SYNOPSIS

Sponsor: Name of Finished Product: **Exenatide Once Weekly Suspension** Name of Active Ingredient: **Exenatide**	Individual Study Table Referring to Part of the Dossier	(For National Authority Use Only)

Protocol: BCB110

Study Title: A TWO-COHORT SINGLE-AND REPEAT-DOSE STUDY TO EXAMINE THE PHARMACOKINETICS, TOLERABILITY, AND SAFETY OF EXENATIDE ONCE WEEKLY SUSPENSION IN HEALTHY SUBJECTS AND IN SUBJECTS WITH TYPE 2 DIABETES MELLITUS

Investigators and Study Centers:

Publication (Reference): NA

Study Period: 29 April 2009 (First Subject Dosed/Lead-In) through 15 August 2009 (Last Subject's Final Visit/Procedure) **Phase of Development:** Phase 2

Objectives:

Primary Objectives:

Cohort 1:

- To characterize the pharmacokinetics of a single dose of exenatide once weekly suspension in healthy subjects

Cohort 2:

- To examine the safety and tolerability, including local tolerability and antibodies to exenatide, of repeat-dose administration of exenatide once weekly suspension in subjects with type 2 diabetes mellitus
- To characterize exenatide pharmacokinetics following repeat-dose administration of exenatide once weekly suspension in subjects with type 2 diabetes mellitus

Secondary Objectives:

Cohort 1:

- To examine the safety and tolerability of a single dose of exenatide once weekly suspension in healthy subjects

Cohort 2:

- To examine the effects of repeat-dose administration of exenatide once weekly suspension in subjects with type 2 diabetes mellitus on HbA1c, fasting plasma glucose concentration, and body weight

Methodology:

Study BCB110 is a Phase 2, 2-cohort, single- and repeat-dose study conducted to assess the pharmacokinetics, tolerability, and safety of exenatide once weekly suspension over a 12-week assessment period.

Cohort 1: Eligible subjects were enrolled and received a single subcutaneous injection of 10-mg EXENATIDE ONCE WEEKLY SUSPENSION, which was followed by a 12-week assessment period during which pharmacokinetic, tolerability, and safety assessments were performed.

Cohort 2: Eligible subjects were randomized to 2 mg exenatide once weekly suspension (Group A) or medium-chain triglyceride (MCT; Miglyol 812) placebo (Group B) in a 2:1 ratio. Subjects received weekly injections of study medication or placebo for a 12-week treatment period, during which pharmacokinetic, pharmacodynamic, efficacy, tolerability, and safety assessments were performed.

Number of Subjects (Planned and Analyzed):

All randomized subjects received at least 1 dose of study medication and were included in the ITT Population (N = 65; Cohort 1 (N = 30) and Cohort 2 (N = 35).

The Cohort 1 Pharmacokinetic Evaluable Population consisted of 30 (100.0%) subjects.

The Cohort 2 Pharmacokinetic Evaluable Population consisted of 18 of 23 (78.3%) subjects treated with exenatide once weekly suspension 2 mg.

Diagnosis and Main Criteria for Inclusion:

In Cohort 1, male and non-pregnant female subjects ranging between 19 and 65 years of age with a body mass index (BMI) of 23 kg/m^2 to 35 kg/m^2 and no clinically significant abnormal laboratory test values or ECG at Screening were eligible to participate.

In Cohort 2, male and non-pregnant female subjects with a diagnosis of type 2 diabetes mellitus, ranging between 19 to 75 years of age, HbA1c of 7.1% to 10.0%, inclusive, BMI of 25 kg/m^2 to 45 kg/m^2, fasting plasma glucose <260 mg/dL (14.4 mmol/L) at Screening, and treated with diet and exercise alone or with a stable regimen of metformin, a TZD, or a combination of metformin and a TZD for a minimum of 2 months prior to Screening were eligible to participate.

Key Demographics:

In Cohort 1, 60.0% of subjects were male and 76.7% of subjects were Caucasian. Mean baseline values for age, weight, and BMI were 41.2 years, 85.9 kg, and 28.5 kg/m^2, respectively.

In Cohort 2, 68.6% of subjects were male and 85.7% were Caucasian. Baseline values for mean age, weight, BMI, HbA1c, and fasting plasma glucose (FPG) were 52.4 years, 104.7 kg, 35.1 kg/m2, 8.0%, and 167.4 mg/dL, respectively.

Duration of Study:

The study duration was 14 weeks and included a 2-week screening period and a 12-week pharmacokinetic assessment period.

Criteria for Evaluation:

Pharmacokinetic (Cohort 1 and Cohort 2): Plasma exenatide concentration

Efficacy and Pharmacodynamic (Cohort 2 only): HbA1c, fasting plasma glucose concentration, body weight

Safety (Cohort 1 and Cohort 2): Adverse events, hematology, chemistry, and urinalysis assessments, vital signs, injection-site examinations, antibodies to exenatide

Study Endpoints:

Cohort 1:

Primary Endpoints:

- The primary endpoints were plasma exenatide concentration $AUC_{(0\text{-}tlast)}$, $AUC_{(0\text{-}8h)}$, $Cmax_{(0\text{-}tlast)}$, $Cmax_{(0\text{-}8h)}$, $Tmax_{(0\text{-}8h)}$, and $Tmax_{(0\text{-}tlast)}$ following a single dose of exenatide once weekly suspension.
- Safety and tolerability endpoints were based on adverse events, concomitant medications, physical examinations, vital signs measurements, clinical laboratory measurements, injection site examinations, and antibodies to exenatide.

