2. GBDB Synopsis

Clinical Study Report Synopsis: Study H9X-MC-GBDB

Title of Study:
A Randomized, Open-Label, Parallel-Arm, Noninferiority Comparison of the Effects of 2 Doses of LY2189265 and Insulin Glargine on Glycemic Control in Patients with Type 2 Diabetes on Stable Doses of Metformin and Glimepiride (AWARD-2: Assessment of Weekly AdministRation of LY2189265 in Diabetes-2)

Number of Investigators:
This multicenter study included 87 principal investigators.

Study Centers:
This study was conducted at 87 study centers in 20 countries.

Publications Based on the Study:
None at this time.

Length of Study:	**Phase of Development:** 3
Date of first patient randomized: 05 May 2010 Date of last patient completed study: 23 November 2012 Planned first patient randomized: 26 May 2010 Planned last patient completed study: 28 November 2012	

Objectives:

The primary objective of this study was to compare the effect of once-weekly dulaglutide 1.5 mg, injected subcutaneously, to that of insulin glargine (titrated to target) on glycosylated hemoglobin (HbA1c) at 52 weeks (change from baseline) in patients with type 2 diabetes mellitus (T2DM) who were taking metformin and glimepiride. Noninferiority of dulaglutide 1.5 mg relative to insulin glargine for HbA1c was demonstrated if the upper bound of the 2-sided 95% confidence interval (CI) for the difference between dulaglutide and insulin glargine was below the margin of noninferiority, 0.4%.

The following key secondary objectives compared glycemic control (as measured by change in HbA1c from baseline) between dulaglutide (1.5 mg and 0.75 mg) and insulin glargine:

- To demonstrate that dulaglutide 0.75 mg was noninferior to insulin glargine at 52 weeks
- To demonstrate that dulaglutide 1.5 mg was superior to insulin glargine at 52 weeks
- To demonstrate that dulaglutide 0.75 mg was superior to insulin glargine at 52 weeks

Additional secondary objectives:

- To compare glycemic control (as measured by change in HbA1c from baseline) between dulaglutide (1.5 mg and 0.75 mg) and insulin glargine:
  - To demonstrate that dulaglutide 1.5 mg was noninferior to insulin glargine at 26 weeks
  - To demonstrate that dulaglutide 0.75 mg was noninferior to insulin glargine at 26 weeks
  - To demonstrate that dulaglutide 1.5 mg was superior to insulin glargine at 26 weeks
  - To demonstrate that dulaglutide 0.75 mg was superior to insulin glargine at 26 weeks
  - To demonstrate that dulaglutide 1.5 mg was noninferior to insulin glargine at 78 weeks
  - To demonstrate that dulaglutide 0.75 mg was noninferior to insulin glargine at 78 weeks
  - To demonstrate that dulaglutide 1.5 mg was superior to insulin glargine at 78 weeks
  - To demonstrate that dulaglutide 0.75 mg was superior to insulin glargine at 78 weeks

- To compare the efficacy of dulaglutide 1.5 mg, dulaglutide 0.75 mg, and insulin glargine with respect to the following at 26, 52, and 78 weeks:
  - Fasting serum glucose (FSG) and glucose values from the 8-point self-monitored plasma glucose (SMPG) profiles (actual values and change from baseline) and percent of patients attaining HbA1c <7% and ≤6.5%
  - Patient-reported outcomes (PROs): EuroQoL 5 dimension (EQ-5D), Impact of Weight on Activities of Daily Living (IW-ADL), Impact of Weight on Self-Perception (IW-SP), and The Low Blood Sugar Survey (LBSS)
- To compare the efficacy of dulaglutide 1.5 mg, dulaglutide 0.75 mg, and insulin glargine with respect to the following at 52 and 78 weeks:
  - Glucagon, the updated Homeostasis Model Assessment of beta-cell function (HOMA2-%B), and the updated Homeostasis Model Assessment of insulin sensitivity (HOMA2-%S) (HOMA2-%B and HOMA2-%S estimated and compared between dulaglutide groups only)
- To compare the safety of dulaglutide 1.5 mg, dulaglutide 0.75 mg, and insulin glargine at 26, 52, and 78 weeks, and at the end of the safety follow-up period, with respect to the following outcomes:
  - Change in body weight and body mass index (BMI) from baseline
  - Cardiovascular (CV) system-related safety: reported and adjudicated CV events, electrocardiogram (ECG) parameters, heart rate (HR), and blood pressure (BP)
  - Pancreas and thyroid gland-related safety: reported and adjudicated events of acute pancreatitis (AP), pancreatic enzymes, and an indicator of thyroid C-cell abnormalities, serum calcitonin
  - Glycemia-related safety: self-reported hypoglycemic events (rate and incidence of documented symptomatic, asymptomatic, severe, nocturnal, and probable symptomatic hypoglycemia), percent of patients requiring additional intervention due to hyperglycemia, and time to initiation of additional intervention due to hyperglycemia
  - Immune system-related safety: dulaglutide anti-drug antibody titer and immune system-related adverse events (AEs)
  - General safety: treatment-emergent adverse events (TEAEs) and laboratory analytes

