2. GBCF Synopsis

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Clinical Study Report Synopsis: Study H9X-MC-GBCF

Title of Study: A Phase 2/3, Placebo-Controlled, Efficacy and Safety Study of Once-Weekly, Subcutaneous LY2189265 Compared to Sitagliptin in Patients with Type 2 Diabetes Mellitus on Metformin

Number of Investigators: This multicenter study included 120 principal investigators.

Study Centers: This study was conducted at 111 study centers in 12 countries. At 6 study sites, the principal investigator changed one time (a total of 2 principal investigators per site). At 1 study site, the principal investigator changed 3 times (a total of 4 principal investigators at this site).

Publications Based on the Study:

Geiger MJ, Skrivanek ZK, Gaydos BL, Chien YL, Berry SM, Berry DA, Anderson JH Jr. An adaptive, dose-finding, seamless Phase 2/3 study of a long-acting glucagon like peptide 1 analog (dulaglutide): trial design and baseline characteristics. J Diabetes Sci Technol 2012;6(6):1319-1327.

Skrivanek ZK, Berry SM, Berry DA, Chien YL, Geiger MJ, Anderson JH Jr, Gaydos BL. Application of adaptive design methodology in development of a long-acting glucagon-like peptide-1 Analog (dulaglutide): statistical design and simulations. J Diabetes Sci Technol 2012;6(6):1305-1318.

Spencer KA, Colvin KS, Braunecker BG, Brackman MA, Ripley JL, Hines PA, Gaydos BL, Geiger MJ. Operational challenges and solutions with implementation of an adaptive seamless Phase 2/3 study. J Diabetes Sci Technol 2012;6(6):1296-1304.

Length of Study:	**Phase of Development:** 2/3
Date of first patient enrolled: 16 October 2008 Date of last patient completed the study: 06 July 2012	

Objectives: Study H9X-MC-GBCF (GBCF) was a confirmatory dulaglutide trial with a primary objective to compare the effect of LY21289265 (hereafter referred to as dulaglutide) high dose and sitagliptin 100 mg daily with respect to the effect on glycemic control after 12 months in patients with type 2 diabetes mellitus (T2DM) treated with metformin. Additional efficacy and safety assessments of the high and low doses of dulaglutide and sitagliptin continued up to 24 months, the full duration of the study. The first 6 months included a placebo arm to enable a placebo comparison for dulaglutide doses. The trial design also incorporated an initial dose-finding stage to enable selection of 1 or 2 doses of dulaglutide (from the 0.25 to 3.0 mg range) to be assessed in the confirmatory part of the study and the remainder of the Phase 3 program.

Primary Objective: The primary objective of Study GBCF was to demonstrate that the glycemic control of the high dose of dulaglutide selected at the Decision Point is noninferior to that of sitagliptin at 12 months (52 weeks), as measured by glycosylated hemoglobin A1c (HbA1c) change from baseline in patients with T2DM on metformin. The noninferiority margin was 0.25%.

Secondary Objectives: The following objectives further assessed the glycemic control of the selected dulaglutide doses as measured by HbA1c change from baseline. These were part of the testing strategy that strongly controlled Type 1 error rate and included the primary objective:

- To demonstrate that the high dose of dulaglutide was superior to placebo at 6 months
- To demonstrate that the high dose of dulaglutide was superior to sitagliptin at 12 months
- To demonstrate that the low dose of dulaglutide was superior to placebo at 6 months
- To demonstrate that the low dose of dulaglutide was noninferior to sitagliptin at 12 months
- To demonstrate that the low dose of dulaglutide was superior to sitagliptin at 12 months

Additional secondary objectives were:

- To compare the efficacy and safety of the selected dulaglutide doses versus sitagliptin at 12 and 24 months with respect to:
  - fasting plasma glucose (FPG) change from baseline
  - fasting insulin change from baseline
  - body weight (kg) and waist circumference (cm) change from baseline
  - proportion of patients who achieved HbA1c <7% or ≤6.5%

- incidence of hypoglycemic episodes
- beta cell function and insulin sensitivity (updated Homeostasis Model Assessment [HOMA2])
- laboratory tests, lipid parameters (12 months only), treatment-emergent adverse events (TEAEs), vital signs, and electrocardiogram (ECG) parameters
- impact of weight loss on physical functioning, self-esteem, and the overall impact on weight-related quality of life as measured by the patient-reported outcomes' (PRO) questionnaire, Impact of Weight on Quality of Life-Lite (IWQoL-Lite)
- health status as measured by the European Quality of Life-5 Dimensions (EuroQoL [EQ-5D]) PRO questionnaire
- resource utilization (for example, hospitalizations and diabetes-specific emergency room visits)

- To compare the efficacy and safety of all dulaglutide doses versus placebo at 6 months with respect to:
  - HbA1c change from baseline
  - FBG change from baseline
  - body weight (kg) change from baseline
  - incidence of hypoglycemic episodes
  - laboratory tests, TEAEs, vital signs, and ECG parameters
- To assess the durability of glycemic control of the selected dulaglutide doses, compared to sitagliptin, as measured by HbA1c change from baseline
- To assess the durability of change in body weight of the selected dulaglutide doses compared to sitagliptin
- To characterize the pharmacokinetics (PK) of dulaglutide and the relationship between dulaglutide exposure and safety and efficacy measures
- To assess for the development of antibodies to dulaglutide

Study Design: Study GBCF was an adaptive, inferentially seamless, Phase 2/3, outpatient multicenter, randomized, placebo-controlled, 24-month, double-blind, parallel clinical trial comparing once-weekly dulaglutide to once-daily sitagliptin (100 mg) and to placebo in patients with type 2 diabetes on metformin. The treatment period for Study GBCF was 24 months, with database locks at 12 and 24 months. The placebo period lasted up to 6 months.

Number of Patients:
Planned: Up to 400 in adaptive or Stage 1 randomization; up to 1566 overall (total of both adaptive [Stage 1] randomization and fixed allocation [Stage 2] randomization); estimated 80% completers in primary treatment arms (selected: placebo/sitagliptin; sitagliptin; dulaglutide 0.75 mg; and dulaglutide 1.5 mg) at 12 Months.
Randomized: Dose-finding (adaptive randomization): 230; 38 placebo/sitagliptin; 42 sitagliptin; 24 dulaglutide 0.25 mg; 25 dulaglutide 0.5 mg; 21 dulaglutide 0.75 mg; 10 dulaglutide 1.0 mg; 25 dulaglutide 1.5 mg; 30 dulaglutide 2.0 mg, 15 dulaglutide 3.0 mg.
Primary treatment arms (adaptive and fixed-allocation randomization): 1098; 177 placebo/sitagliptin; 315 sitagliptin; 302 dulaglutide 0.75 mg; 304 dulaglutide 1.5 mg.
Primary treatment arms (fixed allocation or Stage 2 randomization only): 972; 139 placebo/sitagliptin; 273 sitagliptin; 281 dulaglutide 0.75 mg; 279 dulaglutide 1.5 mg.
Treated (at least 1 dose): same numbers as randomized.*Completed:* Primary treatment arms at 12 Months: 112 (63.3%) placebo/sitagliptin; 238 (75.6%) sitagliptin; 243 (80.5%) dulaglutide 0.75 mg; 238 (73.8%) dulaglutide 1.5 mg.
Primary treatment arms at 24 Months: 95 (53.7%) placebo/sitagliptin; 186 (59.0%) sitagliptin; 184 (60.9%) dulaglutide 0.75 mg; 192 (63.2%) dulaglutide 1.5 mg.

Diagnosis and Main Criteria for Inclusion: This study enrolled male and female patients 18 to 75 years of age (inclusive) who had had T2DM for ≥6 months; had an HbA1c ≥8.0% to ≤9.5% at screening for diet and exercise-treated patients and ≥7.0% to ≤9.5% for all others ; on a qualifying diabetes therapy of diet and exercise, oral monotherapy or oral combination therapy; had a body mass index (BMI) of 25-40 kg/m^2 (inclusive); had stable weight for ≥3 months prior to entry; did not have a clinically significant gastric emptying abnormality or history of bariatric surgery or use drugs that affect gastrointestinal motility; did not have poorly controlled hypertension; did not have serum creatinine ≥1.5 mg/dL or creatinine clearance <60 mL/min and did not have liver disease.

Study Drug, Dose, and Mode of Administration:
Dulaglutide (0.25, 0.5, 0.75, 1.0, 1.5, 2.0, and 3.0 mg) injected subcutaneously (SC) once weekly and placebo tablet taken orally once daily.
Patients must have been on background metformin therapy (oral daily dose ≥1500 mg/day) from Visit 3 throughout the study.

Reference Therapy/Comparator, Dose, and Mode of Administration:
Active comparator: Sitagliptin 100 mg taken orally once daily and placebo injected SC once weekly .
Placebo: Injected SC once weekly and placebo tablet taken orally once daily.
For patients randomized to the placebo/sitagliptin treatment arm, the placebo tablet was replaced in a blinded fashion with sitagliptin 100 mg taken orally once daily after 6 months.
Patients must have been on background metformin therapy (oral daily dose ≥1500 mg/day) from Visit 3 throughout the study.

Duration of Treatment:
Lead-in period: approximately 4 - 11 weeks
Treatment period: up to 24 months.
Safety period: 30 days after last visit for randomized patients

Variables:
Efficacy: HbA1c, fasting glucose, fasting insulin, beta cell function and insulin sensitivity as estimated by HOMA2.
Safety: Vital signs (blood pressure and pulse rate), ECGs, laboratory tests (chemistry panel, complete blood cell count [CBC], urinalysis, albumin/creatinine ratio, calcitonin, amylase, lipase, and lipids), hypoglycemic events, dulaglutide anti-drug antibody (ADA) titers, adjudicated events of death , non-fatal cardiovascular (CV) events and pancreatitis, TEAEs, discontinuations due to adverse events, body weight/BMI, and waist circumference.
Bioanalytical: Human K_3EDTA plasma samples obtained from patients who received dulaglutide treatment during this study were analyzed to determine dulaglutide concentrations, using a validated radioimmunoassay method.
Pharmacokinetic (PK)/Pharmacodynamic (PD): Dulaglutide PK and concentration-response relationships were analyzed for key safety and efficacy measures such as HbA1c, fasting glucose, body weight, pulse rate, and blood pressure.
Health Outcomes: EQ-5D, IWQoL-Lite, health resource utilization (such as hospitalizations and diabetes-specific emergency room visits).

Efficacy: The primary efficacy measure was change in HbA1c from baseline to 12 months to assess noninferiority of dulaglutide 1.5 mg to sitagliptin (noninferiority margin 0.25%). Key secondary efficacy measures included change in HbA1c from baseline at 6 and 12 months. The analyses for the primary and key secondary objectives comprised 6 ordered hypotheses using a tree-gatekeeping testing strategy to control the family-wise Type 1 error rate. The primary analysis was analysis of covariance (ANCOVA) with fixed effects for treatment, country, and baseline HbA1c as a covariate. Missing endpoints were imputed with the last postbaseline observation carried forward (LOCF). If there were no data after the date of randomization, the endpoint was considered missing. The baseline data was not used as an endpoint. A secondary sensitivity analysis was conducted using a mixed-model for repeated measures (MMRM) model. This model used restricted maximum likelihood (REML), with baseline as a covariate, which implicitly adjusts for missing data through a variance-covariance structure. The Type III sums of squares was used to make the treatment comparisons. Durability of effect of HbA1c was assessed by comparing mean treatment effects between the last visit and prior visits using the above MMRM model. The MMRM described above was used to analyze other continuous measures for efficacy.

Statistical Evaluation Methods:

Efficacy (concluded):

The percent of patients achieving HbA1c goals of ≤6.5% and 7% was summarized by treatment group and analyzed by logistic regression and the Cochran-Mantel-Haenszel test. Sustainability was defined as achieving the goal at some visit during the study and at the last visit. This was also analyzed using logistic regression to assess significance of an overall effect and Cochran-Mantel-Haenszel test for pairwise treatment differences. All analyses were conducted in the Intent-to-Treat population (ITT) population and select efficacy analyses, including the primary analysis, were repeated for the per protocol (PP) population. All analyses were conducted using patients randomized to the primary treatment arms throughout the study and select analyses were repeated for patients randomized using the fixed-allocation strategy (Stage 2 randomization) alone. An adjusted, nominal family-wise 1-sided alpha of .02 was used for the analysis of the primary objective and key secondary objectives, to account for potential selection bias (alpha level of .025, 1-sided). All 4 analysis method and population combinations described above for the primary endpoint were repeated for only patients randomized during Stage 2, with no such adjustment to the nominal-alpha level since in this case there was no potential for selection bias. Select analyses were conducted for Stage 1 alone, summarizing the dose response across all 9 doses.

Safety: Safety analyses were conducted on all patients randomized in the trial (ITT), irrespective of when they were randomized. Continuous safety lab measurements were analyzed with nonparametric methods (ANOVA on ranks, Hodges-Lehmann estimator and confidence intervals based on the Wilcoxon rank sum test). Select safety laboratory measurements were also analyzed by shift tables using a likelihood-ratio chi-squared test. Body weight was analyzed using ANCOVA (LOCF) in addition to MMRM.

For categorical measures, a chi-squared test was used for the treatment comparisons if 80% of cells had an expected value of 5%; otherwise a Fisher's exact test was used for analyses of disposition, TEAEs, and serious adverse events (SAEs). Pairwise comparisons were only assessed when there were at least 5% incidence in at least one treatment arm.

Sample Size: Based on a predictive power calculation, 263 patients per active treatment arm was selected as the minimum total sample size needed (sum of Stage 1 and Stage 2). For comparative purposes, in a traditional fixed design, 263 patients per treatment arm would provide approximately 93% power for a 1-sided 0.025 alpha level test based on a two-sample t-statistic, assuming no true difference, a 20% drop-out rate, a standard deviation (SD) of 1.2%, and a noninferiority margin of 0.25% for HbA1c.

Subgroup: Pre-specified subgroup analyses were conducted for HbA1c change, body weight change, and TEAEs. The analyses of HbA1c and body weight changes were conducted based on the primary analysis model (ANCOVA with LOCF) with an interaction term added for the treatment by subgroup interaction. The subgroup analyses of the TEAEs were conducted using generalized Breslow-Day test.

Health Outcomes: Patient reported outcomes were summarized by treatment group. No inferential statistics were produced.

Pharmacokinetic/Pharmacodynamic: Population PK and PK/PD analyses were conducted using commonly accepted pharmacostatistical methods, and covariate screening. The relationship between dulaglutide dose and/or concentration and safety (such as pulse rate and blood pressure) and efficacy measures (such as HbA1c and fasting glucose) and patient or study factors that may explain the variability in PK or PD responses were evaluated using nonlinear mixed-effects models.

Summary:

Patient Disposition, Patient Demographics, and Other Characteristics

Dose-finding, 9 treatment arms (adaptive randomization, Stage 1): Two hundred and thirty patients were randomized to 9 treatment groups during dose-finding portion until Decision Point. Dulaglutide 3 mg treatment arm was discontinued prior to Decision Point as a result of Data Monitoring Committee (DMC) decision that was based on observed safety risks in this arm. There were no significant differences in disposition of patients between the remaining arms that could have affected dose-finding assessments. The most common reason for discontinuation (85 patients) was sponsor decision, which included all patients who discontinued due to dose decision.

Confirmatory, 4 primary treatment arms (adaptive randomization Stage 1; fixed randomization Stage 2): One thousand and ninety-eight patients were randomized to the primary treatment arms (126 enrolled during Stage 1; 972 enrolled during Stage 2). Proportion of patients who completed the 12-month treatment period was 75.7% with similar discontinuation rate across dulaglutide and sitagliptin arms. Proportion of patients who completed the 24-month treatment period was 59.8% (overall discontinuation rate 40.2%; no differences across the groups). The most common reasons for discontinuation were adverse event and subject decision.

Baseline demographic and clinical characteristics of patients in the primary treatment arms randomized during Stage 1 or 2 and included in the ITT population were balanced across the groups. The mean age was 54.08 years, 52.6% were female, the majority of the patients were Caucasian (51.7%), followed by Hispanic (19.1%), East Asian (16.1%), West Asian [Indian Sub-continent] (8.0%), African (4.0%), and Native American or Aboriginal /Torres Strait Islander (0.1%); the mean duration of diabetes was 7.12 years; the mean body weight was 86.41 kg; the mean BMI was 31.22 kg/m^2; mean baseline HbA1c (8.13%) was similar across treatment groups; vital signs and CV risk characteristics were also similar across the groups. Baseline demographic and clinical characteristics of patients in the ITT population randomized in Stage 1 were similarly balanced across treatment groups.

Dose Decision (Decision Point)

At the 10th interim assessment performed by the Statistical Analysis Center (SAC), the 1.5 mg dose had the highest mean clinical utility index (CUI) and was designated as the maxim utility dose (MUD) based on the combined response measure for efficacy and safety; the 0.75 mg dose met pre-specified requirements for the lower dose, thus, dulaglutide 1.5 mg and 0.75 mg doses were selected, and the trial proceeded with allocation of patients to the primary treatment arms only.

Summary of Efficacy Results

Primary Objective and Secondary Objectives - Effects on HbA1c Change from Baseline:

Dulaglutide 1.5 mg treatment was superior to sitagliptin at 12 months (least squares [LS] mean difference [95% confidence interval (CI)]: -0.71% [-0.88; -0.55]), therefore, the primary objective of noninferiority was met. All secondary objectives for comparisons of dulaglutide doses to comparators were also met. The results of these analyses with ANCOVA (LOCF) were supported by analyses with MMRM and when analyses were conducted with the PP population. These results support dose-decision that predicted superior efficacy of dulaglutide 1.5 mg versus sitagliptin.

Primary and secondary analyses in the ITT and PP population that included only patients randomized during Stage 2 were consistent with the results in the overall population (Stage 1 and Stage 2).

The proportion of patients who achieved HbA1c targets <7% and ≤6.5% in the dulaglutide 1.5 mg treatment arm was significantly greater compared to sitagliptin. These results support the long term efficacy of dulaglutide and support the primary efficacy analysis.

Secondary Objectives – Effect on Plasma Glucose and HOMA2-B(%) and HOMA2-S(%)

Dulaglutide 1.5 mg and dulaglutide 0.75 mg groups had significantly greater decreases in fasting plasma glucose (FPG) versus sitagliptin at 6, 12, and 24 months and versus placebo at 6 months. Dulaglutide 1.5 mg-treated patients who participated in the test meal substudy had lower post-meal glucose exposure compared to sitagliptin-treated patients at 1 and 6 months, and versus placebo-treated patients at 1 month, but not at 6 months. Change from baseline in HOMA2-B(%) was significantly greater with dulaglutide compared to sitagliptin at 6, 12, and 24 months

and versus placebo at 6 months. In general, there were no differences between treatment groups in effects on HOMA2-S(%).

Secondary Objective – Effect on Body Weight

Change from baseline in body weight in patients treated with dulaglutide 1.5 mg were consistently greater compared to sitagliptin up to 24 months (LS Mean difference range -1.14 kg to -1.72 kg) and compared to placebo at 6 months; dulaglutide 0.75 mg treatment was associated with greater decrease in body weight than placebo and sitagliptin, but the magnitude of the between treatment difference was smaller than with dulaglutide 1.5 mg treatment.

PK/PD - Efficacy

Clear dose-exposure-response relationships were well characterized for HbA1c and weight using PK/PD models developed. The model predicted robust HbA1c response to dulaglutide following 0.75 mg dose with an additional ~0.2% reduction following 1.5 mg dose. The model predicted maximum weight loss was achieved following dulaglutide dose at ≥1 mg. Body weight and dose had significant influence on the PK of dulaglutide.

Summary of Safety Results

Treatment-Emergent Adverse Events

There was a significant difference in the overall incidence of TEAEs across treatment groups from postbaseline up to 24 months with a higher incidence of TEAEs among dulaglutide 1.5 mg- (85.2%) and dulaglutide 0.75 mg- (84.4%) compared with sitagliptin-treated patients (76.8%). The incidence of specific gastrointestinal (GI) events (nausea, diarrhea, vomiting, constipation, and abdominal distension) as well as decreased appetite was significantly different among treatment groups and was generally higher among dulaglutide- than sitagliptin-treated patients. Similar results were observed during the placebo-controlled period for comparisons between dulaglutide groups and placebo-treated patients.

Four patients (dulaglutide 1.5 mg: 1; placebo/sitagliptin [during the sitagliptin period]: 1; sitagliptin: 2) died in association with this study. Three of the events leading to death were CV in nature (cardiopulmonary arrest, stroke, sudden death) and the other event was non-cardiac (uterine cancer).

The incidence of SAEs was similar across treatment groups (dulaglutide 1.5 mg, 36 [11.8%]; dulaglutide 0.75 mg, 23 [7.6%]; placebo/sitagliptin, 16 [9.0%]; sitagliptin, 32 [10.2%]) at 24 months. Incidence of SAEs was also similar across treatment groups during the placebo-controlled period.

At 24 months, the incidence of patients who reported an adverse event that led to discontinuation or death was similar across treatment groups (dulaglutide 1.5 mg: 64 [21.1%]; dulaglutide 0.75 mg: 64 [21.2%]; sitagliptin: 67 [21.3%]). The most frequently reported event associated with early discontinuation was hyperglycemia which was reported at an incidence ranging from 9.2% (dulaglutide 1.5 mg) to 15.3% (placebo/sitagliptin). At 6 months, the difference between the groups was significant due to higher incidence of discontinuations due to adverse event in the placebo/sitagliptin arm (13.6%) compared to dulaglutide and sitagliptin treatment groups (4.0-7.2%). This difference was mostly related to higher reporting of the adverse event “hyperglycemia” that resulted in discontinuation, as required by the protocol.

Laboratory Measures

There were no clinically relevant observations with respect to hepatic and renal laboratory analytes. Small median increases in p-amylase, total amylase, and lipase were observed across both dulaglutide treatment groups and

sitagliptin with largest increases in dulaglutide groups (p-amylase: 3-4 U/L; total amylase: 6-7 U/L; lipase: 5-6 U/L) but not with placebo during the placebo-controlled period. The increases were also greater for all treatment groups versus placebo during the placebo-controlled period. Differences were also observed for the incidence of treatment-emergent abnormally high values of lipase and p-amylase, mainly for dulaglutide doses versus the comparators. No significant changes in calcitonin values were observed within or between treatment groups. There were no notable differences between groups regarding patients with treatment-emergent abnormally high calcitonin values.

Vital Signs

Systolic blood pressure decreased for all treatments, with the greatest reductions observed during the first 3 months of treatment (maximum absolute LS mean change -3.9 mm Hg) and thereafter the magnitude of change lessened with values returning to approximately baseline by 24 months. From baseline up to 6 months, there were significant between-treatment differences that were the result of greater reductions in SBP for active treatment arms (dulaglutide, sitagliptin) versus placebo. There were no differences between dulaglutide arms and sitagliptin at this time point, or at the primary (12 months) and the final (24 months) endpoints. No dulaglutide concentration-SBP response relationship was observed. No consistent between-treatment differences were observed over time for change in sitting DBP. No dulaglutide concentration-DBP response relationship was observed.

Beginning at 2 weeks postrandomization, dulaglutide 1.5 mg and dulaglutide 0.75 mg doses were associated with greater increases in pulse rate compared with placebo/sitagliptin during the placebo controlled period and compared with sitagliptin through 24 months. Dulaglutide 1.5 mg increased up to LS mean 3.65 bpm (1 month) and dulaglutide 0.75 mg increased up to LS mean 2.87 bpm (2 months) compared with placebo/sitagliptin (largest LS mean increase during the placebo-controlled period: 0.32 bpm, 0.5 months) and sitagliptin (largest LS mean increase: 0.77 bpm, 2 months). Significant changes in heart rate were observed in the dulaglutide concentration-response relationship.

Electrocardiograms

Greater increases for pulse rate in dulaglutide treatment arms were consistent with greater increase in these arms in ECG-derived heart rate compared to placebo/sitagliptin arm up to 6 months and sitagliptin arm up to 24 months. Dulaglutide 1.5 mg and 0.75 mg groups had numerically greater increases in PR interval than the sitagliptin group at most postbaseline visits (maximum LS mean increase observed for each treatment: dulaglutide 1.5 mg, 4.59 msec; dulaglutide 0.75 mg, 3.68 msec; sitagliptin, 3.19 msec). The greatest change in PR interval for the placebo/sitagliptin arm during the placebo period was at 6 months (end of the placebo period; LS mean 2.24 msec). The incidence of abnormal qualitative ECG findings was higher in the dulaglutide 1.5 mg group compared with sitagliptin at 6, 12, and 24 months and compared to placebo/sitagliptin at 6 months, primarily due to increased incidence of atrioventricular (AV) block (1^{st} degree AV block). No notable changes in QT interval, QRS complex, or ECG rhythms were observed within or between treatments during the study.

Exocrine Pancreas Safety

Three events occurring during the treatment period were declared to be acute pancreatitis by adjudication (placebo/sitagliptin: 1 patient during sitagliptin exposure period; sitagliptin: 2 patients) and 1 event was unable to be adjudicated (suspected chronic pancreatitis in dulaglutide 1.5 mg arm).

Thyroid Safety

One patient (dulaglutide 1.5 mg) reported papillary thyroid cancer during the study. An additional patient who received dulaglutide 2 mg for 6 months was reported with medullary thyroid cancer. Diagnostic workup for this patient was initiated because of a high calcitonin level at discontinuation visit (discontinued due to dulaglutide dose not being selected at Decision Point). Calcitonin value was high (≈9 times > upper limit of normal [ULN]) at baseline and did not increase during the treatment period while the patient was exposed to dulaglutide. The patient was RET proto-oncogene positive.

Dulaglutide Immunogenicity, Hypersensitivity Reactions, and Injection Site Reactions

Nine patients from dulaglutide treatment groups (1.3%) developed TE dulaglutide ADAs during the treatment period. There were no systemic hypersensitivity or potentially immune-mediated injection site AEs reported for patients with TE dulaglutide ADAs. The incidence of patients experiencing hypersensitivity AEs was similar across treatment groups with the exception of dulaglutide 1.5 mg having no reports (dulaglutide 0.75 mg: 5 [1.7%]; placebo/sitagliptin: 2 [1.1%]; sitagliptin: 3 [1.0%]). Eleven (1%) patients across the primary treatment arms reported an injection site reaction. The incidence was balanced across treatment groups.

Gastrointestinal Events

The incidence of nausea with dulaglutide 1.5 mg peaked within the first 2 weeks of treatment (14.8%) and gradually declined through 6 months, after which time the incidence was stable (range across 6- to 24-month: 2.6% to 4.9%). The incidence of nausea for dulaglutide 0.75 mg followed a similar pattern with peak incidence of 8.9% at 2 weeks and incidence of 1.0% to 5.3% between 6 and 24 months. Dulaglutide 1.5 mg and dulaglutide 0.75 mg groups reported an incidence of diarrhea (7.9% and 4.0%, respectively) and vomiting (8.9% and 3.6%, respectively), with peak incidence during the first 2 weeks followed by a decline to stable incidence by approximately 6 months. These GI events were mostly mild or moderate in severity and resulted in discontinuation in ≤3% of patients over the whole observational period.

Cardiovascular Safety

Eighteen patients reported CV events that were adjudicated: dulaglutide 1.5 mg, 6 (2.0%); dulaglutide 0.75 mg, 4 (1.3%); placebo/sitagliptin, 3 (1.7%); sitagliptin, 5 (1.6%).

Hypoglycemia

A total of 100 patients (9.1%) reported hypoglycemic episodes during the study. No episodes of severe hypoglycemia were reported. The overall incidence of total hypoglycemia across treatment groups was similar among the active comparators (dulaglutide 1.5 mg: 12.8%; dulaglutide 0.75 mg: 8.6%; sitagliptin: 8.6%) at 24 months. The mean (SD) 1-year adjusted rate was also comparable across treatment groups (dulaglutide 1.5 mg: 0.3 [1.1]; dulaglutide 0.75 mg: 0.2 [2.0]; sitagliptin: 0.2 [1.4]).

Resource Utilization

At baseline and up to 24 months, there was no difference in the number of patients with ≥1 emergency room (ER) trip or no ER trips within the last 6 months (baseline) or since last visit across treatment groups.

PK/PD - Safety

A significant dose-exposure-response relationship was found for pulse rate and ECG-derived HR, but not for SBP or DBP. The PK/PD model developed to assess the effect of exposure on pancreatic enzymes indicated significant dose-exposure-response relationship for lipase, consistent with the results of analyses of this analyte using datasets from final, locked clinical trial database.

Conclusions:

In summary, the results of this study indicate a favorable benefit/risk profile for dulaglutide 1.5 mg dose (or MUD). Dulaglutide 1.5 mg demonstrated a robust, clinically significant reduction in HbA1c over 2 years, balanced against non-persistent GI events, resulting in an acceptable tolerability profile. The benefit/risk profile of dulaglutide 0.75 mg dose was also acceptable, but the effect of dulaglutide 1.5 mg dose on HbA1c and body weight reduction during the dose-finding stage and continuing through the confirmatory part of the trial was greater and more sustained.