Secondary Endpoint:

- The secondary endpoints are average plasma exenatide concentration $Cave_{(0\text{-}168h)}$ and $AUC_{(0\text{-}168h)}$ during the first 168 hours.

Cohort 2:

Primary Endpoints:

- The primary safety and tolerability endpoints were the incidence of treatment-emergent adverse events and the incidence of treatment emergent antibodies to exenatide.
- Other safety and tolerability endpoints were based on concomitant medications, physical examinations, clinical laboratory measurements, and vital signs measurements.

Primary pharmacokinetic endpoints:

- $AUC_{(0\text{-}6h)}$ for time interval 0 to 6 hours at Visit 12 (Week 10) and $AUC_{(0\text{-}168h)}$ for the dosing interval at steady state between Visit 12 (Week 10) to Visit 15 (Week 11), a duration of approximately 168 hours
- $Cave_{(0\text{-}168h)}$ corresponding to $AUC_{(0\text{-}168h)}$
- $Cmax_{(0\text{-}6h)}$ and $Tmax_{(0\text{-}6h)}$ at steady state on visit 12 (Week 10, and $Cmax_{(0\text{-}168h)}$ and $Tmax_{(0\text{-}168h)}$ for the dosing interval at steady state between Visit 12 (Week 10) to Visit 15 (Week 11)
- $AUC_{(0\text{-}tlast)}$ with corresponding $Cave_{(0\text{-}tlast)}$, $Cmax_{(0\text{-}tlast)}$, and $Tmax_{(0\text{-}tlast)}$ for time interval between Visit 12 (Week 10) to Visit 16 (Week 12), a duration of approximately 336 hours

Secondary Endpoints:

- Secondary efficacy and pharmacodynamic endpoints included the change in HbA1c, FPG, and body weight

from baseline (Visit 2 [Day 1] to Visit 16 (Week 12/Study Termination) and intermediate visits, as applicable.

- The percent of subjects achieving HbA1c <7% and ≤6.5% from baseline Visit 2 [Day 1] to Visit 16 (Week 12/Study Termination).

Statistical Methods:

Analyses were summarized for the ITT population within each cohort except for the pharmacokinetic evaluations. The Pharmacokinetic Evaluable Population within each cohort was used to summarize the pharmacokinetic evaluations; In cohort 2, only subjects receiving exenatide were summarized.

Pharmacokinetics:

Pharmacokinetic parameters were determined using the noncompartmental method.

The primary study endpoints used to determine the pharmacokinetic characteristics for each cohort are:

Cohort 1: Exposure (AUC) from 0 minutes to 8 hours at Day 1, and from Day 1 (0 minutes) to t_{last} (Week 12).

Cohort 2: Exposure (AUC) from 0 minutes to 6 hours at Week 10, from Week 10 (0 minutes) to Week 11 for the duration of 168 hours, and to t_{last} from Week 10 (0 minutes) to Week 12, for a duration of 336 hours.

The average plasma exenatide concentration, C_{ave}, for the corresponding AUC; the maximum concentration, C_{max}; the minimum concentration, C_{min}; and the time of maximum concentration, t_{max}; were also summarized.

Efficacy and Pharmacodynamics:

The secondary study endpoint was the change in HbA1c from baseline to Week 12. The least squares (LS) mean change in HbA1c from baseline to Week 12 was estimated for each treatment using an analysis of variance (ANOVA) model. The proportion of subjects achieving HbA1c target values of <6.5% and <7% were compared between treatments. HbA1c change from baseline was summarized by HbA1c strata (<8.5% and ≥8.5%) at screening and antibodies to exenatide titer.

Fasting plasma glucose concentration from Screening to Week 12, and body weight from baseline to Week 12 were analyzed using an ANOVA model to compare treatment groups with respect to change in the analyte, for each cohort.

Safety:

Treatment-emergent adverse events, including events that led to withdrawal and serious events, were summarized by cohort and treatment (for cohort 2). Treatment-emergent hypoglycemic events, potentially immune related events, and injection site adverse events of interest were summarized separately by cohort 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 cohort and treatment.

Pharmacokinetic Results:

Cohort 1: Administration of a single 10-mg dose of exenatide once weekly suspension resulted in a slow, gradual release of exenatide with plasma exenatide concentrations reaching a geometric mean (SE) of 33.9 (8.09) pg/mL at 8 hours following the injection. The maximum geometric mean (SE) plasma exenatide concentration was achieved at Week 7 (243.8 [49.05] pg/mL). Plasma exenatide concentrations gradually decreased over the remainder of the treatment period with detectable levels of exenatide measured in 2 subjects through the end of the treatment period (Week 12) (geometric mean [SE] 43.3 [2.60] pg/mL).

