2. GWCH Synopsis

Clinical Study Report Synopsis: Study H8O-MC-GWCH

Title of Study: Safety and Efficacy of Exenatide Once Weekly Injection versus Metformin, Dipeptidyl Peptidase-4 Inhibitor, or Thiazolidinedione as Monotherapy in Drug-Naïve Patients with Type 2 Diabetes	
Number of Investigators: This multicenter study included 124 investigators.	
Study Centers: This study was conducted at 124 study centers in 22 countries.	
Publications Based on the Study: None at this time.	
Length of Study: Date of first subject visit: 11 December 2008 Date of last subject visit: 09 June 2010	**Phase of Development:** 3

Objectives: The primary objective is to test the hypothesis that exenatide once weekly is superior to metformin, pioglitazone, and sitagliptin in hemoglobin A1c (HbA1c) reduction at 26 weeks compared to baseline, in drug-naïve subjects with type 2 diabetes who are inadequately treated with diet and exercise.

The secondary objectives of the study are to compare exenatide once weekly to metformin, pioglitazone, and sitagliptin with respect to:

- proportion of subjects achieving HbA1c ≤7% and ≤6.5%
- change in fasting serum glucose
- change in body weight
- 7-point self-monitored blood glucose (SMBG) profile
- change in serum lipids (total cholesterol [TC], high-density lipoprotein cholesterol [HDL-C], fasting triglycerides, calculated low-density lipoprotein cholesterol [LDL-C])
- incidence of hypoglycemic events
- change in systolic and diastolic blood pressure
- safety and tolerability
- health outcomes

Study Design: This Phase 3, multicenter, multinational, comparator- and placebo-controlled, double-blind, randomized, 4-arm, parallel study was designed to compare the effects of exenatide once weekly with metformin, pioglitazone, and sitagliptin with respect to glycemic control as measured by HbA1c over 26 weeks. In total, 820 subjects experiencing inadequate glycemic control on diet and exercise were randomly assigned to 1 of 4 active treatments plus placebo in a 3:3:2:2 ratio: exenatide once weekly plus placebo (metformin, pioglitazone, or sitagliptin), metformin plus exenatide once weekly placebo, pioglitazone plus exenatide once weekly placebo, and sitagliptin plus exenatide once weekly placebo.

Number of Subjects:

Planned: 822 subjects
Randomized: 820 subjects; 248 exenatide once weekly, 246 metformin, 163 pioglitazone, 163 sitagliptin
Treated (at least 1 dose): 820 subjects; 248 exenatide once weekly, 246 metformin, 163 pioglitazone, 163 sitagliptin
Completed: 696 subjects; 210 exenatide once weekly, 213 metformin, 133 pioglitazone, 140 sitagliptin

Diagnosis and Main Criteria for Inclusion: Male or female subjects at least 18 years of age with type 2 diabetes who were inadequately treated with diet and exercise and drug-naïve for at least 3 months prior to screening; had HbA1c between 7.1% and 11.0% (inclusive), a body mass index (BMI) of 23 kg/m^2 to 45 kg/m^2 (inclusive), and a history of stable body weight.

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Test Product, Dose, and Mode of Administration: Exenatide once weekly 2 mg, or placebo equivalent, was injected once weekly into subcutaneous tissue of the abdomen.

Comparator, Dose, and Mode of Administration: Metformin or placebo 500-mg tablets (1000 to 2500 mg/day), pioglitazone or placebo 30- and 45-mg capsules (30 to 45 mg/day), sitagliptin or placebo 100-mg tablets (100 mg/day) – administered orally.

