 individuals with type 2 diabetes mellitus were planned to be randomly assigned to 4 treatment groups. All randomized subjects received at least 1 dose of study medication and were included in the Intent-to-Treat (ITT) Population (N = 121; Group A [2 mg EQW], N = 30; Group B [5 mg EQMS] N = 30; Group C [8 mg EQMS] N = 31; Group D [11 mg EQMS] N = 30).

DIAGNOSIS AND MAIN CRITERIA FOR INCLUSION:

All Groups: Male and non-pregnant female subjects 18 years of age and with a diagnosis of type 2 diabetes mellitus, HbA1c of 7.1% to 11.0%, inclusive, stable body weight (i.e., not varying by >3% for at least 3 months), body-mass index (BMI) of 25 kg/m^2 to 45 kg/m^2, fasting plasma glucose <280 mg/dL (15.5 mmol/L) at Screening, and treated with diet and exercise alone or with a stable regimen of metformin, pioglitazone, or a combination of metformin and pioglitazone for a minimum of 2 months prior to Screening were eligible to participate.

Subjects with no clinically significant abnormal laboratory test values or electrocardiogram (ECG) results at Screening were eligible to participate.

TEST PRODUCT, DOSE AND MODE OF ADMINISTRATION, DURATION OF TREATMENT

For EQMS, the exenatide microspheres were suspended in Miglyol 812 immediately prior to injection. Miglyol 812 is a clear oil consisting of a mixture of medium-chain triglycerides. A medically qualified staff member administered all doses of EQMS (Visit 2 [Day 1], Visit 4 [Week 4], Visit 6 [Week 8], Visit 8 [Week 12], and Visit 12 [Week 16], rotating injections by quadrant.

The study duration was 26 weeks, including a screening period (not to exceed 14 days), a 20-week assessment period, and a 4-week follow-up period.

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

For EQW, the exenatide microspheres were reconstituted in an aqueous diluent containing carboxymethylcellulose, polysorbate 20, sodium chloride, monobasic sodium phosphate monohydrate, dibasic sodium phosphate monohydrate, and water for injection. A medically qualified staff member demonstrated the preparation of exenatide once weekly for the subject or a designated caregiver at Visit 2 (Day 1), and administered the first dose of study medication. Subjects then subsequently self-administered study medication once weekly (± 2 days) relative to the date of the first dose of EQW (Visit 2 [Day 1]) through Week 19. On weeks with no scheduled study-site visits, subjects could return to the study site to have the injection procedure monitored by study-site personnel, although

not required. On weeks of scheduled study visits, subjects brought in their study medication treatment kit with them to the clinic and self-administered EQW as directed by study-site personnel.

CRITERIA FOR EVALUATION:

Efficacy:

Primary Endpoints, all groups:

- The primary endpoint is the change in HbA1c from baseline (Visit 2 [Day 1]) to Visit 14 (Week 20).

Secondary Endpoints, all groups:

- Proportions of subjects achieving target values of <7% and ≤6.5% at Visit 14 (Week 20)
- Change in body weight from baseline (Visit 2 [Day 1]) to Visit 14 (Week 20)
- Change in fasting plasma glucose concentration from baseline (Visit 2 [Day 1]) to Visit 14 (Week 20)
- Change in systolic blood pressure and diastolic blood pressure from baseline (Visit 2 [Day 1]) to Visit 14 (Week 20)

Additional Endpoints:

- Change in HbA1c from baseline (Visit 2 [Day 1]) to intermediate visits prior to Visit 14 (Week 20), and to Visit 15 (Week 24)
- Change in fasting plasma glucose concentration from baseline (Visit 2 [Day 1]) to intermediate visits prior to Visit 14 (Week 20), and to Visit 15 (Week 24)
- Change in body weight from baseline (Visit 2 [Day 1]) to intermediate visits prior to Visit 14 (Week 20), and to Visit 15 (Week 24)

Safety:

Safety and tolerability endpoints were based on treatment-emergent adverse events (TEAEs), concomitant medications, physical examinations, vital signs measurements, clinical laboratory measurements, injection site examinations, and antibodies to exenatide.

Pharmacokinetics: Pharmacokinetic evaluations include plasma exenatide concentrations; pharmacokinetic parameters at initial release (Hours 0-8), at steady state (Hours 2016-2688), and overall.

Other:

Patient reported outcomes included change in scores for the 11-item Diabetes Treatment Satisfaction Questionnaire (DTSQs) from baseline (Visit 2 [Day 1]) to Visit 8 (Week 12) and to Visit 14 (Week 20).

STATISTICAL CONSIDERATIONS:

Four populations will be used for the summaries and analyses of the study data. These populations are defined as follows:

- **Randomized**: The Randomized Population will consist of all subjects who are randomized to a treatment group.
- **Intent-to-Treat:** The ITT Population will consist of all randomized subjects who receive at least one dose of study medication.
- **Evaluable:** The Evaluable Population will consist of all ITT subjects who complete study procedures through Visit 14 (Week 20) or beyond in compliance with the protocol and have adequate study medication exposure.
- **Evaluable Population for Pharmacokinetics (PK Evaluable Population):** The PK Evaluable Population will consist of all ITT subjects who have adequate and reliable data for the evaluation of pharmacokinetics of plasma exenatide.

Adjustments may be made to refine the definition of the Evaluable and PK Evaluable Populations prior to the conduct of any analytical procedures. The final definition of the Populations will be documented in the statistical analysis plan.

Demographic and relevant baseline characteristics will be presented and summarized descriptively by treatment for the ITT and Evaluable Populations.

Primary Endpoint:

The primary analysis was conducted using the Evaluable Population. The analysis using the ITT Population was supportive. The primary endpoint was the change in HbA1c from baseline (Visit 2 [Day 1]) to Visit 14 (Week 20), and was summarized descriptively across treatment groups.

Additionally, change in HbA1c by baseline HbA1c stratum (<9.0% or ≥9.0%) was analyzed, and statistical significance testing of the dose-response relationship for the 3 EQMS doses (5 mg, 8 mg, and 11 mg) was conducted at 1-sided significance level of 0.05.

Secondary Endpoints:

The proportion of subjects achieving the HbA1c target value of <7% and ≤6.5% at endpoint (Week 20) was summarized. The changes in fasting plasma glucose and body weight from baseline (Day 1) to endpoint were summarized descriptively by treatment group. The changes in systolic and diastolic blood pressure from baseline to endpoint were also summarized descriptively by treatment group.

Pharmacokinetic assessments:

Pharmacokinetic parameters were determined for the PK Evaluable Population using the standard noncompartmental method. Geometric mean exenatide concentration-time profiles were plotted. The pharmacokinetic parameters and plasma exenatide concentration were summarized descriptively.

Safety:

Treatment-emergent adverse events, including events that led to withdrawal and serious events, were summarized by group. Treatment-emergent hypoglycemic events, potentially immune related events, and injection site adverse events of interest were summarized separately by group and treatment. Clinical hematology, chemistry, and urinalysis results, vital signs, ECG findings, and change in antibodies to exenatide status over time were summarized. P-amylase, lipase, and calcitonin were summarized separately by group and treatment.

SUMMARY OF RESULTS:

Disposition and Baseline/Demographic Characteristics:

Table 1: Subject Disposition

	Group A 2 mg EQW	Group B 5 mg EQMS	Group C 8 mg EQMS	Group D 11 mg EQMS	Overall
Subjects Enrolled, n	30	30	31	30	121
Subjects Treated, n (%)	30 (100)	30 (100)	31 (100)	30 (100)	121 (100)
Completed study, n (%)	30 (100)	27 (90)	29 (93.5)	28 (93.3)	114 (94.2)
Evaluable Population	29 (96.7%)	26 (86.7%)	28 (90.3%)	27 (90.0%)	110 (90.9)
Pharmacokinetic Evaluable Population	26 (86.7)	25 (83.3%)	25 (80.6%)	23 (76.7%)	99 (81.8)
No. of Subjects Discontinued	0	3 (10.0)	2 (6.5)	3 (6.7)	7 (5.8)
Withdrawal of consent	0	1 (3.3)	2 (6.5)	1 (3.3)	4 (3.3)
Adverse event	0	0	0	1 (3.3)	1 (0.8)
Investigator decision	0	2 (6.7)	0	0	2 (1.7)
Protocol violation	0	0	0	0	0
Lost to follow-up	0	0	0	0	0
Administrative	0	0	0	0	0
Loss of glucose control	0	0	0	0	0

Abbreviations: EQW = exenatide once weekly (aqueous solution); EQMS = exenatide once monthly suspension.

Table 2: Baseline and Demographic Characteristics, ITT Population (N = 121)

Characteristic	Group A 2 mg EQW N = 30	Group B 5 mg EQMS N = 30	Group C 8 mg EQMS N = 31	Group D 11 mg EQMS N = 30	Overall N = 121
Sex, n (%)					
Male	20 (66.7)	17 (56.7)	24 (77.4)	17 (56.7)	78 (64.5)
Female	10 (33.3)	13 (43.3)	7 (22.6)	13 (43.3)	43 (35.5)
Age, yr	48.6 (9.8)	49.8 (9.8)	52.4 (10.5)	50.1 (10.4)	50.2 (10.1)
Race					
Asian	0	1 (3.3)	0	2 (6.7)	3 (2.5)
Black or African American	1 (3.3)	4 (13.3)	2 (6.5)	5 (16.7)	12 (9.9)
White	28 (93.3)	24 (80.0)	29 (93.5)	23 (76.7)	104 (86.0)
Other	1 (3.3)	1 (3.3)	0	0	2 (1.6)
Weight, kg	101.2 (20.1)	92.1 (18.0)	101.4 (16.2)	94.1 (20.0)	97.2 (18.8)
BMI, kg/m^2	33.8 (5.3)	33.3 (5.9)	33.8 (5.8)	33.2 (5.9)	33.5 (5.7)
Duration of diabetes, yr	5.9 (5.4)	4.7 (3.5)	6.5 (5.8)	6.8 (5.6)	6.0 (5.2)
HbA1c (%)	8.64 (1.19)	8.54 (1.18)	8.54 (1.18)	8.37 (1.34)	8.52 (1.21)
Diabetes management at screening					
Diet/exercise	3 (10.0)	3 (10.0)	11 (35.5)	6 (20.0)	23 (19.0)
Metformin	22 (73.3)	21 (70.0)	16 (51.6)	24 (80.0)	83 (68.6)
PIO	1 (3.3)	1 (3.3)	1 (3.2)	0	3 (2.5)
Combination metformin/SU	0	1 (3.3)	0	0	1 (0.8)
Combination metformin/PIO	4 (13.3)	4 (13.3)	3 (9.7)	0	11 (9.1)

Abbreviations: ITT = Intent-to-Treat population; EQW = exenatide once weekly (aqueous solution); EQMS = exenatide once monthly suspension; BMI = body mass index; PIO = pioglitazone; SD = standard deviation.
Note: Data are mean (SD) except where noted.

