2. GWBR Synopsis

Approval Date: 24-Sep-2012 GMT

Clinical Study Report Synopsis: Study H8O-MC-GWBR (156-Week Entire Treatment Period)

Title of Study: Efficacy of Once-Weekly Exenatide Long-Acting Release and Once-Daily Insulin Glargine in Patients with Type 2 Diabetes Treated with Metformin Alone or in Combination with Sulfonylurea

Number of Investigator(s): This multicenter study included 72 principal investigator(s).

Study Center(s): This study was conducted at 72 study center(s) in 15 countries.

Publication(s) Based on the Study: Diamant M, Van Gaal L, Stranks S, Guerci B, MacConell L, Haber H, Scism-Bacon J, Trautmann M. Safety and efficacy of once-weekly exenatide compared with insulin glargine titrated to target in patients with type 2 diabetes over 84 weeks. Diabetes Care 2012;35(4):683-9.
Diamant M, Van Gaal L, Stranks S, Northrup J, Cao D, Taylor K, Trautmann M. Once weekly exenatide compared with insulin glargine titrated to target in patients with type 2 diabetes (DURATION-3): an open-label randomised trial. *Lancet.* 2010;375(9733):2234-43.

Length of Study:	**Phase of Development:** 3
Date of first patient visit: 30 April 2008 Date of last patient completed: 30 January 2012	

Objectives: The primary objective was to estimate the difference in change in hemoglobin A1c (HbA_{1c}) from baseline to treatment endpoint (26 weeks) between 2-mg exenatide once weekly (QW; formerly referred to as exenatide l ong acting release) and insulin glargine once daily (QD) using the algorithm described by Yki-Järvinen et al. 2007 in patients with type 2 diabetes and inadequate glycemic control using metformin (MET) alone or in combination with sulfonylurea (SU).

The secondary objectives of the study were to compare exenatide QW and insulin glargine arms with respect to:

- the proportion of patients achieving HbA_{1c} ≤7% and ≤6.5%
- fasting serum glucose (FSG)
- change in body weight
- 1,5-anhydroglucitol (1,5-AG)
- 8-point self-monitored blood glucose (SMBG) profile (blood glucose measurements before and 2 hours after the start of the morning, mid-day, and evening meals, at bedtime, and at the 0300 hour)
- serum lipids (total cholesterol [TC], high-density lipoprotein cholesterol [HDL-C], fasting triglycerides, calculated low-density lipoprotein cholesterol [LDL-C])
- frequency and rate of hypoglycemic events (overall, daytime, and nocturnal) in the set of patients using MET alone or in combination with SU
- safety and tolerability
- patient-reported health outcomes
- long-term maintenance of glycemic control, safety, and tolerability

Unless otherwise specified, the secondary objectives were evaluated for patients using MET alone or in combination with SU. Additional analyses on subsets of patients are described in the statistical analysis plan (SAP).

The exploratory objectives were:

- CCI [redacted]

The exploratory objectives were evaluated for patients using MET alone or in combination with SU. Additional analyses on subsets of patients are described in the SAP.

Study Design: This was a Phase 3, multicenter, open-label, randomized, 2-arm, parallel, comparator-controlled trial. A total of 233 patients, experiencing inadequate glycemic control using MET alone or in combination with SU, were randomly assigned to add 2.0-mg exenatide QW or insulin glargine QD to their current therapy regimen. The number of patients using MET plus SU was limited to no more than approximately 30% of total enrollment. The study included a 26-week core treatment period and an open-ended extension period that lasted at least 130 weeks (2.5 years). The results of the 26-week, core-treatment period was previously reported. In the primary efficacy endpoint, the change from baseline of HbA_{1c} levels to Week 26, exenatide was found to be superior to insulin glargine when added to MET therapy alone or in combination with SU. This report presents the results through Week 156 of treatment that included the 26-week core treatment period and the 130-week extension period.