Duration of Treatment: 26 weeks

Variables:

Efficacy: The primary efficacy analysis was the change in HbA1c from baseline to the primary treatment endpoint at 26 weeks. The following secondary efficacy measures were collected:

- proportion of subjects achieving HbA1c ≤7% and ≤6.5%
- change in fasting serum glucose
- change in body weight
- 7-point SMBG profile
- change in serum lipids
- incidence of hypoglycemic events
- change in systolic and diastolic blood pressure
- safety and tolerability
- health outcomes

Safety: The following safety measures were collected:

- adverse events
- frequency and rate of hypoglycemic events
- clinical chemistry and hematology
- anti-exenatide antibodies
- electrocardiograms
- vital signs

Health Outcomes: Health outcomes were measured in certain countries using the following questionnaires: Impact of Weight on Quality of Life-Lite (IWQOL-Lite), European Quality of Life-5 Dimensions (EQ-5D), Binge Eating Scale (BES), and Diabetes Treatment Satisfaction Questionnaire (DTSQ).

Statistical Evaluation Methods:

Efficacy: Approximately 822 subjects were planned to be randomly assigned to 1 of the 4 treatment groups in the ratio of 3:3:2:2 (exenatide once weekly injection, 246; metformin, 246; pioglitazone, 165; and sitagliptin, 165). Three pair-wise comparisons (exenatide once weekly injection versus each of the 3 comparators) were performed for all the statistical comparisons of efficacy variables. Both superiority and noninferiority comparisons were performed for the primary efficacy variable change in HbA1c. The noninferiority margin was 0.3% (absolute difference). The study sample size was calculated to provide approximately 90% power to detect differences between each of the treatments (exenatide once weekly versus metformin, pioglitazone, and sitagliptin) of 0.4%, 0.5%, and 0.5%, respectively, with a 2-sided *t* test at a significance level of 0.05, assuming a common standard deviation (SD) of 1.2%. The method for the comparisons used the intent-to-treat (ITT) analysis dataset and resulted from a maximum likelihood-based mixed-model repeated measures (MMRM) analysis of covariance (ANCOVA) with change in HbA1c as the dependent variable and treatment, baseline HbA1c, country, week of visit, and treatment-by-week interaction as fixed effects, and patient and error as random effects. All comparisons were 2-sided 95% confidence intervals (CIs). Multiple comparisons were adjusted only for the primary efficacy analyses using the Bonferroni procedure for the noninferiority comparisons followed by the Hommel test for the superiority comparisons and gatekeeping between the noninferiority and superiority test. In addition to MMRM, a last-observation-carried-forward (LOCF) analysis was performed for the primary efficacy variable to support the conclusion of the primary analysis.

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Statistical Evaluation Methods:

Safety: Safety measures were collected at specified visits. Exposure to each therapy during treatment was calculated for each subject and summarized by treatment group. Adverse events were classified by system organ class and preferred term as defined by the Medical Dictionary for Regulatory Drug Activities (MedDRA®) version 13.0. Three pair-wise comparisons (exenatide once weekly injection versus each of the 3 comparators) were performed for all the statistical comparisons of safety variables.

Health Outcomes: Frequency distributions, including measures of central tendency and variability (e.g., means, medians, SDs), were calculated for individual items, each domain, and total scores for each scale.

Summary:

Subject Disposition: Of the 820 subjects randomized in this study, 124 discontinued prior to Week 26 leaving 696 subjects who completed the 2-week treatment period: 210 (85%) exenatide once weekly-, 213 (87%) metformin-, 133 (82%) pioglitazone-, and 140 (86%) sitagliptin-treated subjects. The most common reasons overall for discontinuation were subject decision (exenatide once weekly, 17 [6.9%]; metformin, 9 [3.7%]; pioglitazone, 12 [7.4%]; and sitagliptin 6 [3.7%]) and protocol violation (exenatide once weekly, 5 [2.0%]; metformin, 9 [3.7%]; pioglitazone, 2 [1.2%]; and sitagliptin 5 [3.1%]). A total of 736 subjects completed the 10-week safety follow-up visit.

Subject Baseline Characteristics: A total of 820 subjects (248 exenatide once weekly; 246 metformin; 163 pioglitazone; and 163 sitagliptin) were randomly assigned to study drug and received at least 1 dose. Subjects assigned to each treatment group had similar characteristics at study entry. Most subjects (approximately 67%) were Caucasian, with slightly more males (approximately 59%). The mean age was approximately 54 years. The mean duration of diabetes was approximately 2.7 years, mean baseline HbA1c was approximately 8.5%, mean body weight was approximately 87 kg, and mean BMI was approximately 31 kg/m^2.

