# 2. GBCK Synopsis

# Clinical Study Report Synopsis: Study H9X-MC-GBCK

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| **Title of Study:** Assessment of Dose-Dependent Effects of LY2189265 on Glycemic Control in Patients with Type 2 Diabetes Treated only with Lifestyle Interventions | |
| **Number of Investigators:** This multicenter study included 44 principal investigators. | |
| **Study Centers:** This study was conducted at 44 study centers in 7 countries. | |
| **Publications Based on the Study:** None at this time. | |
| **Length of Study:**<br>Date of first patient visit: 17 November 2008<br>Date of first patient enrolled: 05 January 2009<br>Date of last patient visit: 25 January 2010 | **Phase of Development:** 2 |

**Objectives:** The primary objective was to demonstrate a dose-dependent effect of once-weekly LY2189265 (0.1, 0.5, 1.0, and 1.5 mg) injected subcutaneously on hemoglobin $A_{1c}$ ($HbA_{1c}$) at 12 weeks (change from baseline) in patients with type 2 diabetes mellitus who had discontinued metformin monotherapy or were antihyperglycemic medication-naïve.

In order to assess benefit/risk profile of individual doses of LY2189265 the following secondary objectives were planned:

- To evaluate the dose-dependent effect of LY2189265 (0.1, 0.5, 1.0, and 1.5 mg) on fasting blood glucose as determined by the central laboratory and mean daily self-monitored blood glucose (SMBG) at 12 weeks.
- To compare the LY2189265 (0.1, 0.5, 1.0, and 1.5 mg) and placebo treatment groups with respect to the following at 12 weeks:
  - $HbA_{1c}$ and mean daily blood glucose values from the 7-point SMBG profiles.
  - beta-cell function (HOMA2-B) and insulin sensitivity (HOMA2-S) using the updated Homeostasis Model Assessment (HOMA2).
- To compare the safety of LY2189265 (0.1, 0.5, 1.0, and 1.5 mg) and placebo treatment groups at 12 weeks with respect to the following outcomes:
  - Cardiovascular (CV) system-related safety: electrocardiogram (ECG) data, pulse rate (PR), and blood pressure (BP).
  - Glycemia-related safety: self-reported hypoglycemic events (rate, incidence, symptomatic, asymptomatic, severe, and nocturnal).
  - Immune system-related safety: anti-LY2189265 antibody production and effect.
  - General safety: treatment-emergent adverse events (TEAEs), body weight (kg), and laboratory tests.
- To characterize the pharmacokinetics (PK), potential patient factors that may influence PK of LY2189265, and the relationship between LY2189265 plasma concentration and safety and efficacy measures.

**Study Design:** This was a multicenter, parallel-arm, randomized, 16-week (12 weeks of treatment), double-blind, placebo-controlled study to assess the safety and efficacy of LY2189265 in outpatients with type 2 diabetes mellitus who were antihyperglycemic medication-naïve or had discontinued metformin monotherapy.

Approval Date: 05-Oct-2010 GMT

**Number of Patients**:

Planned: 180 (36 per arm) randomized.

Randomized: 167 patients (0.1 mg LY2189265: 35; 0.5 mg LY2189265: 34; 1.0 mg LY2189265: 34; 1.5 mg LY2189265: 29; 3.0 mg LY2189265: 3; and placebo: 32).

Treated (at least 1 dose): 167 patients (0.1 mg LY2189265: 35; 0.5 mg LY2189265: 34; 1.0 mg LY2189265: 34; 1.5 mg LY2189265: 29; 3.0 mg LY2189265: 3; and placebo: 32).

Completed: 153 completed treatment period (0.1 mg LY2189265: 33; 0.5 mg LY2189265: 31; 1.0 mg LY2189265: 34; 1.5 mg LY2189265: 25; 3.0 mg LY2189265: 0; and placebo: 30), 152 completed safety follow-up period (1 patient in the placebo group was lost to follow-up after the treatment period but before completing the 30-day safety follow-up visit).