Number of Patients:

Planned: 456

Actual enrollment: 467 randomized; 456 treated (at least 1 dose of study drug)

Randomized: 233 exenatide QW (2.0 mg) + MET or MET + SU, 234 insulin glargine + MET or MET + SU

Treated (at least 1 dose): 233 exenatide QW (2.0 mg) + MET or MET + SU, 223 insulin glargine + MET or MET + SU

Patients who completed treatment: 144 (61.8%) exenatide QW (2.0 mg) + MET or MET + SU, 152 (65.0%) insulin glargine + MET or MET + SU

Treatment completers are randomized patients who completed both the 26-week core treatment period and the 130-week extension period.

Diagnosis and Main Criteria for Inclusion: Patients were ≥18 year old with type 2 diabetes mellitus (by World Health Organization criteria) and had sub-optimal glycemic control evidenced by HbA_{1c} between 7.1% and 11.0%, had a body mass index of 25 to 45 kg/m^2 and stable body weight (not varying by >5% for at least 3 months prior to screening); had been taking a stable dose of ≥1500 mg/day immediate-release or extended-release MET alone for at least 8 weeks prior to screening, unless lower doses were required due to tolerability concerns. Alternatively, patients had been taking a stable dose of at least an optimally effective dose of a specific SU for 8 weeks prior to screening. If combined MET plus SU oral antidiabetes agent (OAD) preparations (such as Glucovance®) were used, the total daily dose of each component had to meet the defined criteria. Female patients of child-bearing potential could not be breastfeeding, had to have a negative serum pregnancy test at screening, and were intending to not become pregnant during the study using a protocol accepted method of birth control.

Test Product/Study Drug, Dose, and Mode of Administration: Exenatide QW 2 mg/week, as a subcutaneous injection.

Reference Therapy/Comparator, Dose, and Mode of Administration: Insulin glargine, starting at 10 IU per day and adjusting dose as clinically indicated, QD as a subcutaneous injection.

Duration of Treatment: Up to 156 weeks

Variables:

Efficacy: The key efficacy measure was the change in HbA_{1c} from baseline to Week 156.

Secondary efficacy measures included: the proportion of patients achieving HbA_{1c} <7%, ≤7%, and ≤6.5%, FSG, change in body weight, 1,5-AG, 8-point SMBG profile, and serum lipid panel.

Exploratory efficacy measures included: the proportion of patients achieving HbA_{1c} ≤6.0%, hsCRP, urinary albumin/creatinine ratio, HOMA-B and HOMA-S, and waist and hip circumference, including waist-hip circumference ratio.

Safety: Safety measures included serious and nonserious adverse events, clinical chemistry and hematology, anti-exenatide antibodies, electrocardiograms, and vital signs.

Health Outcomes: Health outcomes were assessed as secondary measures and included: Impact of Weight on Quality of Life-Lite questionnaire (IWQOL-Lite), EuroQol instrument questionnaire (EQ-5D), Binge Eating Scale (BES), Diabetes Treatment Satisfaction Questionnaire Status version (DTSQs), and Diabetes Treatment Satisfaction Questionnaire Change version (DTSQc).

Statistical Evaluation Methods:

Efficacy: The primary efficacy analysis was a maximum likelihood-based mixed-model repeated measures (MMRM) analysis of covariance with change in HbA_{1c} as the dependent variable and treatment, baseline HbA_{1c}, country, OAD stratum, week of visit, and treatment-by-week interaction as fixed effects and patient and error as random effects. All postbaseline measurements of the change in HbA_{1c} were included in the analysis with no imputation of missing data other than that inherent in the MMRM model.

Based on a sample size of 205 per treatment group to provide approximately 92% power to detect a true difference between treatments of 0.4% in change in HbA_{1c} from baseline with a 2-sided *t* test at a significance level of 0.05, assuming a common standard deviation of 1.2%, and a drop-out rate of 10%, approximately 228 patients were required to be enrolled per treatment arm (total 456).

