2. GLBG Synopsis

Clinical Study Report Synopsis: Study I1R-MC-GLBG

Title of Study: A Randomized, Double-Blind, Placebo-Controlled, Phase 2b Study of LY2409021 in Patients with Type 2 Diabetes Mellitus

Number of Investigators: This multicenter study included 44 principal investigators who randomly assigned patients to treatment.

Study Centers: This study was conducted at 44 study centers in 6 countries.

Publications Based on the Study: None at this time.

Length of Study:	**Phase of Development:** 2b
Date of first patient enrolled (entered treatment): 9 March 2011 Date of last patient visit: 19 March 2012	

Objectives:

Primary Objective: To examine the efficacy of LY2409021 administered once daily as monotherapy or in combination with metformin by comparing against placebo the mean change in hemoglobin A1c (HbA1c) from baseline to the end of the 24-week active treatment period.

Secondary Objectives:

- To evaluate the safety and tolerability of oral doses of LY2409021 given once daily for 24 weeks.
- To evaluate and compare the effects of LY2409021 and placebo on blood glucose (fasting and 7-point profile), insulin, glucagon, glucagon-like peptide 1 (GLP-1), and safety parameters.
- To characterize the population pharmacokinetic (PK) and pharmacodynamic (PD) properties of LY2409021 and exploration of covariate correlations.
- To evaluate and compare the effect of LY2409021 and placebo on pancreatic islet beta-cell function by means of the glucose and insulin (Homeostasis Model Assessment B ([HOMA-B]).
- To investigate and compare the effects of LY2409021 and placebo on markers of insulin sensitivity (Homeostasis Model Assessment IR [HOMA-IR]).
- To evaluate and compare the effects of LY2409021 and placebo on blood lipids including total cholesterol (TC), total triglycerides (TG), low-density lipoprotein cholesterol (LDL-C), and high-density lipoprotein cholesterol (HDL-C).
- To evaluate if clinical and serum biomarkers are predictive of the efficacy and safety of LY2409021.

Exploratory Objectives:

- To evaluate if polymorphism of the glucagon receptor (G40S) and type 2 diabetes mellitus (T2DM) risk genes are predictive of the efficacy of LY2409021.
- To evaluate if polymorphism of the G40S and hepatic steatosis risk genes are predictive for liver transaminase elevations with LY2409021.

Study Design: This multicenter, randomized, double-blind, placebo-controlled, 4-arm, parallel-group, fixed-design, outpatient study consisted of a 1-week single-blind placebo lead-in period, a 24-week active treatment period, and a 4-week posttreatment washout period.

Number of Patients:

Planned: 260 (65 patients assigned to placebo and each LY2409021 dose)
Randomized and received at least 1 dose: 263
Evaluable (included in efficacy/safety analyses): 191 LY2409021 (63, 2.5 mg; 64, 10 mg; 64, 20 mg); 63 placebo
Completed: 122 LY2409021 (36, 2.5 mg; 43, 10 mg; 43, 20 mg); 29 placebo

Diagnosis and Main Criteria for Inclusion: Male or female patients with T2DM between 18 and 70 years old, inclusive, treated with diet and exercise alone or in combination with metformin (at least 1000 mg/day stable and unchanged for at least 3 months prior to screening) were eligible for this study. Female patients were not of childbearing potential and males were required to use reliable birth control during and for 3 months after last dose of study drug. Patients were required to have an HbA1c value between 7.0% and 10.5%, inclusive and body mass index (BMI) between 25 and 45 kg/m^2, inclusive. Patients were excluded if they had clinical signs or symptoms of liver disease or liver function tests (LFTs; aspartate aminotransferase [AST] or alanine aminotransferase [ALT]) >2.5 times the upper limit of normal (ULN) as determined by the central laboratory at screening.