Primary Efficacy Measure – HbA1c: The primary objective in this study was to test the hypothesis that exenatide once weekly is superior to metformin, pioglitazone, and sitagliptin with respect to change in HbA1c.

Exenatide once weekly was superior to sitagliptin ($p<.001$) and demonstrated noninferiority to metformin regarding improvements in glycemic control at 26 weeks of treatment (98.3% CI was -0.63% to -0.16% for sitagliptin and -0.26% to 0.17% for metformin). Exenatide once weekly failed to demonstrate noninferiority compared with pioglitazone (98.3% CI was -0.08% to 0.41% for pioglitazone). The change in HbA1c from baseline to Week 26 was not statistically different between exenatide once weekly and pioglitazone.

In the LOCF ANCOVA analysis results of the HbA1c analysis, all treatment groups demonstrated a reduction in HbA1c from baseline to Week 26, thus demonstrating improvement; however, treatment with exenatide once weekly showed a statistically significant reduction in HbA1c compared with sitagliptin (LS mean was -1.5% for exenatide once weekly compared with -1.1% for sitagliptin). No significant differences in change from baseline to endpoint in HbA1c were observed for exenatide once weekly compared with metformin ($p=.204$) or pioglitazone ($p=.982$).

Because the primary analysis of change in HbA1c did not include all postbaseline observations, an analysis (modified MMRM [full ITT] analysis) was done using the same model as the primary analysis but included all postbaseline observations. The conclusion was consistent with the primary analysis.

In the primary efficacy analysis of change from baseline in HbA1c using repeated measures, exenatide once weekly demonstrated a statistically significant reduction in HbA1c compared with all 3 treatment groups at Weeks 8, 12, and 16.

Change in HbA1c by Exenatide Antibody Status: Analysis of change in HbA1c was performed for: 1) 2-level antibody to exenatide status (negative and positive), and 2) 3-level antibody to exenatide status (negative, positive lower, and positive higher). There were no differences in change in HbA1c among subjects with positive versus negative antibody status by 2- and 3-level status measured at endpoint and by the highest titer. The LS mean change from baseline in HbA1c for subjects with positive higher status at the highest titer was -1.16%. Antibody to exenatide once weekly was not a predictor of changes in HbA1c.

Secondary Efficacy Measures – HbA1c ≤7% and ≤6.5%, Fasting Serum Glucose (FSG), and Body Weight:
Exenatide once weekly treatment resulted in a significantly higher percentage of subjects who had HbA1c >7% at baseline that decreased to ≤7% at endpoint compared with sitagliptin (p<.001). No statistically significant difference was observed between exenatide once weekly compared to metformin (p=.151) or pioglitazone (p=.913). Exenatide once weekly treatment demonstrated a significantly higher percentage of subjects who had HbA1c >6.5% at baseline that decreased to ≤6.5% at endpoint compared with metformin (p=.004) and sitagliptin (p<.001). No statistically significant difference was observed between exenatide once weekly compared to pioglitazone (p=.181). Exenatide once weekly treatment demonstrated a significantly higher percentage of subjects who had HbA1c >6% at baseline that decreased to ≤6% at endpoint compared with metformin (p=.007) and sitagliptin (p<.001). No statistically significant difference was observed between exenatide once weekly compared to pioglitazone (p=.110). Exenatide once weekly treatment demonstrated a significantly higher percentage of subjects who had HbA1c ≥7% at baseline that decreased to <7% at endpoint compared with sitagliptin (p<.001). No statistically significant difference was observed between exenatide once weekly compared to metformin (p=.075) or pioglitazone (p=.668).