**Diagnosis and Main Criteria for Inclusion:** Male and nonpregnant female patients between the ages of 18 to 75 years, previously diagnosed with type 2 diabetes based on the World Health Organization disease diagnostic criteria, with an elevated body mass index (BMI) (patients in South and/or East Asia: between 23 and 40 $kg/m^2$; patients outside of South and/or East Asia: between 25 and 40 $kg/m^2$), who were antihyperglycemic medication-naïve (diet and exercise only) or were taking prestudy metformin monotherapy and willing to discontinue it, had a qualifying $HbA_{1c}$ at screening (antihyperglycemic medication-naïve patients: ≥7.0% to ≤9.5%; prestudy metformin patients: >6.5% to ≤9.0) and following a stabilization/washout period at randomization (all patients: ≥6.5% to ≤9.5%), who had a stable weight and were not taking medications to promote weight loss. Patients were excluded from the study if they were taking specific medications (glucagon-like peptide-1 [GLP-1] analog, incretin mimetic, chronic glucocorticoid therapy, or central nervous system stimulants), had certain known conditions or abnormalities (gastric emptying, cardiovascular conditions, abnormal ECG, poorly controlled hypertension, liver disease, pancreatitis, kidney disease, autoimmune abnormality, active or untreated malignancy, drug or alcohol abuse, or a transplanted organ), or were directly affiliated with the sponsor or investigator site personnel.

**Study Drug, Dose, and Mode of Administration:**

LY2189265 0.1, 0.5, 1.0, and 1.5 mg administered by subcutaneous injection once weekly. Three different injection volumes (0.1, 0.5, and 1.0 mL) of LY2189265 were used in this study. To maintain blinding, volumes corresponding to specific doses were not specified.

**Reference Therapy, Dose, and Mode of Administration:** Placebo administered by subcutaneous injection once weekly. Three different injection volumes (0.1, 0.5, and 1.0 mL) of placebo were used in this study to maintain blinding.

**Duration of Treatment:**

12 weeks.

LY2189265 (0.1, 0.5, 1.0, or 1.5 mg ) once weekly for 12 weeks.

Placebo 3 times weekly during the lead-in period and once weekly for 12 weeks.

**Variables:**

Efficacy: The primary efficacy measure of this study was $HbA_{1c}$ change from baseline at 12 weeks, as determined by the central laboratory. Secondary efficacy measures included $HbA_{1c}$ at 4 weeks and 8 weeks; fasting blood glucose (FBG) measured from the central laboratory; 24-hour, 7-point SMBG profiles (prepandial, 2-hour postprandial, and 2-hour postprandial excursions [the difference between the preprandial and the 2-hour postprandial blood glucose values] from the morning, midday, and evening meals; and FBG obtained the following morning); proportion of patients who achieve $HbA_{1c}$ <7% or ≤6.5%, and HOMA2-B and HOMA2-S.

Safety: CV system-related (ECG data, PR, and BP), glycemia-related (self-reported hypoglycemic events [rate, incidence, symptomatic, asymptomatic, severe, and nocturnal], immune system-related [anti-LY2189265 antibody production and effect], and general (treatment-emergent adverse events [TEAEs], body weight [kg], and laboratory tests) measures of safety were assessed.

Pharmacokinetic/Pharmacodynamic: Plasma levels of LY2189265 in all patients.

**Statistical Evaluation Methods:**

Efficacy: Two analysis models were used for the primary efficacy measurement of $HbA_{1c}$ change from baseline. The primary analysis used a mixed-effects model for repeated measures (MMRM) with restricted maximum likelihood (REML). The second analysis was an analysis of covariance (ANCOVA) on the change from baseline to endpoint at Visit 8 with last-observation-carried-forward (LOCF).

The MMRM, which implicitly adjusts for missing data through a variance-covariance structure, included country, dose, prestudy therapy (metformin yes/no), baseline BMI, visit, and dose-by-visit interaction as the fixed effects, baseline $HbA_{1c}$ as a covariate, and patient as a random effect. For categorical measures, a Fisher's exact test comparing all the treatment groups was used for the treatment comparisons, unless otherwise noted. In addition, a Cochran-Armitage exact trend test for dose response was used.