Study Design:

This multicenter, parallel-arm, randomized, 78-week treatment study was designed to assess the safety and efficacy of dulaglutide in approximately 837 randomized patients with T2DM who entered the study treated with 1, 2, or 3 oral antihyperglycemic medications (OAMs). Following the screening visit, the study consisted of the following periods: a 10-week lead-in period, a 52-week treatment period, a 26-week extended treatment period, and a 4-week safety follow-up period.

Number of Patients:

Planned: 837 Patients
Randomized: 810 Patients (273 dulaglutide 1.5 mg; 272 dulaglutide 0.75 mg; 265 insulin glargine)
Treated (at least 1 dose): 807 Patients (273 dulaglutide 1.5 mg; 272 dulaglutide 0.75 mg; 262 insulin glargine)
Completed: 723 Patients (242 dulaglutide 1.5 mg; 243 dulaglutide 0.75 mg; 238 insulin glargine)

Diagnosis and Main Criteria for Inclusion:

Patients randomized in this study were male and nonpregnant female patients aged ≥18 years that were diagnosed with T2DM not optimally controlled with 1, 2, or 3 OAMs (at least 1 of which must have been metformin or a sulfonylurea). Their Visit 1 HbA1c was to be (a) ≥7% and ≤11% if on OAM monotherapy for 3 months before screening AND on the minimal monotherapy required dose or higher at Visit 1 (metformin 1500 mg; glimepiride 4 mg; for other sulfonylureas, the minimal required dose must have been at least 50% of the recommended

maximum daily dose) OR (b) ≥7 and ≤10% if on 2 or 3 OAMs for 3 months before screening; other allowed OAMs were dipeptidyl peptidase-4 (DPP-IV) inhibitors, thiazolidinediones, glinides and alpha-glucosidase inhibitors. They must also have accepted treatment with metformin and glimepiride throughout the trial, as required per protocol, had stable weight (±5%) for at least 3 months, and had a BMI between 23 kg/m2 and 45 kg/m2, inclusive.

Study Drug, Dose, and Mode of Administration:
Two doses of dulaglutide (1.5 mg and 0.75 mg), given as a once-weekly subcutaneous injection

Comparator, Dose, and Mode of Administration:
Insulin glargine titrated to target, given as a once-daily subcutaneous injection

Duration of Treatment: 78 weeks

Variables:

Efficacy:

The primary efficacy measurement in this study was HbA1c change from baseline at 52 weeks, as determined by the central laboratory. Secondary efficacy measures were change in HbA1c, percentages of patients achieving HbA1c of <7.0% or ≤6.5%, FSG, 8-point SMPG profile, body weight, BMI, beta-cell function and insulin sensitivity as estimated by HOMA2-%B and HOMA2-%S and glucagon.

Safety:

AE reporting, monitoring of hypoglycemia episodes, collection of laboratory analytes (including lipid panel), ECG monitoring (including QT intervals), samples for immunogenicity (dulaglutide antidrug antibody), discontinuations due to AEs, collection of vital signs (BP and pulse rate), adjudication of all deaths and nonfatal CV events, adjudication of all definite or possible pancreatic events, and thyroid monitoring (via calcitonin levels).

Health Outcomes:

The EQ-5D questionnaire, IW-ADL questionnaire, IW-SP questionnaire, LBSS

Statistical Evaluation Methods:

Efficacy:

The primary statistical analysis model was an analysis of covariance (ANCOVA) of the HbA1c change from baseline to primary endpoint at Week 52 with fixed effects of treatment, country, and baseline HbA1c as covariates. Last-observation-carried-forward (LOCF) was used to impute missing postbaseline values. This analysis for the primary efficacy measure of HbA1c change from baseline was based upon the intent-to-treat (ITT) population. Measurements taken after initiation of rescue therapy were excluded. Noninferiority of dulaglutide 1.5 mg relative to insulin glargine for HbA1c was demonstrated if the hypothesis of inferiority at a margin of 0.4% was rejected with a nominal alpha of 0.025, 1 sided. The primary and key secondary objectives of HbA1c change from baseline at 52 weeks (Visit 14) were examined using a gatekeeping strategy to control the family-wise Type 1 error rate at a 1-sided 0.025 level. All p-values used in this testing strategy were 1-sided.