All treatments lowered FSG at Weeks 16 and 26, demonstrating improvement. The LS mean (SE) change in FSG for each treatment group at Week 26 was -2.25 (0.14) for exenatide once weekly, -1.98 (0.14) for metformin, -2.57 (0.18) for pioglitazone, and -1.13 (0.18) for sitagliptin. Exenatide once weekly-treated subjects demonstrated a significantly lower FSG from baseline to Week 16 and Week 26 compared with sitagliptin-treated subjects (p<.001 for both comparisons). There were no differences in change in FSG among subjects with positive versus negative antibody status by 2- and 3-level status measured at endpoint and by the highest titer. The LS mean change from baseline in FSG for subjects with positive higher status at the highest titer was -1.75 mmol/L. Antibody to exenatide once weekly was not a predictor of change in FSG. At Week 26, exenatide once weekly treatment significantly lowered mean body weight compared with sitagliptin (p<.001; LS mean difference [SE] -1.28 [0.33] kg) and pioglitazone (p<.001; LS mean difference [SE] -3.56 [0.33] kg). The LS mean change (SE) in weight was -2.04 (0.21) kg for exenatide once weekly, 1.52 (0.26) kg for pioglitazone, and -0.76 (0.26) kg for sitagliptin. The difference in mean body weight compared to metformin was not statistically significant (p=.892; LS mean change [SE] was -2.00 [0.21] kg). Significant reductions in change in weight for exenatide once weekly compared with pioglitazone were observed at Weeks 4 through 26 (all p<.003). Significant reductions in weight for exenatide once weekly compared with sitagliptin were observed at Weeks 8 through 26 (all p<.001).

Secondary Efficacy Measures – SMBG, Serum Lipids: For all SMBG parameters, exenatide once weekly showed significant improvements compared with sitagliptin at Weeks 12 and 26 ($p \leq .001$). Exenatide once weekly showed significant improvement compared with metformin on the SMBG parameters of morning premeal (p=.037), morning postprandial meal (p=.003), evening premeal (p=.028), bedtime (p=.024), daily mean (p=.005), midday postprandial meal (p=.031), and daily postprandial meal (p=.007) at Week 12. Exenatide once weekly showed significant improvement compared with pioglitazone on the SMBG parameters of midday postprandial meal (p=.009), daily postprandial meal (p=.013), and evening postprandial meal (p=.037) at Week 12. Exenatide once weekly-treated subjects demonstrated a significant reduction in the morning 2-hour postprandial excursion compared with metformin-treated subjects (p=.031) at Week 12. Exenatide once weekly-treated subjects demonstrated a significant reduction in the evening 2-hour postprandial excursion (p=.031) and the mean daily 2-hour postprandial excursion (p=.017) compared with pioglitazone-treated subjects at Week 12.

Exenatide once weekly-treated subjects demonstrated a statistically significant decrease in the change of TC at Week 26 compared with pioglitazone- ($p<.001$) and sitagliptin-treated subjects (p=.022). The difference in the change of TC between treatments with exenatide once weekly and metformin was not significant at Week 26. Exenatide once weekly-treated subjects demonstrated a statistically significant decrease in the change of LDL-C at Week 26 compared with pioglitazone- ($p<.001$) and sitagliptin-treated subjects (p=.003). The difference in the change of LDL-C between treatments with exenatide once weekly and metformin was not significant at Week 26. Increases in the change of HDL-C values were observed in all treatment groups at Week 26. This difference in the change of HDL-C was statistically significant for exenatide once weekly- compared with metformin- (p=.004) and pioglitazone- ($p<.001$) treated subjected. Pioglitazone showed a statistically significant decrease in the change of triglycerides compared with exenatide once weekly (p=.009) at endpoint. The differences in the change of triglycerides between exenatide once weekly compared to metformin and sitagliptin were not significant.

Secondary Efficacy Measures – Health Outcomes/Quality of Life Assessments:

Impact of Weight on Quality of Life-Lite Questionnaire (IWQOL-Lite): Exenatide once weekly-treated subjects demonstrated improvement from baseline to endpoint compared with pioglitazone-treated subjects in IWQOL-Lite total scores (p=.003) and 4 of 5 domains of weight-related quality of life (physical function [p=.001]), (self esteem [p=.031]), sexual life [p=.048]), and public distress [p=.033]) but not for work (p=.381).

