2. GMAH Synopsis

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Clinical Study Report Synopsis: Study I2Q-MC-GMAH

Title of Study: A 12-Week, Phase 2, Randomized, Double-Blind, Placebo-Controlled Study of LY2599506 in Patients with Type 2 Diabetes Mellitus Treated with Diet and Exercise, with or without Metformin

Number of Investigators: This multicenter study included 16 principal investigators.

Study Centers: This study was conducted at 16 study centers in 4 countries.

Publications Based on the Study: None at this time

Length of Study:
Date of first patient enrolled: 11 December 2009 (first patient randomized)
Date of last patient completed entire study: Not applicable
Date of early study termination: 14 June 2010

Phase of Development: 2

Objectives: The primary objective of this study was to test the hypothesis that for adult patients with type 2 diabetes mellitus (T2DM) treated with or without metformin, administration of LY2599506 significantly decreases the mean hemoglobin A1c (HbA1c) from baseline to endpoint at 12 weeks compared to placebo.

The secondary objectives of the study were to:

- evaluate the safety and tolerability of LY2599506 in patients with T2DM
- establish the dose-response relationship for change in HbA1c in patients with T2DM administered LY2599506 once daily (QD) or twice daily (BID) with or without metformin
- evaluate the effects of LY2599506 on frequency and severity of hypoglycemia
- evaluate the effects of LY2599506 and placebo on fasting and postprandial glucose
- evaluate the effects of LY2599506 and placebo on insulin sensitivity, glucose clearance, and β-cell function
- evaluate the population pharmacokinetics (PopPK) of LY2599506 and its pharmacodynamic (PD) effects on HbA1c, fasting glucose, fasting insulin, oral glucose tolerance test (OGTT) glucose area under the curve (AUC), and OGTT insulin AUC endpoints
- evaluate the effects of LY2599506 and placebo on fasting lipids and lipoproteins
- evaluate the frequency, extent of dose adjustment, and distribution of doses in the study
- evaluate the effects of LY2599506 and placebo on patient-reported outcomes (e.g., vitality, well-being, hypoglycemia fear, and diabetes-related symptoms)
- evaluate the effects of LY2599506 and placebo on change in body weight from baseline to endpoint

Study Design: Study I2Q-MC-GMAH (GMAH) was a Phase 2, randomized, multicenter, double-blind, placebo-controlled, parallel-design study in patients with T2DM. After initial screening, patients were randomized (randomization ratio of 1.5:1:1:1:1) to placebo or 1 of 4 oral treatments of LY2599506 (50 mg BID, 100 mg BID, 200 mg BID, or 200 mg QD). Randomization of patients was stratified based on concurrent metformin use (yes or no) and HbA1c at Visit 1 (<8.5% or ≥8.5%).

Number of Patients:
Planned: Randomize 120 patients (32 placebo patients and 22 patients in each LY2599506 group) so that 95 patients would complete the study.
Randomized and Treated (at least 1 dose): 78 patients (22 placebo, 12 LY2599506 50 mg BID, 15 LY2599506 100 mg BID, 14 LY2599506 200 mg BID, and 15 LY2599506 200 mg QD)
Completed: 9 patients (5 placebo, 1 LY2599506 50 mg BID, 1 LY2599506 100 mg BID, 1 LY2599506 200 mg BID, and 1 LY2599506 200 mg QD).

Diagnosis and Main Criteria for Inclusion: Male or female patients with T2DM between 18 and 70 years of age, inclusive, treated with diet and exercise alone or in combination with a stable dose of metformin the previous 3 months, with an HbA1c value between 7.0% and 10.0%, inclusive, a body mass index between 20 and 40 kg/m^2, inclusive, and a stable weight for the previous 3 months were eligible for this study.

Test Product, Dose, and Mode of Administration: Combinations of 50 mg and/or 100 mg capsules of LY2599506 were administered orally either QD prior to the morning meal or BID prior to the morning and evening meals to achieve total daily doses of 100 mg, 200 mg, or 400 mg LY2599506.

Reference Therapy, Dose, and Mode of Administration: Placebo was administered orally, BID, as capsules identical in appearance to LY2599506.

Duration of Treatment: 12 weeks
LY2599506 QD or BID: 12 weeks
Placebo BID: 12 weeks

Variables:

Efficacy: Efficacy variables included: HbA1c; fasting glucose; 7-point self-monitored blood glucose (SMBG) profiles; fasting insulin; 75-gram OGTT measuring glucose, insulin, and C-peptide, indices of insulin resistance (IR), insulin sensitivity (%S), and β-cell function (%B) using the Homeostasis Model Assessment (HOMA2) method; and body weight; and adiponectin.

Health Outcomes: Quality of Life (QoL) Assessments: EuroQoL-5 Dimension (EQ-5D); the Diabetes Treatment Satisfaction Questionnaire (DTSQs); the Adult Low Blood Sugar Survey (LBSS-33 Item Scale); the Diabetes Symptom Checklist –Revised (DSC-R).

Pharmacokinetic: PK parameters such as the absorption rate constant (Ka), apparent clearance (CL/F) and apparent volume (V/F) and corresponding intra- and inter-patient variability; dose/response relationship for HbA1c.

Safety: Adverse events (AEs); serious adverse events (SAEs); adverse events of special interest (AESIs) including hypoglycemia, deaths, and non-fatal cardiovascular events (that is, myocardial infarction [MI], hospitalization for unstable angina, and stroke); electrocardiograms (ECGs); heart rate and blood pressure; routine hematology and clinical chemistry tests including lipids, lactate, amylase, and lipase.

Statistical Evaluation Methods: Since the study was terminated and only partial data would be collected, the statistical analysis plan (SAP) was revised prior to database lock because it was thought that the planned endpoint analyses might not provide meaningful statistical interpretations. Therefore, efficacy and safety endpoints were summarized using descriptive statistics by treatment group and study visit. Similarly, last observation carried forward (LOCF) data were only summarized using descriptive statistics by treatment group. This was due to the fact that the LOCF values included measurements from patients discontinuing at different time points during the study, and were therefore difficult to interpret.

Efficacy: Summary statistics (including number of patients, mean, standard deviation [SD], minimum, and maximum) by visit and by treatment group of the raw and change from baseline values were provided for HbA1c, fasting glucose, 7-point SMBG profiles, fasting insulin, and plasma glucose, insulin, and C-peptide from the OGTT, and body weight. The modified intent-to-treat (ITT) population, defined as all randomized patients with at least 1 post-baseline measurement, was used for the analyses.

Pharmacokinetic: A sparse sampling approach was utilized to collect blood samples in this study. The PopPK analysis was conducted using nonlinear mixed effects modeling (using the program NONMEM, version 7). The data from Study GMAH were fit using a 1-compartment model with first-order absorption based on previous PK analyses for this compound (Study I2Q-MC-GMAF). Inter-patient variability was assessed on CL/F and V/F using an exponential error structure. Potentially significant covariates, including body weight, age, gender, and serum creatinine were evaluated individually for influence on the base model. No formal PK/PD modeling was performed. The PK model was used to predict the LY2599506 concentration that was associated with the time of the maximum observed alanine aminotransferase (ALT), and the results were summarized graphically. The time courses of glucose and HbA1c were summarized graphically.

Safety: The ITT population, defined as all randomized patients who received at least dose of study drug, was used for the safety analyses.

Summary: Study GMAH was terminated as a result of evidence that emerged from a nonclinical study suggesting that LY2599506 can induce weak genotoxic effects in the livers of rats ([redacted]). Because the study was terminated early and only partial data was collected, all endpoints were summarized using

descriptive statistics by treatment group and study visit. Similarly, LOCF data were only summarized using descriptive statistics by treatment group.

A total of 78 patients were randomized and received at least 1 dose of study drug, and were included in the ITT population. A total of 9 patients completed the study. The mean age for patients was 57.62 years, and the majority of patients were male (64.1%). Overall, the mean HbA1c value at baseline was 7.86%, and ranged from 7.48% to 8.10% across treatment groups. Approximately 80% of all patients were using metformin at baseline, and patients had been living with a known diagnosis of T2DM for an average of 5.25 years.

Although no statistical comparisons were performed, decreases in mean HbA1c values were observed across all treatment groups (including placebo) from baseline to endpoint (LOCF). Because the study was terminated early, no meaningful conclusions can be made about the effect of LY2599506 treatment on HbA1c.

The population values (inter-patient variability) of CL/F and V/F of LY2599506 were estimated to be 13.9 L/h (39.3%) and 306 L (76.9%), respectively. Moderate to high inter-patient variability in PK was observed. Gender was a statistically significant covariate on CL/F with male patients having approximately a 46% greater CL/F compared to females.

A total of 15 patients were exposed to study drug for 12 weeks; most patients were exposed to study drug for 7 weeks or less.

Overall, 19 patients reported at least 1 treatment-emergent adverse event (TEAE) during treatment with LY2599506; the most frequently reported TEAEs were headache, liver function test abnormal, and nasopharyngitis and were only reported by patients in LY2599506 treatment groups. The majority of TEAEs were mild or moderate in severity. Three SAEs (osteoarthritis [200 mg QD], post-traumatic pain [200 mg QD], and pancreatitis acute [200mg BID]) were reported by 3 patients. All were severe in intensity, and none were considered related to study drug, procedure, or disease. Six patients discontinued due to a TEAE (liver function test abnormal [2 patients], blood glucose increased, acute hepatitis, migraine and osteoarthritis); events of acute hepatitis, migraine, and liver function test abnormal were considered to be related to study drug (LY2599506).

Clinically significant elevations in ALT >3 times the ULN were observed in approximately 14.3% of patients treated with LY2599506 during the study. The relationship between ALT increases and LY2599506 dose amounts was not apparent. A general trend toward a slight increase (<20%) in fasting triglycerides was observed in the LY2599506 treatment groups.

Overall, 19 patients reported 56 episodes of hypoglycemia. Each of the LY2599506 treatment groups had a higher incidence of hypoglycemia compared to the placebo group. Eighteen of 56 patients (32.1%) reported hypoglycemia during treatment with LY2599506 compared to 1 of 22 patients (4.5%) receiving placebo. Hypoglycemia was generally evenly distributed across LY2599506 treatment groups. None of the hypoglycemic episodes were severe.

Conclusions:

- Because the study was terminated early, no meaningful conclusions can be made about the effect of LY2599506 treatment on HbA1c; LY2599506 100 mg BID and LY2599506 200 mg BID regimens appeared to show the most convincing effects on glucose lowering.
- A total of 15 patients completed 12 weeks of treatment and 9 of those completed the entire study. The majority of patients were exposed to study drug for 7 weeks or less. Of patients randomized to a given LY2599506 dose, 52 of 56 patients (92.9%) remained on assigned doses. In the 200 mg BID and 200 mg QD groups, 3 of 14 patients (21.4%) and 1 of 15 patients (6.7%), respectively, required dose reductions as a result of hypoglycemia. No patients in the 50 mg BID or 100 mg BID groups required a reduction in LY2599506 dose due to hypoglycemic episodes.
- Three SAEs (osteoarthritis [200 mg QD], pancreatitis acute [200mg BID], and post-traumatic pain [200 mg QD]) were reported. None of the SAEs was considered to be related to study drug. Six patients discontinued the study due to an AE. Three patients discontinued for events that were considered to be related to study drug (migraine [200 mg BID], and liver function test abnormal [2 patients; 50 mg BID and 200 mg QD]). One patient discontinued for an event considered to be related to study disease (blood glucose increased [placebo]), and 1 patient discontinued for an event that was considered to be related to study drug and disease (hepatitis acute [50 mg BID]).

- A total of 19 of 56 patients (33.9%) patients treated with LY2599506 reported at least 1 TEAE compared to 4 of 22 patients (18.2%) treated with placebo; the most frequently reported TEAEs were headache, liver function test abnormal, and nasopharyngitis, and were only reported by patients in the LY2599506 treatment groups. The majority of TEAEs were of mild or moderate severity.
- Elevations in ALT >3 times the ULN were observed in 8 of 56 (14.3%) patients treated with LY2599506, with no concomitant elevation of bilirubin (>2 times the ULN). The increases in ALT observed during treatment with LY2599506 occurred following 4 to 8 weeks of treatment, returned to normal limits between 4 and 9 weeks of discontinuing study medication, and were not dose-dependent. These elevations in ALT were associated with concomitant increases in AST; however, none met criteria for Hy's law.
- A general trend toward a slight increase (<20%) in fasting triglycerides was observed in the LY2599506 treatment groups. No other clinically relevant changes in clinical laboratory values or vital signs were noted.
- The population mean values (inter-patient variability) of CL/F and V/F of LY2599506 were 13.9 L/h (39.3%) and 306 L (76.9%), respectively. Moderate to high variability in PK was observed. PK was generally consistent with observations from previous studies. Gender was identified as a statistically significant covariate on CL/F with male patients having approximately a 46% greater CL/F compared to females.