Secondary (sensitivity) analyses of the primary and gated key secondary objectives were conducted in the ITT population with a mixed-model repeated measures (MMRM) model, and in the Week 52 per protocol (PP) population with an ANCOVA on LOCF and with an MMRM model. The MMRM model included fixed effects of treatment, time, treatment-by-time, country, and baseline HbA1c as covariates, and a covariance structure for the measurements within each patient. The same gatekeeping strategy was used.

To show noninferiority of the dulaglutide 1.5 mg arm to insulin glargine with 90% power, 279 patients per arm were required. This calculation assumed a zero difference in HbA1c between the dulaglutide 1.5 mg arm and insulin glargine, 0.40% margin of noninferiority, common standard deviation (SD)=1.3% for HbA1c, 0.05 2-sided significance level, and 20% dropout rate at 52 weeks. The required number of completers was 223 per arm.

Evaluation of HbA1c change from baseline at 26 weeks (Visit 11) and 78 weeks (Visit 16) was performed using the same methodology as at 52 weeks (the same gatekeeping strategy used in the primary analysis was used for these endpoints, as well as the same ANOVA on LOCF and MMRM models in the ITT and PP populations).

The actual measurement and change from baseline for fasting PG, SMPG, fasting insulin, and fasting glucagon concentrations and β-cell function and insulin sensitivity (for endogenous insulin, as measured by the updated Homeostasis Model Assessment [HOMA2], of which HOMA2-%B estimates steady state beta-cell function and HOMA2-%S estimates insulin sensitivity) were summarized at each visit at which the respective measurements were taken. Beta-Cell function and insulin sensitivity estimates were only assessed in the dulaglutide groups, including between-group comparisons. The change from baseline for these measurements was analyzed using a repeated-measures model similar to that used for the primary efficacy variable with the covariate being the corresponding baseline value. The ITT population was used for these efficacy measures. Patients who received rescue medication were included in the ITT population, but only measurements obtained prior to the beginning of rescue therapy were included in these analyses.

Safety:

Safety data were summarized and listed. The safety analyses included the measurements of AEs, serious adverse events (SAEs), hypoglycemic episodes, laboratory analytes, body weight, BMI, vital signs, physical findings, ECGs, and dulaglutide antibody. The ITT population was used for the analyses of the safety measurements. Post-rescue data were not excluded, except in analysis of hypoglycemia episodes.

Health Outcomes:

The analysis of the PRO measures included fixed effects for treatment, country, and baseline score as covariates. The LOCF was used to impute missing postbaseline values; treatment contrasts at 26 weeks, 52 weeks, and 78 weeks were used to assess the primary objective.

Summary:

- Overall demographic and baseline characteristics in the ITT population were comparable between arms. The mean age was 57 years, most patients were White (70.6%), and 51.3% were male. Mean (SD) HbA1c at baseline was 8.14% (0.99%), and the mean (SD) duration of T2DM was 9.10 years (6.04). Mean body weight was 86.3 kg, BMI was 31.6 kg/m2, sitting diastolic blood pressure (DBP) was 78.5 mmHg, sitting systolic blood pressure (SBP) was 131.1 mmHg, and sitting HR was 76.6 beats per minute (bpm). The majority (84.1%) of patients were previously treated with ≥2 OAMs.

- Through Week 52 and Week 78, mean (SD) total overall compliance with study medication was 97.72% (10.95%) and 97.69% (10.92%), respectively. Patients randomized to the insulin glargine arm progressively increased their dose throughout the study (adjusted based on self-monitored FPG per the study protocol), from a starting dose of 10 units to a mean dose of 26.5 units (0.29 units/kg) at Week 26, to 29.8 units (0.33 units/kg) at Week 52, and to 32.1 units (0.35 units/kg) at Week 78. Throughout the treatment period, across all 3 arms, metformin dose was generally stable, whereas mean glimepiride dose progressively decreased; approximately 30% and 34% of patients decreased glimepiride dose and/or discontinued glimepiride by Weeks 52 and 78, respectively.