EuroQol Health-Related Quality of Life (EQ-5D): Exenatide once weekly-treated subjects experienced significant improvement at endpoint compared with pioglitazone-treated subjects in 1 of 5 dimensions of health-related quality of life (mobility [p=.023]) in the EQ-5D UK population-based Index Score (p=.012), and the EQ-5D US population-based Index Score (p=.019).

Binge Eating Scale (BES): A statistically significant improvement in the BES total score was observed at endpoint for exenatide once weekly compared with pioglitazone (p=.002). No statistically significant differences were observed at endpoint for exenatide once weekly compared with metformin (p=.961) or sitagliptin (p=.058).

Diabetes Treatment Satisfaction Questionnaires (DTSQs and DTSQc): No statistically significant differences were observed between treatment with exenatide once weekly and metformin, pioglitazone, or sitagliptin in the DTSQs or DTSQc Total treatment satisfaction scores at endpoint.

Exploratory Efficacy Measures: Exenatide once weekly-treated subjects experienced significant improvement in the proinsulin/insulin ratio at endpoint compared with pioglitazone-treated subjects (p=.002). No significant differences in the proinsulin/insulin ratio were observed between treatment with exenatide once weekly and metformin (p=.729) or sitagliptin (p=.212) at endpoint.

1,5 AG: At Week 26, exenatide once weekly-treated subjects had a significantly lower increase in 1,5-AG compared with metformin-treated subjects (p=.019). No significant differences in 1,5-AG were observed at Week 16 for treatment with exenatide once weekly compared with metformin, pioglitazone, or sitagliptin.

hsCRP: Exenatide once weekly-treated subjects experienced significant improvement in hsCRP at endpoint compared with sitagliptin-treated subjects (p<.001). No significant differences in hsCRP were observed at endpoint for treatment with exenatide once weekly compared with pioglitazone (p=.966) or metformin (p=.226).

Urinary albumin/creatinine ratio: In the ITT analysis set, exenatide once weekly-treated subjects experienced significant improvement at endpoint in urinary albumin/creatinine ratio (p=.025) compared with metformin-treated subjects. No significant differences were observed at endpoint in urinary albumin/creatinine ratio for treatment with exenatide once weekly compared with pioglitazone (p=.117) or sitagliptin (p=.145).

HOMA-B: Exenatide once weekly-treated subjects had a greater change in beta cell function compared with metformin-, sitagliptin-, and pioglitazone-treated subjects in the ratio of LOCF endpoint to baseline (p<.001).

HOMA-S: Treatment with metformin and pioglitazone had a higher measure of insulin sensitivity than exenatide once weekly from the LOCF endpoint to baseline (p<.001). No significant differences in insulin sensitivity were observed for treatment with exenatide once weekly compared with sitagliptin from the LOCF endpoint to baseline (p=.329); insulin LOCF endpoint to baseline (p=.772).

Waist and hip circumference: Exenatide once weekly-treated subjects had a significant reduction at endpoint in waist (p<.001) and hip circumference (p<.001) compared with pioglitazone-treated subjects and a significant reduction in waist circumference compared with sitagliptin-treated subjects (p=.002). No significant differences in waist-to-hip ratio were observed at endpoint for treatment with exenatide once weekly compared with metformin (p=.873), pioglitazone (p=.178), or sitagliptin (p=.345).

Safety Measure – Treatment Exposure: Doses of exenatide once weekly (2 mg) and sitagliptin (100 mg/day) were to remain unchanged throughout the study. Subjects treated with metformin underwent dose titration from 1000 mg/day up to 2500 mg/day; at Week 16, approximately 88% of metformin-treated subjects were treated with doses ≥2000 mg/day. Subjects treated with pioglitazone underwent dose titration from 30 to 45 mg/day; at Week 16, approximately 76% of pioglitazone-treated subjects were treated with the maximum 45-mg/day dose. The mean (SD) duration of exposure for subjects dosed with study drug was 173 (48.0), 172 (45.0), 164 (52.5), and 178 (34.5) days for exenatide once weekly-, metformin-, pioglitazone-, and sitagliptin-treated subjects, respectively.