Cohort 2: Plasma exenatide concentrations increased gradually from Day 1 through Week 8. Steady-state plasma exenatide concentrations were achieved within approximately 8 weeks and had a geometric mean (SE) concentration of 263.8 (30.12) pg/mL. Following Week 8 plasma exenatide concentrations remained generally stable and consistent through Week 12.

Efficacy and Pharmacodynamic Results:

Efficacy evaluations were not conducted for Cohort 1(healthy subjects without diabetes).

Cohort 2:

HbA1c: The mean (SE) baseline HbA1c for subjects (N = 23) receiving exenatide once weekly suspension 2 mg was 7.9 (0.19) %, compared to 8.1 (0.24) % for the placebo group (N = 12). The LS mean (SE) change in HbA1c from baseline to Week 12 in the exenatide once weekly suspension group was -0.90 (0.18)%, a significantly greater reduction than that observed in the placebo group (+0.1 [0.23]%; p <0.0013 between treatments).

Fasting Plasma Glucose: Mean baseline fasting plasma glucose concentrations were 167 mg/dL for exenatide once weekly suspension-treated subjects and 168 mg/dL for subjects in the placebo group. At the end of the 12-week treatment period, mean (SE) fasting plasma concentration in the exenatide once weekly suspension treatment group was 139 (7.8) mg/dL (7.7 [0.4] mmol/L), compared to 180 (15.5) mg/dL (10.0 [0.9] mmol/L), in the placebo treatment group.

Body Weight: Mean (SE) baseline body weight for the exenatide once weekly suspension 2mg group was 104.9 (4.84) kg and 104.4 (5.85) kg for the placebo group. At Week 12, exenatide once weekly suspension 2 mg-treated subjects exhibited an LS mean (SE) change in body weight from baseline of -1.4 (0.6) kg; placebo-treated subjects exhibited an LS mean change in body weight of -0.4 (0.7) kg, which was not statistically different from the exenatide once weekly suspension treatment group.

Safety Results:

Treatment-Emergent Adverse Events: During the 12-week treatment period, the overall incidence of adverse events was 87% in subjects treated with exenatide once weekly suspension 10 mg (Cohort 1) and 96% in subjects treated with exenatide once weekly suspension 2 mg (Cohort 2). Subjects receiving placebo had a slightly lower incidence of treatment-emergent adverse events (75%).

Serious Adverse Events: No serious adverse events occurred in subjects treated with exenatide once weekly suspension in either Cohort. One subject randomized to placebo experienced 2 treatment-emergent serious adverse events of infected skin ulcer and wound infection unrelated to study medication. Both adverse events resolved.

Adverse Events Leading to Withdrawal: There were no treatment-emergent adverse events leading to withdrawal.

Deaths: No deaths were reported during Study BCB110.

Hypoglycemia: There were no events of hypoglycemia reported during the study.

Injection-Site Adverse Events: The most common treatment-emergent adverse events in Cohort 1 were injection-site pruritus (33%), injection-site pain (20%), and headache (20%). The most common treatment-emergent adverse event in Cohort 2 subjects treated with exenatide once weekly suspension were injection-site erythema (52%), injection-site pruritus (48%), injection-site haematoma (39%), decreased appetite (22%), and diarrhea (17%). In placebo-treated subjects the most common treatement-emergent adverse events were injection-site haematoma (50%) and diarrhea (17%).

Clinical Laboratory Evaluations, Vital Signs, and Physical Examinations:

Treatment-Emergent Antibodies to Exenatide:

In Cohort 1, the overall incidence of low (≤125) and higher (≥625) antibody titers peaked at Week 8 with 76% of subjects exhibiting positive antibody titers and 41% of subjects exhibiting higher titers. At Week 12, the incidence of antibodies to exenatide was 67%, 43% of subjects had low antibody to exenatide titers and (23%) subjects exhibited higher treatment-emergent antibody to exenatide titers. Injection-site reactions potentially related to a localized immune response (most commonly pruritus) were less frequently observed in antibody negative subjects (10%) compared with antibody positive subjects (55%). Treatment emergent antibodies to exenatide titers were otherwise not associated with patient tolerability or safety.

Cohort 2: Approximately 4% of subjects exhibited low titers after 2 weeks of treatment. After 4 weeks of treatment 22% of subjects had low titers and 22% had higher titers. The percentage of subjects with higher titers increased through Week 6 and peaked at Week 8 (43%). The incidence of overall and higher titers after Week 6 was maintained through Week 12.

At the last visit, 6 (26%) subjects exhibited low titers and 9 (39%) subjects exhibited higher titers.

Injection-site reactions potentially related to a localized immune response (most commonly pruritus or erythema) were less commonly observed in antibody to negative subjects (38%) compared with those observed in antibody positive subjects (80%). Treatment-emergent antibodies to exenatide were otherwise not associated with patient tolerability or safety.

Conclusions:
Date of Report: