2. GBDC Synopsis

Clinical Study Report Synopsis: Study H9X-MC-GBDC

Title of Study: The Impact of LY2189265 versus Metformin on Glycemic Control in Early Type 2 Diabetes Mellitus (AWARD-3: Assessment of Weekly AdministRation of LY2189265 in Diabetes-3)

Number of Investigators: This multicenter study included 97 principal investigators.

Study Sites: This study was conducted at 101 study sites in 19 countries.

Publications Based on the Study: None at this time.

Length of Study:	**Phase of Development:** 3
Date first patient enrolled: 24 May 2010 Date last patient completed: 19 June 2012	

Objectives:

The primary objective was to demonstrate the effect of once-weekly LY2189265 (dulaglutide) (1.5 mg) injected subcutaneously, compared to metformin, on glycosylated hemoglobin A1c (HbA1c) change from baseline at 26 weeks in patients with type 2 diabetes mellitus (T2DM). Noninferiority of dulaglutide (1.5 mg) relative to metformin for HbA1c change was demonstrated if the upper bound of the two-sided 95% confidence interval (CI) for dulaglutide minus metformin was below the noninferiority margin of 0.4%.

The following key secondary objectives, analyzed using a sequential tree gate-keeping strategy to control the familywise Type 1 error, compared glycemic control (as measured by change in HbA1c from baseline) between dulaglutide (1.5 mg and 0.75 mg) and metformin:

- to demonstrate that dulaglutide 1.5 mg was superior to metformin at 26 weeks
- to demonstrate that dulaglutide 0.75 mg was noninferior to metformin at 26 weeks
- to demonstrate that dulaglutide 0.75 mg was superior to metformin at 26 weeks

Additional secondary objectives were as follows:

1) to compare the effect of dulaglutide (1.5 mg and 0.75 mg) and metformin with respect to the following at 26 and 52 weeks:
   - HbA1c change (52 weeks) and fasting serum glucose (FSG), as determined by the central laboratory
   - percentage of patients achieving an HbA1c $<7\%$ or $\leq 6.5\%$
   - mean fasting, preprandial, and postprandial self-monitored plasma glucose (SMPG), and mean plasma glucose (PG) values from 8-point SMPG profiles
   - Beta-cell function and insulin sensitivity as estimated by the updated Homeostasis Model Assessment 2 of beta-cell function (HOMA2-%B) and Homeostasis Model Assessment 2 for insulin sensitivity (HOMA2-%S), respectively
2) to compare dulaglutide (1.5 mg and 0.75 mg) and metformin with respect to patient-reported outcomes at 26 and 52 weeks:
   - Impact of Weight on Activities of Daily Living (IW-ADL)
   - Impact of Weight on Self-Perception (IW-SP)
   - Diabetes Treatment Satisfaction Questionnaire (status: DTSQs) and (change: DTSQc)
   - Diabetes Symptoms Checklist–revised (DSC-r)

Objectives (continued):
Additional secondary objectives were as follows:

3) to compare the safety of dulaglutide (1.5 mg and 0.75 mg) versus metformin at 26 and 52 weeks, with respect to the following measures:
   - Cardiovascular (CV) system-related safety: Electrocardiogram (ECG) data, pulse rate, and blood pressure (BP)
   - glycemic-related safety: self-reported hypoglycemic events (rate, incidence, symptomatic, asymptomatic, severe, and nocturnal)
   - lipid panel (cholesterol, high-density lipoprotein cholesterol [HDL-C], low-density lipoprotein cholesterol [LDL-C], triglycerides)
   - immune system-related safety: dulaglutide anti-drug antibody (ADA) production and effect
   - general safety: treatment-emergent adverse events (TEAEs), body weight (kg), body mass index (BMI), and laboratory tests. In this study, body weight and BMI were reported with efficacy measures.
   - pancreatic enzyme monitoring (total and pancreatic amylase and lipase)
   - thyroid monitoring (calcitonin)
4) to characterize the pharmacokinetics (PK) of dulaglutide and the relationship between dulaglutide exposure and safety and efficacy measures

Study Design: This 52-week, Phase 3, multicenter, randomized, parallel-arm, active comparator, double-blind, double-dummy, noninferiority monotherapy study compared glycemic control achieved with 2 doses of dulaglutide (1.5 mg or 0.75 mg once-weekly) or metformin in patients with early T2DM. The study consisted of 3 periods: a lead-in period of approximately 2 weeks, a 52-week treatment period, and a 4-week safety follow-up period. An optional Test Meal Addendum was also part of the study.

Number of Patients:
Planned: 753 randomized
Randomized and Treated: 807 (dulaglutide 1.5 mg: 269; dulaglutide 0.75 mg: 270; metformin: 268)
Completed 26 weeks: 701 patients completed 26 weeks of treatment: dulaglutide 1.5 mg, 233; dulaglutide 0.75 mg, 242; metformin, 226.
Completed 52 weeks: 651 patients completed the treatment period: dulaglutide 1.5 mg, 220; dulaglutide 0.75 mg, 218; metformin, 213.
751 patients completed the follow-up safety visit: dulaglutide 1.5 mg, 249; dulaglutide 0.75 mg, 250; metformin, 252.
Test Meal Addendum: 409 patients participated in the optional Test Meal Addendum: dulaglutide 1.5 mg, 133; dulaglutide 0.75 mg, 136; metformin, 140.

Diagnosis and Main Criteria for Inclusion: Patients who were diagnosed with T2DM for at least 3 months and ≤5 years, with a screening HbA1c ≥6.5% to ≤9.5%, who entered the study not optimally controlled with diet and exercise and either treatment-naïve or on 1 oral antihyperglycemic medication (OAM) (excluding thiazolidinediones). Patients on OAM monotherapy were on a dose ≤50% of the recommended maximum daily dose (per the local label) at Visit 1 for ≥3 months.

Study Drug, Dose, and Mode of Administration: Dulaglutide 1.5 mg or 0.75 mg subcutaneously injected once-weekly.

Comparator, Dose, and Mode of Administration: Metformin given as two 500-mg tablets 2 times daily by mouth (total dose of 2000 mg/day) or three 500-mg tablets (1500 mg/day) as tolerated by the patient.

Duration of Treatment:
Dulaglutide 1.5 mg/week (52 weeks)
Dulaglutide 0.75 mg/week (52 weeks)
Metformin 1500 mg/day or 2000 mg/day (52 weeks)

Variables:
Efficacy:

The primary efficacy measurement in this study was HbA1c change from baseline at 26 weeks, as determined by the central laboratory. Secondary efficacy measures were change in HbA1c, FSG, 8-point SMPG profile, body weight, BMI, beta-cell function and insulin sensitivity as estimated by HOMA2-%B and HOMA2-%S, and percentages of patients achieving HbA1c of <7.0% or ≤6.5%.

Patient-Reported Outcomes: The IW-ADL, IW-SP, DTSQs and DTSQc, and DSC-r were completed by patients at prespecified visits.

Bioanalytical: Human K_3EDTA plasma samples obtained during this study were analyzed for LY2189265, using a validated radioimmunoassay method.

Pharmacokinetic/Pharmacodynamic: Plasma dulaglutide concentrations were determined from blood samples obtained from patients receiving dulaglutide treatment.

Test Meal Addendum: The primary outcome of the Test Meal Addendum was the glucose postprandial area under the curve (AUC) from minute 0 to minute 180 ($AUC_{glucose}$). Additional analyses for the Test Meal included the following: Postprandial AUC from minute 0 to minute 180 for insulin, C-peptide, glucagon, and triglycerides ($AUC_{insulin}$, $AUC_{C\text{-}peptide}$, $AUC_{glucagon}$, and $AUC_{triglycerides}$); incremental AUC from minute 0 to minute 180 of glucose, insulin, C-peptide, glucagon, and triglycerides ($AUCExcursion_{glucose}$, $AUCExcursion_{insulin}$, $AUCExcursion_{C\text{-}peptide}$, $AUCExcursion_{glucagon}$, and $AUCExcursion_{triglycerides}$); indices of beta-cell function: $AUC_{insulin}/AUC_{glucose}$, insulin secretion rate (ISR) at a reference glucose value, potentiation factor ratio, glucose sensitivity, rate sensitivity; and indices of insulin sensitivity: Composite Insulin Sensitivity Index, Oral Glucose Insulin Sensitivity, and Insulin Sensitivity Index-Stumvoll. In addition, laboratory glucose values were summarized at each scheduled time point for the Test Meal Population. Postprandial glucose (PPG) means were calculated and summarized.

Safety: In addition to adverse event (AE) reporting at each study visit following screening, safety was assessed via monitoring of hypoglycemia episodes, collection of laboratory analytes (including lipid panel), ECG monitoring (including QT intervals), samples for immunogenicity (dulaglutide ADAs), discontinuations due to AEs, collection of vital signs (BP and pulse rate), adjudication of all deaths and nonfatal CV events, adjudication of all suspected pancreatitis events, completion of the Skin Evaluation Checklist and Gastroparesis Cardinal Symptom Index , and thyroid monitoring (via calcitonin levels).

Statistical Evaluation Methods:

Statistical: Patients were stratified by country and prior OAM (not on OAM and on OAM prior to study entry). The primary analysis model was analysis of covariance (ANCOVA) for the change from baseline to endpoint, with treatment, country, and prior medication group (not on OAM versus on OAM) as fixed effects, and baseline value as a covariate. Missing endpoints were imputed with the last observation carried forward (LOCF) (for postbaseline values only). If there were no data after the date of randomization, the endpoint was considered missing. The baseline data were not used as an endpoint. The analyses for the primary efficacy measure of HbA1c change from baseline at 26 weeks examined the 4 hypotheses (noninferiority of both dulaglutide groups to metformin, and superiority of both dulaglutide groups to metformin) using a sequential tree gatekeeping strategy to control the familywise Type 1 error rate. The two-sided 95% CI for the least-squares mean (LS mean) difference between dulaglutide 1.5 mg and metformin in HbA1c at Week 26 (dulaglutide minus metformin) was computed from the model.

The secondary analysis for the primary endpoint was a mixed-effects model for repeated measures (MMRM) analysis using restricted maximum likelihood, with treatment, country, prior medication group (not on OAM versus on OAM), visit, treatment by visit interaction as fixed effects, and baseline as a covariate. The Type III sums of squares was used to make the treatment comparisons.

The above ANCOVA and MMRM were based upon the intent to treat (ITT) population to make inferences comparing the dulaglutide dose (1.5 mg or 0.75 mg) to metformin. These analyses were repeated using the per-protocol (PP) population.

To show noninferiority of dulaglutide 1.5 mg to metformin with 90% power, 251 randomized patients per group were required. This calculation assumed a 0 difference in HbA1c change at 26 weeks between the dulaglutide 1.5 mg group and the metformin group, a noninferiority margin of 0.4%, a common SD of 1.3%, a two-sided significance level of 0.05, and an 11% dropout rate at 26 weeks. The rationale to choose an SD of 1.3% was based on historical data and an effort to retain consistency throughout this study program. The required number of completers was 223 per group at 26 weeks; in total, 753 randomized patients were required. If the upper limit of the CI was below 0.4%, the dulaglutide 1.5 mg dose was declared noninferior to metformin.

The actual measurement and change from baseline for FSG, SMPG, fasting insulin concentrations, and beta-cell function as measured by HOMA2-%B and HOMA2-%S were summarized by treatment group and by visit. Changes from baseline for FSG, fasting insulin concentrations, and beta-cell function were analyzed using a repeated-measures model, and changes from baseline for SMPG were analyzed using an ANCOVA model. Both models were similar to that used for the primary efficacy variable, with the covariate being the corresponding baseline value.

For continuous measures, summary statistics included sample size, mean, SD, median, minimum, and maximum for both the actual and the change from baseline measurements. Least-squares means and SEs derived from the model were displayed for the change from baseline. Treatment comparisons were displayed showing the treatment difference (dulaglutide minus metformin) LS mean and the 95% CIs of the treatment differences along with the p-value for the treatment comparison.

For categorical measures, summary statistics included sample size, frequency, and percentages. Unless otherwise noted, a chi-square test was used if at least 80% of cells had an expected number of events no less than 5; otherwise a Fisher's exact test was used. The proportions of patients who had an HbA1c of $<7.0\%$ or $\leq 6.5\%$ were analyzed with a logistic regression model that included country, treatment, and baseline HbA1c.

Patient-Reported Outcomes: The patient-reported outcomes analyses consisted of 4 instruments that were analyzed with models broadly consistent with the overall statistical analysis plan in terms, including fixed effects for treatment, country, prior medication group, and baseline score as a covariate.

Pharmacokinetic/Pharmacodynamic: Population PK analyses were conducted using commonly accepted pharmacostatistical methods (for example, nonlinear mixed-effects modeling) and covariate screening. The relationships between dulaglutide dose and/or concentration and safety measures were examined. Only dulaglutide concentration versus ECG parameters will be reported here; others will be reported on a program level.

Test Meal Addendum: The statistical analyses were based on the Test Meal Population, which was a subset of the ITT population. The primary analysis for the changes from baseline to 26 and 52 weeks for the Test Meal measures was an ANCOVA model with treatment, pooled country within Test Meal Population, prior medication group, and milk factor* as fixed effects, and the baseline value of the dependent variable as a covariate. Analyses were conducted using 2-sided tests and a significance level of 0.05. No multiplicity adjustment was applied. Sensitivity analyses were also conducted.
*A milk factor was added to the Test Meal analysis model to account for a change in the carbohydrate content of the milk provided in the standard Test Meal after study conduct began.
Safety: Safety data were summarized and listed. The ITT population was used for analyses of safety parameters. For most continuous laboratory measurements, an analysis of variance (ANOVA) on rank-transformed data was

used for the changes from baseline, and p-values for the difference between the dulaglutide doses and metformin were reported. For lipid parameters, the ANOVA model above was used to analyze percent changes from baseline. Categorical changes (ie, shift tables) for laboratory parameters were evaluated at the 26- and 52-week visits (LOCF) compared to baseline values (measured at screening) by examining the proportion of patients whose test values were within and outside the reference ranges (low, normal, high); within-treatment shifts were analyzed using McNemar's test, and between-treatment comparisons were performed using a likelihood-ratio chi-square test.

Summary:

- In the ITT population, the mean (SD) HbA1c at baseline was 7.60% (0.87), and mean (SD) duration of T2DM was 2.63 (1.83) years. Mean body weight was 92.3 kg, and mean BMI was 33.3 kg/m^2. Mean seated systolic blood pressure (SBP) was 129.6 mm Hg and mean seated diastolic blood pressure (DBP) was 79.6 mm Hg. The majority (75.1%) of patients were previously treated with an OAM. Overall, demographic and baseline characteristics were comparable between the treatment groups.

- The primary objective of the study was met: dulaglutide 1.5 mg was noninferior to metformin. Least-squares mean changes from baseline in HbA1c to 26 weeks (ITT) were: dulaglutide 1.5 mg, -0.78%; metformin, -0.56%; LS mean treatment difference (95% CI) for dulaglutide minus metformin was -0.22% (-0.36%, -0.08%) (adjusted p-value<0.001 for noninferiority).

- Key secondary objectives of the study were met: dulaglutide 1.5 mg was superior to metformin (adjusted p-value=0.002 for superiority). Dulaglutide 0.75 mg was noninferior to metformin. Least-squares mean changes from baseline in HbA1c to 26 weeks (ITT) were: dulaglutide 0.75 mg, -0.71%; metformin, -0.56%; LS mean treatment difference, -0.15% (adjusted p-value<0.001 for noninferiority). Dulaglutide 0.75 mg was superior to metformin (adjusted p-value=0.020 for superiority).

- Similar results were observed in the PP population (ANCOVA), with the exception that dulaglutide 0.75 mg did not achieve superiority to metformin. Similarly, in the MMRM (ITT) analysis, dulaglutide 0.75 mg did not achieve superiority to metformin.

- At 52 weeks (ITT), using ANCOVA with LOCF, dulaglutide 1.5 mg was superior to metformin, and dulaglutide 0.75 mg was noninferior to metformin in reduction of HbA1c from baseline (LS mean changes from baseline were: dulaglutide 1.5 mg, -0.70%; dulaglutide 0.75 mg, -0.55%; metformin, -0.51%).