- The primary objective of the study was met: Dulaglutide 1.5 mg was noninferior to insulin glargine. Least-squares mean (LSmean) changes from baseline to 52 weeks in HbA1c (ITT) were: dulaglutide 1.5 mg, -1.08%; insulin glargine, -0.63%. The LSmean treatment difference (unadjusted 95% CI) for dulaglutide 1.5 mg minus insulin glargine was -0.45% (-0.60%, -0.29%) (adjusted p-value <.001 for noninferiority). Sensitivity analyses supported these results.

- Two of the 3 key secondary objectives were met: Dulaglutide 1.5 mg was superior to insulin glargine (adjusted p-value <.001 for superiority). Dulaglutide 0.75 mg was noninferior to insulin glargine. LSM changes from baseline to 52 weeks in HbA1c (ITT) were: dulaglutide 0.75 mg, -0.76%; insulin glargine, -0.63%; LSmean treatment difference, -0.13% (adjusted p-value<.001 for noninferiority). Dulaglutide 0.75 mg was not superior to insulin glargine (adjusted p-value=.050 for superiority). Sensitivity analyses supported these results.

- At Week 78, dulaglutide 1.5 mg was superior to insulin glargine and dulaglutide 0.75 mg was noninferior to insulin glargine. At Week 26, dulaglutide 1.5 mg was superior to insulin glargine and dulaglutide 0.75 mg was superior to insulin glargine. Sensitivity analyses supported these results.
- At Weeks 52 and 78, significantly greater percentages of patients in the dulaglutide 1.5 mg arm had HbA1c decreased to <7% and ≤6.5% compared to insulin glargine. The comparisons for dulaglutide 0.75 mg to insulin glargine were not significant except for the ≤6.5% target at 52 weeks (more patients reaching target with dulaglutide).
- At Week 52, the decrease of FSG with insulin glargine was significantly greater than with dulaglutide 0.75 mg. At Week 78, the decrease in FSG with insulin glargine was significantly greater than with both dulaglutide doses.
- At Weeks 52 and 78, SMPG measures at all timepoints decreased from baseline in all 3 arms. At Weeks 52 and 78, significantly greater decreases in SMPG were shown at the fasting timepoint (morning premeal) with insulin glargine compared to both dulaglutide doses, while in general, the evening timepoints showed greater decreases with dulaglutide 1.5 mg compared to insulin glargine.
- At Weeks 52 and 78, fasting insulin and HOMA2-%B increased from baseline in both dulaglutide arms, while HOMA2-%S decreased. Dulaglutide and insulin glargine both resulted in significant and similar decreases in fasting glucagon.
- As is typically observed in studies comparing glucagon-like peptide-1 (GLP-1) receptor agonists to insulin glargine, patients in the insulin glargine arm showed an increase in mean body weight and those in the dulaglutide arms showed a decrease, resulting in a mean difference between dulaglutide 1.5 mg and insulin glargine of 3.3 kg at 52 weeks. The difference was less pronounced when comparing dulaglutide 0.75 mg to insulin glargine.
- None of the subgroup analyses indicated a lack of dulaglutide effect in a particular subgroup. The subgroup analyses supported dulaglutide's effect on HbA1c change and weight change in the subgroups considered.
- Consistent with the clinical data, during the treatment period, patients in the dulaglutide 1.5 mg arm experienced significant improvements from baseline in PROs. Mean improvement from baseline was greater with dulaglutide 1.5 mg compared to insulin glargine at Week 78 for the IW-SP, IW-ADL, LBSS worry and behavior scores, and LBSS total score.
- The TEAE profile for dulaglutide in this study was similar to that previously observed in other dulaglutide studies. A majority of patients (72.0%) experienced at least 1 TEAE during the 78-week treatment period; the percentages were similar across the treatment groups. The 3 most frequently reported TEAEs occurring in at least 5% of patients were diarrhea, nausea, and nasopharyngitis. Overall, 239 of the 807 patients (29.6%) in the ITT population experienced at least 1 gastrointestinal (GI) TEAE; the majority were mild in severity. Among GI TEAEs, diarrhea, nausea, dyspepsia, and vomiting were the most frequently reported terms; all were significantly more frequent in dulaglutide arms except for diarrhea. A total of 92 patients (11.4%) reported a total of 111 SAEs; the incidence was similar among the 3 arms. Three deaths occurred during the study; 2 in dulaglutide-treated patients (cardiac failure and respiratory failure) and 1 in an insulin glargine-treated patient (sudden death). At Week 78, 3.1% of patients had discontinued from the study due to an AE or death; this frequency was similar between the 3 arms. Thirty patients (3.7%; all in dulaglutide arms) discontinued the study drug due to an AE; 21 of these 30 patients completed the study and 9 patients later discontinued the study before completion.
- The overall adjusted mean rates of total, documented symptomatic, asymptomatic, nocturnal, and nonnocturnal hypoglycemia (PG≤3.9 mmol/L) were significantly higher for insulin glargine than both dulaglutide arms at 52 and 78 weeks. Through Week 52, the rates of total hypoglycemia were 5.18 events/patient/year with dulaglutide 1.5 mg, 4.82 events/patient/year with dulaglutide 0.75 mg, and 7.86 events/patient/year with insulin glargine. In general, incidences and rates were higher for nonnocturnal versus nocturnal hypoglycemia in all 3 treatment arms. As expected, insulin glargine patients

had relatively higher nocturnal rates than nonnocturnal rates compared to dulaglutide patients. Four events of severe hypoglycemia were reported throughout the treatment period, 2 in the insulin glargine arm and 2 in the dulaglutide 1.5 mg arm, 1 of which occurred in a patient off glimepiride.

- Median p-amylase, total amylase, and lipase increased significantly in both dulaglutide arms compared to insulin glargine at Week 78; at 30 days after last study visit (LV30), pancreatic enzymes were near pretreatment median levels. There were 49 events submitted for pancreatic adjudication, 2 of these events were confirmed as AP and 1 as chronic pancreatitis (all in dulaglutide arms).
- No overall significant differences in calcitonin changes from baseline were observed among the 3 arms. Eight patients reported 9 thyroid-related TEAEs with similar frequency across the 3 arms: 1 patient had an event of thyroid nodules and another event of papillary thyroid carcinoma in the dulaglutide 1.5 mg arm; the patient was discontinued from the study as per protocol. There were no reports of C-cell hyperplasia or medullary thyroid carcinoma throughout the study.
- There were 22 CV events confirmed upon adjudication in 19 patients (4 patients in the dulaglutide 1.5 mg arm, 6 patients in the dulaglutide 0.75 mg arm, and 9 patients in the insulin glargine arm); 20 were nonfatal and 2 were fatal (respiratory failure [insulin glargine] and cardiac failure [dulaglutide 0.75 mg]). A third death (sudden death [insulin glargine]) occurred during the study; this event was adjudicated as death type "Unknown."
- A minimal and persistent increase in mean HR was observed with dulaglutide; the maximal mean increase with dulaglutide 1.5 mg was 2.68 bpm at Week 2; at Week 78, the LSM change from baseline was 1.31 bpm, 0.61 bpm, and 0.91 bpm for dulaglutide 1.5 mg, dulaglutide 0.75 mg, and insulin glargine, respectively. Mean HR returned to baseline levels at LV30. SBP and DBP changes were small and generally similar across the arms. No deleterious impact on lipids or ECGs was observed in any arm.
- Clinical laboratory results for hematology, hepatobiliary, renal, and other clinical chemistries indicated no concern.
- A total of 539 (98.9%) dulaglutide-treated patients were assessed at least once for dulaglutide antidrug antibody postbaseline; the majority of them (97.2%) did not develop treatment-emergent dulaglutide antidrug antibody. Fifteen (2.8%) dulaglutide-treated patients (with no reported prior exposure to a GLP-1 receptor agonist) developed treatment-emergent dulaglutide antidrug antibody; 5 of these patients had dulaglutide-neutralizing antibodies. Four patients were cross-reactive to nsGLP-1; none developed nsGLP-1-neutralizing antibodies. Review of individual patients' HbA1c values over time for the 15 patients with treatment-emergent dulaglutide antidrug antibody did not show any unusual pattern. None of the 15 patients with treatment-emergent dulaglutide antidrug antibody had AEs suggestive of systemic hypersensitivity or TEAEs suggestive of potentially immune-mediated local injection site reactions. None of these 15 patients discontinued the study or the study drug.
- Few patients (0.5%) reported injection site reaction events (all in dulaglutide arms); none were serious or resulted in discontinuation of the study drug or the study.
- There were no reported events of hypersensitivity reactions in Study GBDB.

Conclusions:

While superiority of dulaglutide 1.5 mg versus insulin glargine was statistically demonstrated in this study, it is reasonable to recognize that, with more aggressive insulin glargine dose titration, only noninferiority of dulaglutide 1.5 mg may have been demonstrated. Nonetheless, despite the final insulin glargine doses achieved and the observed HbA1c change from baseline, higher hypoglycemia rates and weight gain were observed with insulin glargine. These results, combined with the overall efficacy, safety, and tolerability data, support the use of dulaglutide to treat patients with T2DM who fail to achieve optimal glycemic control on maximal and stable doses of metformin and glimepiride.