Safety: Adverse events were classified by system organ class and preferred term defined by the Medical Dictionary for Regulatory Activities™ (MedDRA). Adverse events were collected from Visit 3 (Week 0) through the last study visit. Adverse events that occurred on or after Visit 1 (Week -2) up to Visit 3 (Week 0) were classified as pretreatment (non-treatment-emergent) and were listed only. Treatment-emergent adverse events (TEAEs) were defined as those occurring on or after randomization through study termination or as pre-existing conditions that worsened after randomization through study termination.

Descriptive statistics of changes from study entry, measured from Visit 1 (Week -2) for laboratory assessments (including clinical chemistry and hematology) and vital signs, are presented. Descriptive statistics of anti-exenatide antibody data are presented. Change in HbA_{1c} within anti-exenatide antibody status groups (based on antibody titer levels) were analyzed as exploratory analysis.

Health Outcomes: Frequency distributions, including measures of central tendency and variability (e.g., means, medians, standard deviations), were calculated for individual items, each domain, and total scores for each scale. Details are presented in the SAP.

Summary:

This Phase 3, multicenter, multinational, open-label, randomized, 2-arm, parallel study was designed to compare the effects of 2.0 mg exenatide QW plus OADs and insulin glargine QD plus OAD, with respect to glycemic control as measured by HbA_{1c}, in 467 patients with type 2 diabetes who experienced inadequate glycemic control with OAD alone. Results of the 26-week Core Treatment Period and the 84-week interim analyses have been presented in separate reports. The current report includes the results of the Extension Period with a follow-up of 10 weeks.

Primary Efficacy Measure – HbA_{1c}: The primary objective of the study as reported in the 26-week CSR, was achieved with exenatide QW demonstrating superiority to insulin glargine with respect to change in HbA_{1c}. At Week 156, Treatment Endpoint, both treatment groups had significant decline in HbA_{1c} levels compared to Baseline and the decrease in HbA_{1c} in the exenatide QW arm was superior to the insulin glargine arm (LS mean difference in HbA_{1c} decrease -0.20%; p=0.033, 2-sided 95% CI, -0.39 to -0.02) based on MMRM analysis.

Secondary Efficacy Measures – HbA_{1c} ≤7% and ≤6.5%: For the Treatment Completer population, the percentage of patients who had HbA_{1c} values ≤6.5% at Treatment Endpoint was 27.9% for the exenatide QW arm and 17.7% for the insulin glargine arm , with a significant difference ($p<0.025$). The percentage of patients who had HbA_{1c} values <7.0% at Treatment Endpoint was 47.9% for the exenatide QW arm and 38.1% for the insulin glargine arm, with a significant difference ($p=0.046$).

Secondary Efficacy Measures – FSG, Body Weight, 1,5-AG and SMBG and serum lipids: Insulin glargine treatment significantly lowered FSG at Week 156 compared with exenatide QW treatment ($p<0.001$). Patients in both treatment groups had a statistically significant decrease in FSG from Baseline to Week 156 ($p<0.001$).

Patients in both treatment groups demonstrated significant improvements in pre- and postprandial blood glucose concentrations at all meals, bedtime, and 0300 hours (all changes $p<0.001$) compared to Baseline. At Week 156, exenatide QW-treated patients demonstrated a significant within-treatment reduction in postprandial blood glucose excursion following the morning (LS mean [SE] change: -0.88 [0.27] mmol/L; $p<0.001$) and evening (LS mean [SE] change: -0.52 [0.24] mmol/L; $p=0.029$) meals. The Treatment Endpoint postprandial blood glucose excursions at morning ($p<0.001$) was significantly lower for exenatide QW than insulin glargine-treated patients.

Compared with insulin glargine, treatment with exenatide QW significantly lowered mean body weight ($p<0.001$) at all timepoints.

Exenatide QW treatment demonstrated a significant increase in 1,5-AG from Baseline to Week 156 compared to insulin glargine-treatment ($p=0.009$). Both groups demonstrated a significant within-treatment change from Baseline to Week 156 (5.1 μg/mL exenatide QW; 3.8 μg/mL insulin glargine). These changes mirror the change in HbA_{1c}.

At Week 156, there was a significant decrease from Baseline in HDL cholesterol within both treatment groups ($p=0.003$ for both). A significant decrease in LDL cholesterol was demonstrated at Week 156 from Baseline for within group comparison for both exenatide QW ($p=0.001$) and insulin glargine groups ($p=0.018$). A significant decrease in TC was demonstrated at Week 156 from Baseline for within group comparison for exenatide QW ($p=0.005$).

Secondary Efficacy Measure – Health Outcomes: There was no significant difference from Baseline to Treatment Endpoint (Week 156; LOCF) between treatment groups in the IWQOL-Lite total score, EQ-5D index score, and BES, DTSQc, total scores. A significant difference was observed in favor of exenatide QW compared to insulin glargine treatment groups ($p=0.035$) in DTSQs total scores.

Patients taking exenatide QW and insulin glargine treatment demonstrated a significant improvement from Baseline to Treatment Endpoint on IWQOL-Lite, BES, and DTSQs total scores. Only patients taking exenatide QW treatment demonstrated a significant improvement from Baseline to Treatment Endpoint on the EQ-5D index UK and US score.

Exploratory Efficacy Measures: CCI [redacted]

CCI [redacted]

[redacted]

Safety Measure – Treatment Exposure: The mean duration of exposure of patients to insulin glargine was similar to that of exenatide QW. By the end of the study, the mean dose of insulin glargine had nearly tripled from 10 IU/day at beginning of treatment to 31 IU/day for insulin glargine-treated patients. Approximately 25% of patients in the exenatide QW treatment group and 23% in the insulin glargine treatment group reduced their SU dose anytime during the study.

Safety Measures – Serious TEAEs and Discontinuations due to TEAEs: There were 2 deaths that occurred during the study; 1 in the exenatide QW arm due to myocardial infarction that was judged to be not related to study drug, and 1 in the insulin glargine QD arm due to colon cancer that was judged to be related to study drug.

Thirty-six exenatide QW and 33 insulin glargine-treated patients experienced at least 1 SAE. Four patients, from the exenatide QW treatment group, had SAEs (1 edematous pancreatitis, cholelithiasis, cholecystitis acute and pancreatitis acute) that were considered to be related to study drug. The patient with edematous pancreatitis discontinued due to the SAE. The SAE of 1 patient, colon cancer stage 4 was considered related to the study drug in the insulin glargine arm and the patient discontinued from the study. There was 1 case of pancreatitis of moderate intensity in a patient receiving insulin glargine treatment. The event was considered an SAE unrelated to treatment.

Approximately 9% (n=22) of exenatide QW- and 2% (n=5) of insulin glargine-treated patients discontinued from the study because of TEAEs. The most frequent AEs reported (>1 patient in any arm) that lead to discontinuation in exenatide QW arm were nausea in 4 patients considered to be severe in intensity and injection site nodule in 3 patients (2 considered severe and 1 moderate). In the insulin glargine arm, the nausea in 1 patient who discontinued the study was considered to be of mild intensity.

Safety Measure – Nonserious TEAEs: Overall, treatment was generally well-tolerated in patients treated with either exenatide QW or insulin glargine. Approximately, 192 (82.4%) patients in the exenatide QW arm and 175 (78.5%) patients in insulin glargine arm reported at least 1 TEAE during the Treatment Period. Exenatide QW-treated patients most frequently reported TEAEs of nasopharyngitis (n=30 [12.9%]), nausea (n=30 [12.9%]), headache (n=23 [9.9%]), diarrhea (n=20 [8.6%]), injection site nodule (n=13 [5.6%]), and vomiting (n=10 [4.3%]). Insulin glargine-treated patients most frequently reported TEAEs of nasopharyngitis (n=39 [17.5%]) and headache (16 [7.2%]). All events of nausea, headache, and diarrhea were of mild or moderate intensity; 1 exenatide QW patient reported vomiting that was severe in intensity, 3 patients had severe injection site nodules and all others were mild (n=7) or moderate (n=3).