Study Drug, Dose, and Mode of Administration:
LY2409021 2.5-mg/day, 10-mg/day, or 20-mg/day doses taken orally once daily as capsules. All patients orally administered 4 capsules per day to achieve the assigned dose: for the 2.5-mg dose, 1 2.5-mg capsule and 3 placebo capsules; for the 10-mg dose, 4 2.5-mg capsules; and for the 20-mg dose, 2 2.5-mg capsules, 1 15-mg capsule, and 1 placebo capsule.

Reference Therapy, Dose, and Mode of Administration: Placebo, taken orally once daily as 4 capsules.

Duration of Treatment: 24 weeks of once daily placebo or LY2409021 (2.5 mg, 10 mg, or 20 mg) preceded by a 1-week placebo lead-in period and followed by a 4-week posttreatment washout period.

Variables:
Efficacy: HbA1c, fasting glucose, 7-point self-monitored blood glucose (SMBG) profile, fasting insulin, fasting GLP-1 (active and total), fasting lipids (TC, TG, LDL-C, HDL-C), lipoprotein subfractions, free fatty acids, indices of insulin sensitivity and beta-cell function (HOMA-B, HOMA-IR, and quantitative insulin sensitivity check index [QUICKI]).
Safety: Adverse events (serious and nonserious), vital signs, electrocardiograms (ECGs), laboratory measures (including glucagon; total amylase, lipase; ALT; AST; gamma-glutamyl transferase (GGT); alkaline phosphatase (ALK); and total, direct, and indirect bilirubin).
Bioanalytical/Pharmacokinetic: Plasma LY2409021 concentrations.
Pharmacogenomics: polymorphism of G40S; methodology and results are presented in an addendum to this report.
Health Outcomes: ENterprising SElective Multi-instrument BLend for hEterogeneity-analysis (ENSEMBLE) battery (administered prior to treatment only).

Statistical Evaluation Methods:
All efficacy analyses, including the primary analyses, were performed on the Modified Intent-to-Treat (MITT) population (all patients randomly assigned to treatment with at least 1 postbaseline measurement), unless otherwise stated. Support for analyses of the MITT population was provided based on analyses using the Per-Protocol population (all patients randomly assigned to treatment who were compliant with study drug and completed the protocol). Safety analyses were performed using the Safety population (all patients randomly assigned to treatment who took at least 1 dose of study medication). An internal assessment committee reviewed an interim analysis of efficacy, safety, and PK data. This committee was unblinded. Members of this assessment committee had no direct contact with study sites.

Sample Size: Approximately 260 patients were planned to be randomized to 1 of 4 treatment arms so that 180 patients would complete the study. Sixty-five randomized patients (45 completers) per arm were expected to provide at least 90% power to detect 0.8% HbA1c difference with placebo assuming a standard deviation (SD) for change in HbA1c of 1.2% (0.05 1-sided type I error). This sample size was also expected to provide an estimated 90% power to exclude a 10% incidence in ALT increases >3xULN assuming the observed rate of 1%.

Efficacy: The primary endpoint for change in HbA1c from baseline (Week 0) to Week 24 was analyzed using mixed-model repeated measures (MMRM). The least-squares (LS) mean differences, 90% confidence interval (CI), and unadjusted p-values (no multiplicity adjustment) were based on a model that included baseline HbA1c as a covariate, metformin use, visit, treatment, and visit by treatment interaction as fixed effects, with variance-covariance structure set to unstructured. Supportive analyses were performed using an analysis of covariance (ANCOVA) model including baseline HbA1c as a covariate and metformin use and treatment as fixed effects in the model. Multiple comparisons were performed using Dunnett's 2-sided adjustment. Analyses of secondary efficacy measures with continuous data were performed using similar statistical models. Analyses of secondary efficacy measures with categorical data were analyzed using a Cochran-Mantel-Haenszel (CMH) test.

Safety: Percentages of patients with ≥2-, ≥3-, and ≥5-fold ULN in ALT; AST; GGT; ALK; and total, direct, and indirect bilirubin were summarized. A change from baseline to each time point analysis was performed. Change from baseline in hepatobiliary analytes was analyzed using MMRM and ANCOVA. For any patient who had ALT values above 3xULN at any postbaseline visit, the time course of the patient's entire ALT profile was plotted. A similar plot was also generated for patients with ALT 2xULN to 3xULN. Treatment-emergent adverse events (TEAEs), vital signs, ECG parameters, and clinical laboratory data were summarized and analyzed using MMRM, ANCOVA, or Fisher's exact test.