For continuous measures, treatment arms were compared using an analysis of variance (ANOVA) model with treatment as a fixed effect. Patients from the discontinued 3-mg LY2189265 treatment group (N=3) were included in the MMRM analyses to increase the accuracy of the variance estimate, but the dose was not included in the dose response contrast nor in the summary tables due to the small sample size. Data from this group were also excluded from other statistical analyses and summaries but included in safety listings.

A sample size of 180 randomized patients was planned. Excluding the placebo arm, a planned sample size of 144 completers was determined to achieve a 90% power to detect a linear dose response with 0.60 slope in change from baseline $HbA_{1c}$ for each 1-mg change in dose. With a sample size of 36 patients per treatment group (LY2189265 or placebo), a 0.9% change in $HbA_{1c}$ value could be detected between any LY2189265 treatment group and the placebo treatment group with a power of 80% when standard deviation (SD) equaled 1.2%.

Safety: Unless otherwise noted, all tests of treatment effects and dose-response relationships were assessed at a 2-sided alpha level of 0.05 and confidence intervals (CIs) were calculated at 95%, 2-sided. Statistical analyses of adverse events (AEs) were performed for TEAEs using the Medical Dictionary for Regulatory Activities (MedDRA) system organ class (SOC) and preferred-term levels, unless otherwise specified. A Cochran-Armitage exact test was used to examine a dose response across doses. Analysis of serious adverse events (SAEs) using Fisher's exact test was done if frequency (# of events) in all treatment groups (LY2189265 and placebo) was ≥5. Incidence of hypoglycemia was summarized using frequencies and percentages for each treatment group and visit, as well as overall. Treatment differences in incidence of hypoglycemic episodes were assessed at each visit and overall using Fisher's exact test. Cochran-Armitage exact test was used to examine a dose response across doses at each visit and overall with and without placebo. Descriptive statistics by visit were performed for laboratory analytes. Descriptive statistics for the actual measurements and change from baseline by visit and treatment group for heart rate and systolic and diastolic BP were presented. The analysis for the change from baseline was performed using the MMRM used in the primary analysis. Quantitative ECG parameters (QTcF, HR, RR, QT, PR, and QRS) were reported using descriptive statistics by visit. Analysis of mean change from baseline using the MMRM was performed using the safety population. A listing of the ECG results was presented along with a separate listing of abnormal results. For qualitative ECG data, a report on incidence was generated. Each treatment arm was compared to placebo and all LY2189265 treatment arms combined were compared to placebo using Fisher's exact test.

Bioanalytical: Human plasma samples obtained during this study were analyzed [redacted] in St. Charles, MO, USA. The samples were analyzed for LY2189265 using a validated radioimmunoassay (RIA) method.

Pharmacokinetic/Pharmacodynamic: Population PK analyses were conducted using sparse PK sampling and commonly accepted pharmacostatistical nonlinear mixed effects modeling and covariate screening using NONMEM Version 6. Blood samples were collected during Visits 6, 7, and 8 for population PK analyses using a nonlinear mixed effects modeling approach. The scheduled PK sample window followed a randomized sequence of 1 to 24 hours, 24 to 96 hours, and 120 to 168 hours. The individual LY2189265 concentration listing and the datasets used for the pharmacokinetic/pharmacodynamic (PK/PD) analyses are on file. The PK model was developed using a dataset of all available observations from Study GBCK. The study- or patient-specific factors that were tested as potential covariates on the PK of LY2189265 included dose, gender, age, weight, BMI, and ethnic origins (Caucasian, African American, Hispanic, and Asian).