The formation of small, asymptomatic, SC nodules at the injection site is expected with exenatide QW as a result of the PLG sustained-release delivery system. Notably, few patients have reported accompanying symptoms of pain, induration, redness, bleeding, or inflammation (Study 2993 LAR-104). In Study GWBR, injection site nodules occurred in 5.6% (n=13) of exenatide QW- versus 0% in insulin glargine-treated patients.

Safety Measures – TEAEs and Anti-Exenatide Antibody Status: Of 233 exenatide QW-treated patients whose antibody status was known, there were a total of 163 (69.9%) antibody-negative patients and 65 (27.9%) antibody-positive patients at Treatment Endpoint. Approximately 83% of anti-exenatide antibody-negative patients and 83% of anti-exenatide antibody-positive patients reported at least 1 TEAE. Among the antibody-negative and treatment-emergent antibody-positive patients, the most frequent TEAEs, by system organ class, were "infections and infestations" (63%in antibody-negative patients; 43% in antibody-positive patients) followed by "gastrointestinal disorders" (46.0% in antibody-negative patients; 35% in antibody-positive patients).

Of 233 exenatide QW-treated patients whose antibody status was known, 51 patients experienced at least 1 TEAE from the list of TEAEs broadly selected for their potential association with an immune response (31% treatment-emergent anti-exenatide antibody-positive and 19% anti-exenatide antibody-negative). Incidence of injection site erythema (1 negative status [0.6%] versus 2 positive status patients [3.1%]); injection site induration (3 negative status [1.9%] versus 2 positive status patients [3.1%]); injection site nodule (4 negative status [2.5%] versus 9 positive status patients [13.8%]) and injection site reaction (3 negative status [1.9%] versus 3 positive status patients [4.6%]) were higher for anti-exenatide-positive status patients than negative status patients.

At Treatment Endpoint 137 (71.7%) patients were antibody-negative, 39 (20.4%) were positive-low, and 11 (5.8%) were positive-higher. At the 10-Week Follow-up, the percentage of antibody-negative patients increased to 145 (75.9%) with a corresponding decrease in the percentage of positive-low (17.8%) and positive-higher (3.7%) patients.

Safety Measure – Laboratory Outcomes and Vital Signs: No patients had amylase or lipase values >5 or >10 times the upper limit of normal at Treatment Endpoint. At Baseline, no patients had amylase levels >3 times the upper limit of normal, but 2 patients treated with exenatide QW had values >3 times the upper limit of normal at Treatment Endpoint. At Baseline, 4 patients had values >3 times and 1 patient had >5 times the upper limit of normal for lipase; 3 exenatide QW-treated patients had values >3 times the upper limit of normal at Treatment Endpoint. These increases in amylase and lipase were not of clinical relevance. Increases in these enzymes, without accompanying symptoms, are not diagnostic or indicative of any disease state. No other clinically relevant laboratory results were identified within and between treatment groups. A mean increase in heart rate of 2.4 bpm and a mean reduction of 2.4 mm Hg in systolic blood pressure were observed at Treatment Endpoint for exenatide QW-treated patients.

Safety Measure – Hypoglycemia: A total of 3 patients (1 patient taking exenatide QW with MET therapy alone, 1 patient taking insulin glargine with MET therapy alone, and 1 patient taking insulin glargine with MET plus SU therapy) each experienced 1 episode of hypoglycemia that required the assistance of another person as assessed by the Investigator during the Treatment Period. This study site documentation resulted in the classification of these events as major hypoglycemia although none of these events fit the definition of a major hypoglycemia (severe impairment in consciousness or behavior). All 3 episodes resolved with oral carbohydrate administration and did not lead to study discontinuation.

Overall, exenatide QW was associated with a significantly lower incidence/rate of hypoglycemic episodes or symptoms of hypoglycemia than insulin glargine in patients receiving MET therapy alone (non-SU ITT analysis set) and in patients receiving MET plus SU therapy.