- At 26 weeks (ITT, LOCF), the percentages of patients achieving a target HbA1c <7.0% or ≤6.5% were significantly greater in both dulaglutide groups compared to metformin. At 52 weeks (ITT, LOCF), significantly greater percentages of patients had HbA1c decreased to <7.0% or ≤6.5% with dulaglutide 1.5 mg compared to metformin.

- At 26 weeks, no significant differences between dulaglutide and metformin in LS mean decreases from baseline in FSG were observed. At 52 weeks, dulaglutide 1.5 mg demonstrated a significant LS mean decrease from baseline in FSG compared to metformin. At 26 weeks, LS mean decreases from baseline in 8-point SMPG parameters were similar in all treatment groups; the exception was a significant LS mean decrease observed for dulaglutide 1.5 mg compared to metformin in the premorning meal PG. At 52 weeks, the mean of all 8-point, mean of all preprandial, and mean of all postprandial measurements as well as each preprandial measurement and the postmorning meal measurement were significantly decreased with dulaglutide 1.5 mg compared to metformin. No significant differences were observed in comparisons

of dulaglutide 0.75 mg and metformin. No significant differences in decreases from baseline in PPG excursions (for individual meals or the overall mean) were observed between dulaglutide and metformin.

- For HOMA2-%B (insulin) and HOMA2-%B (C-peptide), significant LS mean increases from baseline were observed for both doses of dulaglutide compared to metformin at 26 and 52 weeks, with the greatest increases observed in the dulaglutide 1.5 mg group. For HOMA2-%S (insulin), at 26 and 52 weeks, the LS mean increases for metformin were significantly greater compared with both doses of dulaglutide. Fasting glucagon decreased significantly from baseline in both dulaglutide groups compared with metformin at 26 weeks; no significant difference between the groups was noted at 52 weeks.

- At 26 weeks (ITT), the LS mean changes from baseline (SE) in body weight were -2.29 (0.24) kg for dulaglutide 1.5 mg, -1.36 (0.24) kg for dulaglutide 0.75 mg, and -2.22 (0.24) kg for metformin. At 52 weeks (ITT), the LS mean changes from baseline (SE) in body weight were -1.93 (0.29) kg for dulaglutide 1.5 mg, -1.09 (0.29) kg for dulaglutide 0.75 mg, and -2.20 (0.29) kg for metformin. The differences in LS mean changes from baseline in mean body weight at 26 and 52 weeks for dulaglutide 1.5 mg compared to metformin were not significant. Least-squares mean changes from baseline in mean body weight indicated a significantly greater decrease with metformin compared to dulaglutide 0.75 mg at 26 and 52 weeks. Results for BMI were consistent with the results for body weight.

- As measured by patient-reported outcomes instruments, there was a significant improvement from baseline in the average impact of weight on self-perception, treatment satisfaction, and perceived hyperglycemia at 26 and 52 weeks in all treatment groups. Additionally, a significant improvement in patient-perceived hyperglycemia was observed with both doses of dulaglutide compared to metformin.

- In the Test Meal Addendum analysis, $AUC_{glucose}$ decreased similarly with dulaglutide and metformin at 26 weeks, but $AUCExcursion_{glucose}$ (incremental) decreased significantly more with dulaglutide 1.5 mg compared to metformin. Both dulaglutide doses significantly increased the ratio of $AUC_{insulin}/AUC_{glucose}$ compared to metformin at 26 weeks, indicating an enhancement of insulin secretion induced by dulaglutide. These results were aligned with those of the beta-cell function model estimates, with results for glucose sensitivity and ISR at a fixed glucose concentration supporting the conclusion that dulaglutide enhances the beta-cell dose-response more than metformin does. The effect on beta-cell function was clear with dulaglutide 1.5 mg compared to metformin, and less-marked with dulaglutide 0.75 mg compared to metformin.

- Steady-state plasma concentrations of dulaglutide were evaluated in patients following 4, 13, 26, and 52 weeks of dulaglutide treatment. Dulaglutide plasma concentrations tended to be consistent over time.

- The TEAE profile for dulaglutide in this study was similar to that previously observed in other dulaglutide studies. A majority of patients (65.2%) experienced at least 1 TEAE during the 52-week treatment period; the percentages were similar across the treatment groups at 26 and 52 weeks. Nausea, diarrhea, and vomiting were the most commonly reported TEAEs overall. The only pairwise significant difference between metformin and dulaglutide treatment among these 3 TEAEs was for diarrhea at 26 weeks (metformin significantly more than dulaglutide 0.75 mg). A total of 51 patients reported at least 1 serious adverse event; the incidences were similar among the treatment groups. A total of 33 patients had an AE identified on the AE case report form (CRF) as resulting in discontinuation from the study (dulaglutide 1.5 mg, 14 [5.2%]; dulaglutide 0.75 mg, 8 [3.0%]; and metformin, 11 [4.1%]). One additional metformin-

treated patient was identified on the status CRF as discontinued due to an AE, but did not have an AE identified on the AE CRF as resulting in discontinuation. There were no deaths during the study.

- The incidence of total hypoglycemia (PG ≤70 mg/dL) was low (12%). No significant differences between treatment groups were observed in the incidence or rates of total, documented, or asymptomatic hypoglycemia. No severe hypoglycemic episodes occurred during the study. The incidences and rates of hypoglycemia (PG <54 mg/dL) were negligible in all treatment groups.
- All 3 treatments increased pancreatic amylase, total amylase, and lipase postbaseline; across all 3 enzymes and all treatment groups, the median increases from baseline at 52 weeks were ≤5.50 U/L. The increases in pancreatic amylase and lipase at 26 and 52 weeks and in total amylase at 26 weeks were significant with both doses of dulaglutide compared to metformin. Endpoint median values were within the normal range for all 3 enzymes for all treatment groups. In general, the proportions of patients with pancreatic amylase, total amylase, or lipase shifting to a higher category postbaseline were numerically higher in both dulaglutide groups compared to metformin. The clinical significance of these biochemical changes is unknown. None of the pancreatic events submitted for adjudication resulted in a diagnosis of acute pancreatitis, including 2 reported TEAEs of pancreatitis in the dulaglutide 1.5 mg group.
- No median changes from baseline in serum calcitonin were observed in any treatment group at 26 or 52 weeks, and no significant difference was observed among the 3 treatment groups in the proportions of patients shifting to a higher category postbaseline. Three patients (dulaglutide 1.5 mg, 2; dulaglutide 0.75 mg, 1) met the criteria for retest according to the calcitonin-monitoring algorithm; all showed stable values during follow-up. No patient met the calcitonin algorithm criteria for discontinuation. Other than 2 patients reporting TEAEs of benign neoplasm of the thyroid gland and 1 reporting blood calcitonin increased, no reports of thyroid neoplasm, including C-cell hyperplasia or medullary thyroid carcinoma, occurred during the study.
- No significant differences were observed between treatment groups for any CV event at baseline or postbaseline. Four CV events were adjudicated: 1 in the dulaglutide 1.5 mg group (transient ischemic attack [TIA]), 2 in the dulaglutide 0.75 mg group (1 non Q-wave myocardial infarction [MI] and 1 ischemic stroke), and 1 in the metformin group (TIA). No fatal CV event occurred during the study.
- In general, minimal changes from baseline were observed in triglycerides and total cholesterol with dulaglutide treatment. In pairwise comparison, metformin significantly decreased LDL-C (median percent change from baseline -7.23%) compared to both doses of dulaglutide at 52 weeks. Changes in non-HDL-C at 52 weeks were consistent with changes in LDL-C; the pairwise comparison for non-HDL-C was significant for metformin versus dulaglutide 0.75 mg. All 3 treatments had similar increases from baseline in HDL-C.
- Least-squares mean changes from baseline in SBP and DBP were similar in the dulaglutide and metformin groups at both Weeks 26 and 52. Other than a significant LS mean increase from baseline in pulse rate at Week 4 with dulaglutide 1.5 mg (2.88 bpm) compared to metformin (1.48 bpm) and a significant difference between LS mean changes from baseline in dulaglutide groups and metformin at Week 39 (dulaglutide 1.5 mg, 2.14 bpm; dulaglutide 0.75 mg, 2.97 bpm; and metformin, -0.57 bpm), similar changes between the dulaglutide and metformin groups were noted at Weeks 26 and 52. At Week 52, LS mean changes from baseline in seated pulse rate were dulaglutide 1.5 mg, 1.84 bpm; dulaglutide 0.75 mg, 1.63 bpm; and

metformin, 1.12 bpm. Results for all 3 vital sign parameters (SBP, DBP, and pulse rate) in the supine and standing positions were similar to the results in the seated position.

- Consistent with vital sign findings, LS mean increases in heart rate measured by ECG were observed in all treatment groups at 26 and 52 weeks. Dulaglutide 0.75 mg significantly increased heart rate (2.57 bpm) when compared to metformin (0.82 bpm) at 26 weeks; no other significant between-group differences were observed at 26 or 52 weeks. At 52 weeks, a small but significant LS mean PR interval prolongation was observed with both dulaglutide doses (LS mean change ≤1.5 msec) compared to metformin (LS mean change -2.9 msec); mean endpoint values remained within the normal range for all treatment groups. Small but significant LS mean QT prolongations occurred with dulaglutide 1.5 mg compared to metformin at 26 and 52 weeks (model-based QT, QTcF [Fridericia's correction for QT], and QTcB [QT interval, Bazett's correction for QT]) and with dulaglutide 0.75 mg at 26 weeks (QTcB only). At 52 weeks, LS mean changes from baseline in QTcF were ≤3.8 msec for the dulaglutide groups and -0.5 msec for metformin. No patient had a QTcF >500 msec during the study. The changes in ECG intervals are unlikely to be clinically meaningful.

- In the majority (98.1%) of dulaglutide-treated patients who provided at least 1 postbaseline ADA sample, treatment-emergent (TE) dulaglutide ADAs were not detected at baseline, during treatment, or at follow-up. Ten (1.9%) dulaglutide-treated patients (with no reported prior exposure to a glucagon-like peptide-1 [GLP-1] receptor agonist) developed TE dulaglutide ADAs; 6 of these patients had dulaglutide neutralizing antibodies. All 10 patients were crossreactive to native sequence GLP-1 (nsGLP-1); none developed nsGLP-1 neutralizing antibodies. Review of individual patients' HbA1c values over time for the 10 patients with TE dulaglutide ADAs did not show any unusual pattern. Two patients with TE dulaglutide ADAs reported injection site reactions; both completed the study on study drug. None of the remaining 8 patients with TE dulaglutide ADAs reported injection site reactions on the Skin Evaluation Checklist or had TEAEs suggestive of potentially immune mediated local injection site reactions.

- A total of 20 patients experienced at least 1 TEAE related to injection site reactions. Hematoma was the most common injection site TEAE. At each visit the majority of patients reported no events of pain, pruritus or rash; fewer than 5% of patients reported any event at any single visit. There were no significant between-group differences observed for any item at any visit. The majority of the events were mild in severity; 5 severe events (pruritus, 4; rash, 1) were reported, in a total of 4 dulaglutide 1.5 mg-treated patients. In total, 3 dulaglutide-treated patients with TEAEs of injection site reactions or severe intensity events reported on the Skin Evaluation Checklist discontinued study drug due to AE. Other than 2 patients, no patient with a positive response on the Skin Evaluation Checklist and/or a TEAE of injection site reaction developed TE dulaglutide ADAs.

- With respect to hypersensitivity reactions, a total of 6 patients (dulaglutide 0.75 mg, 3; metformin, 3) experienced at least 1 TEAE of urticaria, and 1 patient (dulaglutide 0.75 mg) experienced a TEAE of lip swelling. The overall comparison between the treatment groups was not significant for either TEAE. None of these patients developed TE dulaglutide ADAs.

Conclusions:

In summary, results from Study H9X-MC-GBDC demonstrated that once-weekly dosing of both dulaglutide 1.5 mg and 0.75 mg was efficacious in improving glycemic control in patients with early stage T2DM. Dulaglutide 1.5 mg was also efficacious in decreasing weight (LS mean change from baseline). The tolerability profile was similar to metformin, with gastrointestinal disorders the most commonly reported TEAEs. Overall, the efficacy and safety results were consistent with prior dulaglutide studies and support the use of dulaglutide in monotherapy in this population of patients with T2DM.