**Summary:**

- The study population was evenly balanced across treatment groups with respect to demographic and clinical characteristics at entry. At baseline, there was no difference between treatment groups in any of the primary or secondary efficacy or safety measures, and the groups did not differ in exposure and discontinuations.
- The primary analysis demonstrated a statistically significant dose-effect of LY2189265 on $HbA_{1c}$ after 12 weeks of treatment in the ITT population, and similar results were observed in all secondary confirmatory analyses (in the per protocol and BMI 25-40 kg/m² populations). Numerically, the greatest changes in $HbA_{1c}$ change from baseline were at Visit 8 (LS mean changes ±SE) (placebo: 0.01%±.13; 0.1 mg LY: -0.37%±.11; 0.5 mg LY: -.89%±.12; 1.0 mg LY: -1.03%±.11; and 1.5 mg LY: -1.04%±.13). At Visit 8, 71.4% of patients in the 1.5-mg LY2189265 arm and 75.0% in the 1.0-mg LY2189265 arm compared to 21.4% in the placebo arm reached the $HbA_{1c}$ target of <7.0%. At Visit 8, 52.4% of patients in the 1.5-mg LY2189265 arm compared to 7.1% of patients in the placebo arm reached the $HbA_{1c}$ target of ≤6.5%.
- Similar to changes in $HbA_{1c}$, SMBG values (mean premeal BG, mean post prandial BG, and mean postprandial excursion) and FBG measured in the central laboratory showed similar dose response curves across the range of LY2189265 doses.
- The TEAE profile for LY2189265 in Study GBCK is similar to that previously observed in other trials. Gastrointestinal AEs, and in particular, nausea, vomiting, and diarrhea, have been the most frequently reported events for drugs in this class. A total of 4 patients reported an SAE. Of these, 1 patient was diagnosed with hemorrhagic pancreatitis (an adverse event of interest) during Study GBCK in a patient randomized to placebo. No deaths occurred. No patient reported an event related to thyroid safety.
- The incidence of nausea and vomiting over the 12-week treatment period was not statistically different between groups.
- The increases in p-amylase and lipase were observed in all treatment groups after randomization, irrespective of the patients' prerandomization status. A proportion of patients in all treatment groups had increased pancreatic enzymes prior to randomization (at Visit 1 and/or Visit 4). Analysis of change from baseline did not show statistically significant differences between the groups at the endpoint, but the magnitude of change correlated with LY2189265 dose, and the dose-response was statistically significant. However, the LY2189265 concentration-response for change from baseline in lipase throughout the entire treatment period was not statistically significant. A higher proportion of patients in the LY2189265 groups had increases in pancreatic enzyme above the ULN, mostly in lipase and p-amylase. Two of these patients (both randomized to the 1.5-mg LY2189265 arm) had repeatedly increased concentrations of lipase and/or p-amylase above 3 times the ULN but normal CT scans. Categorical summaries as well as shift tables indicate that changes in pancreatic enzyme levels are fluctuating in nature. These biochemical changes did not predict acute pancreatitis or any other adverse event, and their clinical relevance remains unclear.
- Other laboratory tests did not reveal any new clinically relevant or statistically significant finding.
- Assessments of vital signs at endpoint did not show any clinically relevant difference between treatment groups at endpoint.
- Statistically significant increases compared to placebo were observed in the PR interval in 0.1-, 1.0- and 1.5-mg LY2189265 treatment groups (p=.010, p=.045, and p<.001) 2 weeks after the first dose of study drug. This effect was not observed at any other visit, including endpoint. The overall incidence of conduction

abnormalities (including first degree atrioventricular [AV] block) from the descriptive ECG assessment was not statistically different across treatment groups.

- Treatment-emergent anti-LY2189265 antibody (≥4-fold increase) was observed in 1 patient during Study GBCK. There were no reports of local or systemic immunoreactions to LY2189265 in this patient.
- There was a statistically significant linear dose response for LY2189265 without placebo in both body weight and BMI at Visit 6 and Visit 8. There was no statistically significant difference in change from baseline to endpoint in body weight or BMI in all LY2189265 treatment arms compared to placebo at Visit 8.
- The efficacy and safety profile for LY2189265 in Study GBCK is similar to that previously reported. The dose response curve observed in this study supports, in general, the dose decision made in Stage 1 of Study GBCF to further develop 0.75- and 1.5-mg LY2189265 doses in the Phase 3 development program of this compound.