Table 3: Baseline and Demographic Characteristics, Evaluable Population (N = 110)

Characteristic	Group A 2 mg EQW N = 29	Group B 5 mg EQMS N = 26	Group C 8 mg EQMS N = 28	Group D 11 mg EQMS N = 27	Overall N = 110
Sex, n (%)					
Male	19 (65.5)	15 (57.7)	23 (82.1)	15 (55.6)	72 (65.5)
Female	10 (34.5)	11 (42.3)	5 (17.9)	12 (44.4)	38 (34.5)
Age, yr	49.0 (9.8)	50.0 (10.1)	52.3 (10.7)	49.9 (10.6)	50.3 (10.2)
Race					
Asian	0 (0.0)	1 (3.8)	0 (0.0)	2 (7.4)	. 3 (2.7)
Black or African American	1 (3.4)	3 (11.5)	2 (7.1)	4 (14.8)	10 (9.1)
White	27 (93.1)	21 (80.8)	26 (92.9)	21 (77.8)	95 (86.4)
Other	1 (3.4)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.9)
Weight, kg	101.1 (20.4)	92.4 (17.1)	102.7 (16.0)	95.4 (19.6)	98.1 (18.6)
BMI, kg/m^2	33.8 (5.4)	33.4 (6.0)	34.0 (6.0)	33.8 (5.7)	33.8 (5.7)
Duration of diabetes, yr	6.0 (5.5)	5.0 (3.6)	6.4 (5.9)	6.7 (5.8)	6.0 (5.3)
HbA1c (%)	8.63 (1.21)	8.42 (1.14)	8.61 (1.22)	8.36 (1.34)	8.51 (1.22)
Diabetes management at screening					
Diet/exercise	3 (10.3)	2 (7.7)	10 (35.7)	5 (18.5)	20 (18.2)
Metformin	21 (72.4)	19 (73.1)	14 (50.0)	22 (81.5)	76 (69.1)
PIO	1 (3.4)	1 (3.8)	1 (3.6)	0 (0.0)	3 (2.7)
Combination metformin/PIO	4 (13.8)	4 (15.4)	3 (10.7)	0 (0.0)	11 (10.0)

Abbreviations: ITT = Intent-to-Treat population; EQW = exenatide once weekly (aqueous solution); EQMS = exenatide once monthly suspension; BMI = body mass index; PIO = pioglitazone; SD = standard deviation.
Note: Data are mean (SD) except where noted.

Efficacy Results:

Primary Endpoints, All Groups:

Monthly administration of all doses of exenatide suspension resulted in clinically meaningful reductions in HbA1c from baseline (Table 4). These changes were similar in the ITT population. Additionally, analysis of dose-response relationship showed no statistically significance difference between EQMS doses on change in HbA1c.

Table 4: Summary of Primary Endpoint, Change in HbA1c from Baseline (Day 1) to Endpoint (Week 20), Evaluable Population (N = 110)

Variable	Group A 2 mg EQW	Group B 5 mg EQMS	Group C 8 mg EQMS	Group D 11 mg EQMS
Evaluable population, n	29	26	28	27
Baseline HbA1c (Day 1), %	8.63 (1.214)	8.42 (1.139)	8.61 (1.220)	8.36 (1.338)
Endpoint HbA1c (Week 20), %	7.09 (1.226)	7.13 (0.976)	7.30 (1.405)	6.91 (1.259)
Mean (SE) change in HbA1c from baseline to endpoint, %	-1.54 (0.234)	-1.29 (0.210)	-1.31 (0.313)	-1.45 (0.179)

Abbreviations: ITT = Intent-to-Treat; EQW = exenatide once weekly (aqueous solution); EQMS = exenatide once monthly suspension; LS = least squares; NA = not applicable; SE = standard error; SD = standard deviation.
Note: Data are mean (SD) except change in HbA1c, mean (SE).

Secondary Endpoints, All Groups:

Similar or greater proportions of subjects in EQMS groups achieved HbA1c target of <7.0% compared to EQW (Table 5). Reductions in body weight were observed in all groups at Week 20 and were general similar between treatment groups (Table 5), although reductions were numerically lower in the EQMS 8 mg group. Reductions in fasting plasma glucose concentrations were observed with all doses of exenatide once monthly suspension (Table 5), with similar reductions observed with all EQMS doses compared to EQW at Week 20. Systolic and diastolic blood pressure decreased in the EQW group and increased in the EQMS groups, although absolute values at endpoint were similar between groups.