Bioanalytical/Pharmacokinetic: A validated liquid chromatography with tandem mass spectrometric (LC-MS/MS) detection method was used for measurement of LY2409021 in plasma samples. A population analysis approach with a nonlinear mixed-effect model (NONMEM) was used to characterize the time course of plasma LY2409021. Pharmacokinetic parameters estimated from the model included first-order absorption rate constant, apparent clearance, and apparent volume of distribution.

Health Outcomes: For prognostic analyses, the summary scores of the ENSEMBLE components were evaluated to relationship with HbA1c. In the subset of placebo-treated patients, each binary ENSEMBLE item was assessed with the primary variable with 2-tailed Wilcoxon rank-sum tests, and all other summary measures were compared with 2-tailed Spearman non-parametric correlation tests AND linear regression models that included ENSEMBLE component score (performed for each summary score). For the latter case, the p-value of the ENSEMBLE component score (2-tailed test) was of interest. For predictive analyses, each ENSEMBLE variable was included in a linear regression analysis (performed for summary score). Each regression utilized an interaction of therapy and ENSEMBLE variable in a model that also included therapy and ENSEMBLE variable as a main effect. The 2-tailed interaction term was the p-value of interest.

Summary and Discussion:

The primary objective of this study was to examine efficacy of 2.5-mg, 10-mg, and 20-mg doses of LY2409021 administered once daily, compared with placebo, as measured by the mean change in HbA1c from baseline to the end of the 24-week active treatment period. Additional goals included determining the margin between efficacy and hepatic safety by evaluating the extent of changes in hepatic aminotransferases at efficacious dose(s) as well as to determine the minimum efficacious dose during 24 weeks of dosing with LY2409021.

A total of 254 patients were randomly assigned to study treatment, received a dose of drug, and were included in efficacy and safety analyses. Most patients (86%) were taking metformin at study entry. Patients had a mean age of 56 years and diabetes duration of 6 years. The mean HbA1c was 8.0% at study entry. Most patients were White in race (91%) and 29% were Hispanic/Latino. Baseline characteristics were similar across treatment groups. Most patients (59%) completed the study. The most common reason for early discontinuation was Sponsor decision (19%). Most of these discontinuations were due to loss of glycemic control at Week 14 when discontinuation criteria became more stringent. This reason for discontinuation was more common in placebo patients (27%) than in patients receiving LY2409021 (22%, 2.5 mg; 19%, 10 mg; 9%, 20 mg).

The primary objective was tested in the MITT population using a MMRM analysis. At Week 24, the LS mean difference between treatments (LY2409021 minus placebo) for the 10 mg group was -0.62% ($p<0.001$) and for the 20 mg group was -0.77% ($p<0.001$). The change in HbA1c for the 2.5 mg group was not statistically significantly different from that of placebo at Week 24. Similar results were observed when the analyses were performed using ANCOVA analyses. When change in HbA1c was analyzed using the Per-Protocol population, the placebo group demonstrated a greater reduction in HbA1c likely due to the exclusion of patients who dropped out due to loss of glucose control. Thus, the placebo-adjusted changes in HbA1c for LY2409021 doses were lower than those observed for the MITT population. Nonetheless, the overall dose-dependent pattern of HbA1c reductions was similar to that of the MITT population.

Secondary efficacy analyses included comparisons of fasting glucose and SMBG profiles. Results of these analyses were similar overall to those of HbA1c with dose-dependent results indicating efficacious responses for 20 mg and 10 mg LY2409021 versus placebo and little effect with 2.5 mg LY2409021.

None of the ENSEMBLE health outcomes measures demonstrated evidence as predictive or prognostic measures for HbA1c change from baseline over 24 weeks.

LY2409021 concentrations observed in this study were consistent with those of previous Phase 1 and Phase 2a clinical studies with LY2409021. Plasma concentrations of LY2409021 reached steady state by 4 weeks of treatment and maintained similar exposures until the end of the 24-week dosing period. LY2409021 plasma concentrations were used to develop a population PK model with 1 compartment and first order absorption of LY2409021. Screening body weight was identified as a covariate on the apparent volume of distribution of LY2409021, where higher body weight led to higher apparent volume of distribution.

The overall safety profile of LY2409021 was similar to that observed in previous studies for LY2409021 with a dose dependency for hepatic aminotransferases and fasting glucagon. While LS mean ALT and AST values increased significantly from baseline compared with placebo in the 20 mg and 10 mg groups, the values reversed either with continued treatment or following cessation of treatment and returned to baseline or near baseline values. A similar pattern was observed for fasting glucagon, which had an approximate 4-fold increase from baseline that plateaued by Week 4 in the 20 mg group.

Individual patients with elevations in ALT and AST that were considered of special interest were reviewed. Nine LY2409021-treated patients (2, 2.5 mg; 4, 10 mg; 3, 20 mg) met prespecified criteria based on laboratory measures. Seven patients had ALT ≥3xULN but <5xULN and total bilirubin <2xULN, 1 patient had ALT ≥5xULN, and 1 patient had AST ≥5xULN. One patient with an ALT ≥3xULN but <5xULN and total bilirubin <2xULN also had an AST ≥5xULN. Importantly, no cases of Hy's law were reported, and individual abnormal aminotransferase values appeared to resolve either during continued treatment or after treatment discontinuation.

The most frequently reported TEAEs were ALT increased (7%), AST increased (5%), and headache (6%). The majority of patients (89%) reporting TEAEs had events rated mild or moderate as their greatest severity. Serious adverse events were reported by 7 patients. Four of these patients received LY2409021: atrial fibrillation (1 patient, 10 mg), AST increased (1 patient, 10 mg; 1 patient, 20 mg), and ALT increased (1 patient, 20 mg).

The frequency of hypoglycemia was low and not different across treatment groups with 17 patients (7%) reporting a total of 20 events. None of the cases was severe. All cases were self-treated with oral carbohydrates, and the lowest reported blood glucose for a hypoglycemic episode was 60 mg/dL.

No pregnancies, cardiovascular events of special interest, nonlocalized skin reactions, or marked abnormalities in vital signs, total amylase, or fasting lipids were observed. Body weight changed by less than 1 kg (LS mean change from baseline) across study visits with LY2409021 treatment.

One patient had a lipase value ≥2xULN, which was not resolved at the time of last report. This patient reported no adverse events (for example, abdominal pain or nausea) that would suggest pancreatitis or compromised pancreatic function.

The 2.5 mg treatment group had a significant increase in Fridericia-corrected QT interval (QTcF) relative to placebo (LS mean change for LY2409021 minus placebo: 7.38 msec). One patient treated with 2.5 mg LY2409021 reported a QTcF change from baseline of 60 msec that returned to baseline during the posttreatment washout. When mean regression lines and 90% CIs were applied to scatterplots of the change from baseline in QTcF and placebo-corrected change from baseline in QTcF versus LY2409021 concentration, the slopes of the lines were not statistically different from zero, suggesting that LY2409021 did not impact QTc over the range of concentrations explored in this study.

Conclusions

- 10-mg and 20-mg once-daily doses of LY2409021 led to statistically and clinically significant reductions in HbA1c and secondary efficacy measures over 24 weeks of treatment without notable weight gain or increased risk for hypoglycemia.
- Dose-dependent elevations in hepatic aminotransferases (mainly ALT and AST) and fasting glucagon were observed with 10-mg and 20-mg doses, but these effects reversed during or following cessation of treatment.
- The safety and efficacy observed in this study are consistent with observations of Phase 1 and Phase 2a studies for LY2409021 and support the continued study of this compound.