**Conclusions:** The population in Study GBCK was comprised of individuals with early type 2 diabetes mellitus, patients treated with lifestyle measures only or patients on metformin monotherapy. It was expected that patients at this stage of the disease would have partially preserved pancreatic beta cell responsiveness, a position supported by the relatively short mean duration of their diabetes and the mean $HbA_{1c}$ level that was only modestly higher than the standard treatment target of <7% at the end of the lead-in period. Some level of beta-cell responsiveness is important for assessment of efficacy of GLP-1 analogs because their main mechanism of action is improvement of glucose-dependent insulin secretory function of these cells. Since the purpose of Study GBCK was to assess dose-response characteristics in patients taking LY2189265 monotherapy over a range of doses, it was important to include individuals with early type 2 diabetes. The lead-in period was included in the study design to allow patients on metformin monotherapy to discontinue their prestudy therapy and participate in the trial after an appropriate washout and stabilization period. Patients were randomized in a blinded fashion to 5 treatment arms that had similar demographic and clinical characteristics at entry and demonstrated similar patient disposition, study drug compliance and study drug exposure at endpoint.

The primary analysis shows a statistically significant dose-effect of LY2189265 on the change in $HbA_{1c}$ from baseline at the 12-week endpoint in the ITT population ($HbA_{1c}$ LS mean change from baseline [SE]: 0.1 mg LY: -0.37% [.11]; 0.5 mg Ly: -0.89% [.12]; 1.0 mg LY: -1.03% [.11]; and 1.5 mg LY: -1.04% [.13]). Several confirmatory analyses supported the outcome of the primary analysis ($HbA_{1c}$ change in the per protocol and BMI between the 25 and 40 kg populations, and mean daily BG change). The 3 highest LY2189265 doses (0.5 mg, 1.0 mg and 1.5 mg) showed statistically significant greater decrease in $HbA_{1c}$ compared to placebo and compared to the lowest LY2189265 dose (0.1 mg), but these 3 doses were similar in their effect on the primary efficacy measure. The short treatment period (12 weeks), small number of participants per treatment group, and only modestly increased $HbA_{1c}$ at baseline may have contributed to the lack of difference in change in $HbA_{1c}$ between these 3 LY2189265 groups. Although mean $HbA_{1c}$ at baseline was only modestly increased above the target value, a robust decrease in this parameter was observed in the 1.0- and 1.5-mg LY2189265 groups at endpoint, as compared to placebo (LS mean difference versus placebo -1.04% for both groups), resulting in high proportions of patients from these groups reaching $HbA_{1c}$ targets (<7% and ≤6.5%).

As expected, LY2189265 decreased BG from daily BG profile in a dose-dependent fashion. This was observed for fasting BG, combined daily pre-meal BG, and combined daily postprandial BG. The effect on fasting/pre-meal BG was similar to that on postprandial BG in magnitude.

One of the mechanisms of action of LY2189265 is increased glucose-dependent beta cell insulin secretion. Analysis of HOMA2B (%) in Study GBCK supports observations from completed preclinical and clinical studies that showed this effect on the beta cell. As expected, no effect on peripheral glucose utilization was observed.

Overall, TEAEs reported during the trial were similar across treatment groups. Only 4 SAEs were reported. Pancreatitis was defined in the Study protocol as an event of special interest because of previously reported cases of acute pancreatitis in individuals exposed to GLP-1-receptor agonists. One case of pancreatitis was reported as an SAE during the trial. The patient was randomized to the placebo group. Two additional patients developed increased levels of pancreatic enzymes during the study that were repeatedly above 3xULN and underwent CT scans. In both cases, no morphological changes characteristic of pancreatitis were observed. Laboratory abnormalities of pancreatic enzymes improved in both participants with study drug continued and regularly administered. Serial measurements of amylase (total and pancreatic) and lipase indicated that patients on LY2189265 and placebo had frequent increase in levels of these laboratory analytes, although the frequency was higher in the LY2189265 groups, especially in those on higher doses of LY2189265 (1.0 and 1.5 mg). These biochemical changes did not predict acute pancreatitis or any other adverse event, and their clinical relevance remains unclear. Posttreatment follow up (4 weeks after the treatment period) indicated a trend towards decrease in mean concentration of these enzymes in patients treated with LY2189265.

Nausea, vomiting, abdominal pain and diarrhea are typically reported with increased frequency with the use of GLP-1 analogs. In Study GBCK, there was a low incidence of these events during treatment with LY2189265 that was similar to that in the placebo group.

Assessment of vital signs did not show any significant difference between the groups with respect to the blood pressure (systolic or diastolic) or pulse rate. Analyses of ECG-derived HR yielded results similar to the analyses of pulse rate. There was a statistically significant dose response across LY2189265 groups in HR in the first 8 weeks of treatment but not at endpoint. The greatest change in LS mean HR was observed in the 1.5-mg group (≈3.5 bpm difference versus placebo).

Analyses of ECG parameters showed a temporary prolongation of the PR interval at Visit 5 in 3 out of 4 LY2189265 groups versus placebo. No differences between the groups were observed at subsequent visits and at endpoint. The PR interval prolongation at Visit 5 was greatest in the 1.5-mg LY2189265 group and was associated with 2 cases of treatment-emergent first-degree AV block at that visit. At the LOCF endpoint, there were 3 reported cases of first-degree AV block, 2 cases in the 1.0-mg group and 1 case in the 1.5-mg group. No other clinically relevant outcome was reported in relation to this finding. While the mechanism of PR interval prolongation is unclear, one possible explanation may relate to the physiologic compensatory prolongation due to increase in HR that is sometimes described with the use of LY2189265. Modest, temporary PR interval prolongations without obvious clinical relevance were reported in already completed clinical trials with LY2189265. No other relevant CV finding was reported in this trial.

Hypoglycemia risk was low and no difference between the groups was observed. No severe hypoglycemia was reported in Study GBCK.

Body weight change showed expected dose-response across LY2189265 doses without placebo, with maximum effect in the 1.5-mg group of ≈1.5 kg decrease. There was no statistically significant difference between any of the LY2189265 groups and placebo in body weight and BMI because of an unusual, greater than expected mean decrease in body weight in the placebo group. One of the reasons for this outcome were 2 patients in the placebo

group whose body weight decreased 11.3 kg and 11.2 kg, respectively, during the 12-week treatment period (due to acute pancreatitis and non-pharmacological weight-reducing intervention). This was confirmed in the post hoc analysis of body weight changes without outliers (using a standard criterion of >3 stamdard devoatopm [SD] for exclusion of patients).

No thyroid abnormalities were reported in Study GBCK.

The PK/PD models established ($HbA_{1c}$, heart rate, blood pressure and body weight) predicted robust long-term responses of these variables, supporting the 0.75- and 1.5-mg doses selected in Stage 1 of Study GBCF that will be further evaluated in Phase 3 trials.

In conclusion, Study GBCK confirms robust, dose-dependent effect of LY2189265 on $HbA_{1c}$ and daily BG, associated with reduction in body weight in patients on higher doses of this drug (0.5 to 1.5 mg) and low risk of hypoglycemia. These results support the outcome of the dose-decision stage of Study GBCF to further develop 0.75-mg and 1.5-mg LY2189265 doses in Phase 3 development. Although no significant difference between the 0.5-, 1.0- and 1.5-mg LY2189265 groups were observed with respect to change in $HbA_{1c}$ and change in body weight, no conclusion regarding separation of these LY2189265 doses can be made based on this report due to relatively small treatment groups, low baseline $HbA_{1c}$, and short follow-up period. Reported safety findings do not change the already established safety profile of the drug. No new relevant findings were reported with respect to the pancreas, CV system or the thyroid gland.