Safety Measures – Serious Treatment-Emergent Adverse Events (TEAEs) and Discontinuations due to TEAEs: No deaths occurred during the 26-week treatment period. At least 1 SAE was reported by 28 subjects: 4 exenatide once weekly, 12 metformin, 9 pioglitazone, and 3 sitagliptin. Five of those SAEs led to subject discontinuation: 1 exenatide once weekly (hyperglycemia), 2 metformin (gastric cancer, loss of consciousness), and 2 pioglitazone (bronchopneumopathy, hepatic neoplasm malignant). A total of 4 SAEs were considered to be related to study drug: 1 metformin (loss of consciousness) 3 pioglitazone (anemia, vomiting, nausea). In addition, 1 metformin-treated subject experienced the SAE, injection site nodule, which was considered to be related to placebo injection. A total of 18 subjects discontinued from the study because of AEs (exenatide once weekly, 6 [2.4%]; metformin, 6 [2.4%]; pioglitazone, 5 [3.1%]; and sitagliptin, 1 [0.6%]). Most of the events were mild or moderate. There were 4 events considered severe: gastric cancer, loss of consciousness, bronchopneumopathy, and hepatic neoplasm.

Safety Measure – Nonserious TEAEs: Overall, treatment was generally well-tolerated in subjects treated with exenatide once weekly, metformin, pioglitazone, or sitagliptin. Overall, TEAEs were reported in approximately 65% (161/248), 64% (158/246), 62% (101/163), and 60% (97/163) of exenatide once weekly-, metformin-, pioglitazone-, and sitagliptin-treated subjects, respectively. The most frequently reported TEAE was headache (exenatide once weekly, 20 [8.1%]; metformin, 30 [12.2%]; pioglitazone, 13 [8.0%]; and sitagliptin, 15 [9.2%]), followed by diarrhea (exenatide once weekly, 27 [10.9%]; metformin, 31 [12.6%]; pioglitazone, 6 [3.7%]; and sitagliptin, 9 [5.5%]), injection site nodule (exenatide once weekly, 26 [10.5%]; metformin, 25 [10.2%]; pioglitazone, 6 [3.7%]; sitagliptin, 11 [6.7%]), nasopharyngitis (exenatide once weekly, 19 [7.7%]; metformin, 11 [4.5%]; pioglitazone, 14 [8.6%]; and sitagliptin, 16 [9.8%]), and nausea (exenatide once weekly, 28 [11.3%]; metformin, 17 [6.9%]; pioglitazone, 7 [4.3%]; and sitagliptin, 6 [3.7%]).

Safety Measures – TEAEs and Antibodies to Exenatide Status: Of 248 exenatide once weekly-treated subjects, antibody to exenatide status was obtained for 231 subjects. At endpoint, 38.7% (96/248) of subjects were of antibody-negative status and 54.4% (135/248) of subjects were of antibody-positive status. The proportions of antibody-negative (38%) and antibody-positive subjects (44%) reporting at least 1 TEAE differed slightly. Among the antibody-negative and antibody-positive subjects, the most frequent TEAE by system organ class was "gastrointestinal disorders" (antibody-negative, 31.3%; treatment-emergent antibody-positive, 27.4%) followed by "general disorders and administration site conditions" (antibody-negative, 11.5%; treatment-emergent antibody-positive, 23.7%). From the category "general disorders and administration site conditions," events with higher incidence in antibody-positive subjects primarily included injection site-related events. Some incidence of local irritation is expected with medical use of PLG technology as evidenced in this study by injection site AEs reported in subjects who were receiving placebo injection not containing active drug.

Of 231 exenatide once weekly-treated subjects whose antibody status was known, 53 subjects (6 [12.8%] antibody-negative, 47 [25.5%] antibody-positive) experienced at least 1 TEAE from the list of TEAEs broadly selected for their potential association with an immune response. There was a difference in the incidence of events related to an injection site event observed at endpoint between antibody-negative and antibody-positive subjects. Most of these events were related to an injection site event and were typically assessed by the investigator as mild in severity.