Similar efficacy and pharmacodynamic results were obtained for the ITT Population.

Table 5: Summary of Secondary Endpoints from Baseline (Day 1) to Endpoint (Week 20), Evaluable Population (N = 110)

	Subjects, n (%)			
Variable	**Group A 2 mg EQW N = 29**	**Group B 5 mg EQMS N = 26**	**Group C 8 mg EQMS N = 28**	**Group D 11 mg EQMS N = 27**
Proportion of subjects achieving HbA1c target at endpoint				
<7.0%	14 (48.3)	13 (50.0)	16 (57.1)	19 (70.4)
≤6.5%	13 (44.8)	7 (26.9)	11 (39.3)	13 (48.1)
Fasting glucose, mg/dL				
Baseline (Day 1)	186.6 (52.66)	182.0 (37.03)	185.3 (39.53)	182.8 (46.82)
Endpoint (Week 20)	152.4 (43.72)	156.9 (46.71)	155.5 (54.50)	132.1 (47.41)
Mean (SE) change from baseline to endpoint	-34.2 (8.99)	-25.1 (8.49)	-29.8 (9.88)	-48.9 (9.35)
Body weight, kg				
Baseline (Day 1)	101.09 (20.401)	92.42 (17.058)	102.72 (15.970)	95.37 (19.618)
Endpoint (Week 20)	99.72 (20.500)	91.32 (17.525)	102.31 (16.514)	94.23 (18.880)
Mean (SE) change from baseline to endpoint	-1.36 (0.641)	-1.10 (0.774)	-0.41 (0.559)	-1.14 (0.676)
Diastolic blood pressure, mmHg				
Baseline (Day 1)	82.1 (6.86)	79.3 (8.10)	80.1 (8.96)	76.5 (8.60)
Endpoint (Week 20)	80.6 (9.65)	82.2 (10.96)	81.3 (12.28)	78.5 (9.69)
Mean (SE) change from baseline to endpoint	-1.8 (1.61)	2.8 (1.60)	1.6 (1.84)	2.0 (1.60)
Systolic blood pressure, mmHg				
Baseline (Day 1)	131.4 (11.14)	128.9 (14.62)	128.5 (12.99)	122.0 (14.71)
Endpoint (Week 20)	128.1 (11.39)	131.6 (18.54)	128.5 (16.08)	127.0 (18.84)
Mean (SE) change from baseline to endpoint	-2.9 (2.50)	3.2 (3.50)	-0.3 (2.57)	5.1 (2.36)

Abbreviations: EQW = exenatide once weekly (aqueous solution); EQMS = exenatide once monthly suspension; ITT = Intent-to-Treat; LS = least square; BP = blood pressure
[a]Based on pairwise comparison using Exenatide QW 2 mg as the reference group.
[b]Data are mean (SD).
Note: General linear model; data are presented as mean (SE) except where noted.

Safety Results: The safety analysis was based on the ITT population. For subjects who received EQMS, the most frequently observed TEAEs were headache and nausea, with the incidence of headache ranging from 16.7% with the 5 mg dose to 26.7% with the 11 mg dose and the incidence of nausea ranging from 16.7% with the 5 mg dose to

23.3% with the 11 mg dose (Table 6). For subjects who received EQW, the most frequent TEAEs were headache (30.0%) and diarrhea (26.7%). In all treatment groups, the majority of adverse events were assessed by the investigator as mild in intensity.

Although all doses were generally well-tolerated, a general trend of increased incidence of gastrointestinal adverse events with increased EQMS dose was observed. The majority of gastrointestinal adverse events were mild to moderate in intensity, with the exception of 1 event each of severe nausea (11-mg group) and diarrhea (11-mg group) that did not lead to discontinuation of study participation. Overall, the incidence of gastrointestinal events with EQMS was generally comparable to EQW.