The incidence of minor hypoglycemia in patients on MET therapy receiving exenatide QW was 19 patients (3.0% patients; 56 total episodes) and receiving insulin glargine was 63 patients (40.0%; 233 total episodes). The incidence of minor hypoglycemia in patients on MET plus SU therapy receiving exenatide QW was 21 patients (30.0%; 101 total episodes) and in the insulin glargine arm 42 patients (62.7%; 244 total episodes).

Conclusions

- Treatment with exenatide QW significantly improved glycemic control, and was maintained through Week 156. This treatment effect was statistically superior to that of insulin glargine when added to MET therapy alone or in combination with SU.
- Both treatment groups had a significant decrease in FSG from Baseline at all measured timepoints, with insulin glargine having a significantly greater decrease in FSG at Week 156 compared with exenatide QW. This is not unexpected as the insulin glargine dose was titrated to achieve a target FSG level though the study. Exenatide QW significantly reduced postprandial glucose excursion compared to insulin glargine. Therefore, insulin glargine predominately improved fasting glucose, whereas exenatide QW improved both fasting glucose and postprandial glucose excursions.
- Exenatide QW significantly reduced patient body weight, whereas insulin glargine titration was associated with significant progressive weight gain. Overall, exenatide QW was associated with a significantly lower incidence/rate of hypoglycemic episodes or symptoms of hypoglycemia than insulin glargine in patients receiving MET therapy alone and in patients receiving MET plus SU therapy. Additionally, as SUs stimulate insulin release independent of blood glucose levels, patients receiving MET plus SU therapy in either treatment group had a higher incidence/rate of hypoglycemic episodes and symptoms of hypoglycemia (overall) than those using MET therapy alone.
- Nasopharyngitis (24%), headache (15.9%), diarrhea (13.7%), nausea (15.5%), influenza (9.0%), bronchitis (6.0%), arthralgia (7.7%), back pain (7.7%), gastroenteritis (7.7%), urinary tract infection (6.0%), and injection site nodule (6.0%), oropharyngeal pain (5.6%), and hypertension (5.2%), were the most frequently reported TEAEs in the exenatide QW treated patients. Most events were mild in intensity.
- Approximately 70% of exenatide QW-treated patients tested negative for anti-exenatide antibodies at the last study visit and antibody-negative patients had better response in HbA_{1c} than treatment-emergent antibody-positive patients; however, regardless of antibody status, both groups experienced meaningful improvements in HbA_{1c}. Approximately, 31% of treatment-emergent anti-exenatide antibody-positive and 19% of anti-exenatide antibody-negative patients reported at least 1 TEAE potentially related to an immune response. Most of the TEAEs related to the immune response were related to an injection site event (that is, injection site erythema, injection site induration, injection site nodule or injection site reaction). There was no correlation between antibody status and occurrence of TEAEs in the exenatide QW patients.

- The incidence of lipase and amylase values >3 times the upper limit of normal was similar at Baseline and Treatment Endpoint for exenatide QW-treated patients and was not accompanied by symptoms. One case of edematous pancreatitis and a case of pancreatitis acute were observed in this study (patient was taking exenatide QW). Additionally, a case of pancreatitis was reported in a patient treated with insulin glargine. All 3 events were reported as SAEs from which the patients recovered.
- No notably different incidence or type of TEAEs, or hypoglycemia rate was reported at completion of the safety follow up period as compared to the Treatment Endpoint.
- Overall, the 156-week results presented in this report are consistent with those previously reported in the 26-week and 84-week interim reports. Treatment with exenatide QW significantly improved glycemic control and weight control, compared to the insulin glargine treatment. Safety findings at 156 weeks were consistent with those reported at 26 and 84 weeks. Exenatide QW treatment with MET alone or MET with SU was generally safe and well tolerated and provides a safe and effective QW dosing option for treatment of patients with type 2 diabetes.