The formation of small, asymptomatic, SC nodules at the injection site is expected with exenatide once weekly as a result of the sustained-release delivery system. Notably, few subjects have reported accompanying symptoms of pain, induration, redness, bleeding, or inflammation; events are typically mild and transient and do not interfere with therapy. In Study GWCH, injection site nodules occurred in approximately 10% (26/248), 10% (25/246), 4% (6/163), and 7% (11/163) of exenatide once weekly-, metformin-, pioglitazone-, and sitagliptin-treated subjects, respectively. However, due to the differences in data collection between Study GWCH and previous studies, meaningful comparisons of nodules and accompanying symptoms cannot be concluded.

Safety Measure – Laboratory Outcomes and Vital Signs: For the 26-week treatment period, no subjects had total amylase levels >3 times the ULN at endpoint. For lipase, 2 (0.8%) metformin-treated subjects had a lipase value >3 times the ULN at endpoint. One sitagliptin-treated subject with elevated lipase values at screening experienced moderate chronic pancreatitis and discontinued from study treatment. The subject returned for the 10-week safety follow-up visit. The event was not considered related to study drug. No subjects had calcitonin values >2 the ULN at endpoint. No other clinically relevant laboratory results were identified within and between treatment groups.

Mean increases in heart rate BPM of 1.5, 0.3, and 0.5 were observed at endpoint in the exenatide once weekly, metformin, and sitagliptin treatment groups, respectively. A mean decrease in heart rate of -1.7 BPM was observed at endpoint for pioglitazone-treated subjects. Mean decreases in systolic blood pressure of -1.23 mm Hg, -0.03 mm Hg, -2.67 mm Hg, and -2.51 mm Hg were observed in the exenatide once weekly, metformin, and sitagliptin treatment groups, respectively.

Safety Measure – Hypoglycemia: Episodes of minor hypoglycemia were reported in 2.0% of exenatide once weekly-treated subjects; no minor hypoglycemia events were reported in the other treatment groups. Hypoglycemia symptoms were reported in 5.2% versus 4.1%, 3.7%, and 3.1% of exenatide once weekly-, metformin-, pioglitazone-, and sitagliptin-treated subjects. No major hypoglycemia occurred during the study.

Safety Measures – 10-Week Follow-Up Period: A total of 736 subjects completed the 10-week safety follow-up visit.

One subject, who was treated for approximately 5 months with metformin, died from gastric cancer approximately 2 months after withdrawing from the study. No medical history of GI disorders was reported for this subject; the death was assessed as unrelated to study drug or study procedures. A total of 11 subjects (1 exenatide once weekly, 2 metformin, 5 pioglitazone, 3 sitagliptin) experienced 19 SAEs in the 10-week follow-up period. None of the SAEs prevented subjects from completing their 10-week follow-up visit and none was considered related to study drug. Overall, TEAEs were reported in approximately 14% (35/248), 13% (32/246), 16% (26/163), and 14% (22/163) of the exenatide once weekly, metformin, pioglitazone, and sitagliptin treatment groups in the 10-week follow-up period. No TEAEs with a total incidence >1% across treatment groups began during the 10-week follow-up period. No subjects discontinued the 10-week follow-up period due to an AE. No episodes of major hypoglycemia were reported during the 10-week follow-up period; the incidence of minor hypoglycemia was low for all subjects. No other clinically relevant safety data were reported for subjects completing their 10-week follow-up visit.

Conclusions:

The Committee for Medicinal Products for Human Use (CHMP) scientific advice working party suggested that the study should demonstrate superiority of exenatide once weekly over placebo. A placebo arm was not included in the study.

All comparator groups (metformin, pioglitazone, and sitagliptin) demonstrated clinical efficacy as anticipated from the published literature and label information. Therefore, assay sensitivity is not in question.

Subjects who had previously been treated with diet and exercise alone entered the study, continued to follow their diet and exercise therapy, and initiated 1 of 4 treatments: exenatide once weekly (2 mg), metformin (titrated to 2500 mg/day), pioglitazone (titrated to 45 mg/day), and sitagliptin (100 mg/day). The majority of metformin-treated subjects (88%) were treated with ≥2000 mg/day at Week 16 of this 26-week study.