The overall incidence of injection site-related adverse events was low with EQMS, did not appear to be related to dose level, and was less that than observed for EQW. All events of injection-site related adverse events were categorized as mild in intensity and the majority of events resolved within 7 days.

Table 6: Summary of Treatment-Emergent Adverse Events, ITT Population (N = 121)

Subjects, n (%)	Group A 2 mg EQW	Group B 5 mg EQMS	Group C 8 mg EQMS	Group D 11 mg EQMS
All treatment-emergent AEs	27 (90.0)	25 (83.3)	20 (64.5)	24 (50.0)
All serious treatment-emergent AEs	0 (0.0)	2 (6.7)	0 (0.0)	0 (0.0)
All treatment-emergent AEs leading to withdrawal	0 (0.0)	0 (0.0)	0 (0.0)	1 (3.3)
Frequent AEs				
Headache	9 (30.0)	5 (16.7)	7 (22.6)	8 (26.7)
Nausea	4 (13.3)	5 (16.7)	7 (23.3)	7 (23.3)
Diarrhoea	8 (26.7)	2 (6.7)	4 (12.9)	5 (16.7)
Decreased appetite	4 (13.3)	1 (3.3)	3 (9.7)	6 (20.0)
Vomiting	3 (10.0)	2 (6.7)	4 (12.9)	5 (16.7)
Injection site pruritus	5 (16.7)	4 (13.3)	1 (3.2)	2 (6.7)
Dyspepsia	3 (10.0)	1 (3.3)	5 (16.1)	3 (10.0)
Eructation	0 (0.0)	2 (6.7)	4 (12.9)	4 (13.3)
Injection site erythema	4 (13.3)	2 (6.7)	1 (3.2)	2 (6.7)
Nasal congestion	4 (13.3)	0 (0.0)	3 (9.7)	1 (3.3)
Fatigue	1 (3.3)	1 (3.3)	3 (9.7)	3 (10.0)
Upper respiratory tract infection	1 (3.3)	4 (13.3)	1 (3.2)	1 (3.3)
Cough	3 (10.0)	3 (10.0)	0 (0.0)	0 (0.0)
Dysmenorrhoea	1 (10.0)	1 (7.7)	0 (0.0)	0 (0.0)
Diabetes mellitus inadequate control	3 (10.0)	0 (0.0)	2 (6.5)	0 (0.0)
Abdominal distension	0 (0.0)	1 (3.3)	1 (3.2)	3 (10.0)

Abbreviations: EQW = exenatide once weekly (aqueous solution); EQMS = exenatide once monthly suspension; ITT = Intent-to-Treat; AE = adverse event.

No deaths were reported. Two serious adverse events (acute coronary syndrome and acute myocardial infarction) were reported in subjects receiving 5 mg exenatide once monthly suspension treatment. Both events (unrelated to study medication) resolved and subjects continued study participation. One subject treated with 11 mg exenatide once monthly suspension was withdrawn due to moderate vomiting that was classified by the investigator as related to study drug. The event resolved the day after onset. No treatment-emergent major or minor hypoglycemia adverse events were reported. One subject treated with 5 mg exenatide once monthly suspension reported a

symptom of hypoglycemia (feeling shaky) that was mild and not accompanied with a blood glucose reading. Of note, there was no evidence of prolonged adverse event duration or incremental safety concerns with EQMS, consistent with the established profile of EQW.

Antibodies to exenatide:

Antibodies to exenatide data obtained with EQMS were generally consistent with data obtained with EQW (Table 7). Potentially Immune-related TEAEs were reported at a similar frequency between the EQW and 5-mg EQMS groups in subjects with a negative antibody titer (1 [14.3%] and 1 [16.7%] subject, respectively) and with a positive titer (7 [30.4%] and 7 [29.2%] subjects), with fewer events reported in the 8-mg and 11-mg EQMS groups (negative titer: no subjects in either group; positive titer: 2 [8.3%] and 4 [14.8%] subjects, respectively).