This Phase 3, multicenter, multinational, comparator- and placebo-controlled, double-blind, randomized, 4-arm, parallel trial compared the effects of exenatide once weekly 2-mg injection as monotherapy to 3 active comparators (metformin, pioglitazone, and sitagliptin) with respect to glycemic control, measured by HbA1c over a 26-week treatment period in 820 drug-naïve subjects with type 2 diabetes mellitus treated with diet and exercise.

The data through Week 26 support the following conclusions:

- From baseline to Week 26, exenatide once weekly demonstrated superiority over sitagliptin ($p<.001$) with respect to change in HbA1c. Exenatide once weekly demonstrated noninferiority to metformin and sitagliptin regarding improvements in glycemic control at 26 weeks of treatment. Exenatide once weekly failed to demonstrate noninferiority compared with pioglitazone. In subjects who had HbA1c ≥7% at baseline, exenatide once weekly demonstrated a statistically significant higher percentage of subjects who achieved HbA1c <7% at endpoint compared to sitagliptin ($p<.001$). Exenatide once weekly demonstrated a statistically significant higher percentage of subjects achieving HbA1c ≤7% compared to sitagliptin. All treatments lowered FSG at Week 26, demonstrating improvement; exenatide once weekly demonstrated statistically significant improvement in FSG compared to sitagliptin.

- Weight decreased in 26 weeks with exenatide once weekly (-2.0 kg), metformin (-2.0 kg; p=.892), and sitagliptin (-0.8 kg; p<.001), but increased with pioglitazone (+1.5 kg; p<.001) (LS means). For all SMBG parameters, exenatide once weekly showed significant improvements compared with sitagliptin at Week 26 (p≤.001). There were no significant differences between exenatide once weekly compared to metformin or pioglitazone for any of the 7 time points or for daily mean SMBG from baseline to endpoint. Mean reductions in SMBG postmeal excursions after 26 weeks were similar among all treatment groups. Change in HOMA-B (ratio of endpoint [LOCF] to baseline) was significantly improved with exenatide once weekly compared with metformin, pioglitazone, and sitagliptin. Insulin sensitivity, as measured by geometric mean HOMA-S (C-peptide) values, were significantly (both p<0.001) improved with metformin and pioglitazone compared with exenatide once weekly; change with exenatide once weekly was similar to sitagliptin.
- Subjects in the exenatide once weekly treatment group reported significant improvements compared to pioglitazone in measures related to quality of life and binge eating from baseline to Week 26.
- Exenatide once weekly, metformin, pioglitazone, and sitagliptin were generally well-tolerated and exhibited similar safety profiles. Withdrawals due to AEs were infrequent. No events of major hypoglycemia were observed in the study. Minor treatment-emergent hypoglycemia was observed infrequently.
- Mild to moderate headache was the most frequently reported event (8% exenatide once weekly, 12% metformin, 8% pioglitazone, 9% sitagliptin) with no withdrawals due to this event.
- One event of chronic pancreatitis was reported in the sitagliptin treatment group, with no events reported for subjects treated with exenatide once weekly, metformin, or pioglitazone.
- The overall incidence of injection site-related events was low (13.7%), with consistent rates (8% to 19%) observed between subjects receiving once-weekly injections of exenatide once weekly and placebo.
- Most TEAEs had resolved by the end of the 26-week treatment period and the 10-week safety follow-up period, with few TEAEs starting during the 10-week safety follow-up period. No TEAEs with a total incidence >1% across treatment groups began during the 10-week follow-up period.

As monotherapy, exenatide once weekly demonstrated superior improvements as measured by change in HbA1c compared to the maximum dose of sitagliptin and noninferiority to metformin, but did not reach the noninferiority measure with pioglitazone. Treatment with exenatide once weekly significantly lowered mean body weight compared to sitagliptin and pioglitazone. Exenatide once weekly and metformin led to similar mean body weight reduction. The comparable safety profiles observed between all 4 treatments demonstrate that exenatide once weekly provides a once-weekly dosing option for initial therapy in patients diagnosed with type 2 diabetes.