Table 7: Proportion of Patients Negative or Positive for Anti-exenatide Antibodies, All Groups, ITT Population (N = 121)

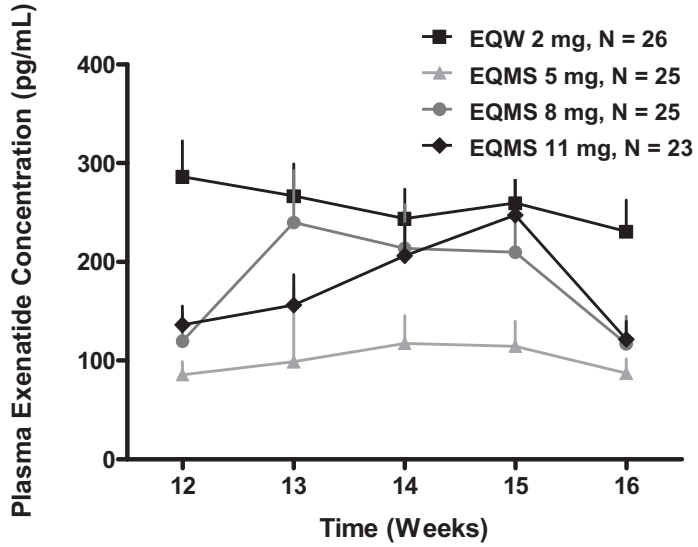
Parameter	Group A 2 mg EQW	Group B 5 mg EQMS	Group C 8 mg EQMS	Group D 11 mg EQMS
Week 2 (subjects with available titer, n)	30	30	30	30
Negative, n (%)	27 (90.0)	30 (100%)	30 (100%)	29 (96.7)
Low titer (<625), n (%)	3 (10.0)	0 (0.0)	0 (0.0)	1 (3.3)
High titer (≥625), n (%)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Week 20 (subjects with available titer, n)	30	26	29	28
Negative, n (%)	7 (23.3)	8 (30.8)	9 (31.0)	9 (32/1)
Low titer (<625), n (%)	15 (50.0)	10 (38.5)	15 (51.7)	15 (53.6)
High titer (≥625), n (%)	8 (26.7)	8 (30.8)	5 (17.2)	4 (14.3)

Abbreviations: EQW = exenatide once weekly (aqueous solution); EQMS = exenatide once monthly suspension; ITT = Intent-to-Treat.

Pharmacokinetic Results:

Exenatide concentrations from Weeks 12 to 16 (steady-state dosing interval for EQMS) are shown in Figure 1. While the pharmacokinetics of EQMS were not dose proportional, the 2 highest EQMS doses (8 and 11 mg) achieved average steady-state concentrations (C_{ave} geometric mean [SE], 247.38 [39.504] pg/mL and 218.07 [27.437] pg/mL, respectively) similar to that observed with EQW (262.92 [30.395] pg/mL) in this study, and with concentrations within the range previously shown to be effective in improving glycemic control. The average monthly exposure observed fell within the therapeutic range of exenatide that results in a robust glycemic response. With EQMS, exenatide concentrations approached undetectable levels 8 weeks after last injection, similar to the timeframe previously established with EQW (approximately 10 weeks).

Figure 1: **Geometric Mean (SE) Plasma Exenatide Concentration (pg/mL) Weeks 12 to 16 with Exenatide Once Weekly or Exenatide Once Monthly Suspension (Pharmacokinetic Evaluable Population [N = 99])**



EQW = exenatide once weekly; EQMS = exenatide once monthly suspension

Patient reported outcomes:

Total scores for treatment satisfaction from the DTSQs numerically improved compared to baseline in total score and for most dimensions of DTSQs for all groups.

CONCLUSIONS:

DATE OF REPORT: