2. GMAJ Synopsis

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Clinical Study Report Synopsis: Study I2Q-MC-GMAJ

Title of Study: A 12-Week, Phase 2, Randomized, Double-Blind, Active-Controlled Study of LY2599506 Given as Monotherapy or in Combination with Metformin in Patients with Type 2 Diabetes Mellitus

Number of Investigators: This multicenter study included 14 principal investigators.

Study Centers: This study was conducted at 14 study centers in 6 countries.

Publications Based on the Study: None at this time

Length of Study:
Date of first patient enrolled: 2 March 2010 (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 hemoglobin A1c (HbA1c) from baseline to endpoint at 12 weeks as compared to glyburide.

The secondary objectives of the study were to:

- evaluate the safety and tolerability of LY2599506 in patients with T2DM
- evaluate the effects of LY2599506 and glyburide on frequency and severity of hypoglycemia
- evaluate the effects of LY2599506 and glyburide on fasting and postprandial glucose
- evaluate the effects of LY2599506 and glyburide on insulin sensitivity, glucose clearance, and β-cell function
- evaluate the population pharmacokinetics (PopPK) and pharmacodynamics (PD) of LY2599506 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 glyburide on fasting lipids and lipoproteins
- evaluate the frequency, extent of dose adjustment, and distribution of doses during 12 weeks of treatment for LY2599506 and glyburide
- evaluate the effects of LY2599506 and glyburide on patient-reported outcomes (e.g., vitality, well-being, hypoglycemia fear, and diabetes-related symptoms)
- evaluate the effects of LY2599506 and glyburide on change in body weight from baseline to endpoint

Study Design: Study I2Q-MC-GMAJ (Study GMAJ) was a Phase 2, randomized, multicenter, double-blind, active-controlled, parallel-design study comparing LY2599506 with glyburide in the treatment of patients with T2DM. After initial screening, patients were randomized 1:1 to receive either LY2599506 or glyburide given orally, twice daily (BID), at doses individually titrated to achieve pre-specified glycemic targets. Patients were stratified at randomization based on screening HbA1c (<8.5% or ≥8.5) and prior sulfonylurea use (yes or no). Patients treated with metformin prior to the study were allowed to continue their stable dose of metformin throughout the study.

Number of Patients:
Planned: Randomize 192 patients so that 154 patients (77 LY2599506 and 77 glyburide) completed the study.
Randomized and Treated (at least 1 dose): 38 patients (16 LY2599506, 22 glyburide)
Completed: No patients completed the study due to the sponsor's decision to terminate the study early.

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 diet and exercise in combination with a stable dose of metformin, or diet and exercise in combination with a stable dose of sulfonylurea, or diet and exercise in combination with stable doses of metformin and sulfonylurea having had diabetes for at least 6 years, with an HbA1c value between 7.0% and 10.0%, inclusive, a body mass index between 20 and 40 kg/m^2, inclusive, and stable weight for the previous 3 months were eligible for this study.

Test Product, Dose, and Mode of Administration:
Combinations of 50 or 100 mg capsules of LY2599506 or matching placebo capsules were administered orally in escalating doses up to 800 mg/day. Doses were expected to range from 50 mg to 400 mg administered BID prior to morning and evening meals.

Reference Therapy, Dose, and Mode of Administration: 2.5 mg capsules of glyburide or matching placebo capsules were given orally in escalating doses up to 20 mg/day to achieve BID doses of 2.5 mg, 5 mg, 7.5 mg, or 10 mg, administered prior to morning and evening meals.

Duration of Treatment:
Total: 12 weeks
LY2599506 BID: 12 weeks
Glyburide BID: 12 weeks

Variables:

Efficacy: Efficacy variables included: HbA1c; fasting blood glucose concentration; 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; body weight; and adiponectin.

Health Outcomes: Quality of Life (QoL) Assessments: EuroQoL-5 Dimension (EQ-5D); the Diabetes Treatment Satisfaction Questionnaire (DTSQ); the Adult Low Blood Sugar Survey (LBSS-33 Item Scale); the Diabetes Symptom Checklist –Revised (DSC-R); and the Perceptions about Medications in Diabetes-21 items (PAM-D21).

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; exploratory plots for fasting blood glucose and 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 blood 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 postbaseline measurement, was used for the analyses.

Pharmacokinetic: A sparse sampling approach was utilized to collect blood samples in this study. PopPK analyses were performed using nonlinear mixed effects modeling (using the program NONMEM, version 7). The data from Study GMAJ were fit using a 1-compartment model with first order absorption based on previous PK analyses for this compound. Inter-patient variability was assessed on CL/F and V/F using an exponential error structure. The estimate for Ka was fixed to the population value from Study I2Q-MC GMAH (GMAH) due to the limited data available in the current study. Gender was previously identified as a potential covariate in Study GMAH and the estimate of the influence of gender on CL/F was fixed to the population value from Study GMAH. 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. Time courses of fasting plasma glucose (FPG) and HbA1c, and the 7-point SMBG profiles were summarized graphically.

Safety: The ITT population, defined as all randomized patients who received at least 1 dose of study drug, was used for the safety analyses.

Summary: Study GMAJ 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 38 patients (16 LY2599506; 22 glyburide) were randomized and received at least 1 dose of study drug and were included in the ITT population. No patients completed the study. The mean age for patients was 59.54 years and the majority of patients were male (65.8%). Baseline HbA1c values were comparable between treatment groups (7.90% and 7.78% for the LY2599506 and glyburide groups, respectively). None of the patients were taking a sulfonylurea at baseline, and patients had been living with a known diagnosis of T2DM for an average of approximately 7 years.
LY2599506 appeared to lower glucose effectively and the use of a titration design appeared to minimize the risk of hypoglycemia observed during the study. No severe hypoglycemia episodes were reported.
The population mean values (inter-patient variability) of CL/F and V/F of LY2599506 were estimated to be 23.2 L/h (46.1%) and 431 L (71.3%), respectively. Moderate to high inter-patient variability in PK was observed.
One patient (glyburide) completed 12 weeks of treatment. The majority of patients in both treatment groups were exposed to study drug for ≤4 weeks.
Overall, the incidence of treatment-emergent adverse events (TEAEs) was slightly higher in the LY2599506 group than the glyburide group, with 5 (31.3%) patients in the LY2599506 group and 5 (22.7%) patients in the glyburide group reporting at least 1 TEAE. The most frequently reported TEAE was headache (2 patients, 5.3%). One patient (LY2599506) reported an SAE (acute hepatitis) during the study. The event was moderate in severity, and considered by the investigator to be related to study drug. There were no deaths or discontinuations due to AEs during the study.
Elevations of alanine aminotransferase ≥3 times the ULN were noted in 3 of the 16 patients (18.8%) treated with LY2599506. Alanine aminotransferase elevations occurred within 6 to 8 weeks of treatment and resolved upon discontinuation of study drug. None of these cases met the criteria of Hy's law. The LY2599506 group had slight decreases from baseline to endpoint in all cholesterol parameters assessed, and a <20% increase in fasting triglycerides from baseline to endpoint.
A total of 12 patients (3 LY2599056, 9 glyburide) reported at least 1 hypoglycemic episode; none of the episodes were severe.

Conclusions:

- Because the study was terminated early, no meaningful conclusions can be made about the effect of LY2599506 treatment on HbA1c; however, LY2599506 appeared to lower glucose effectively.
- One patient (glyburide) completed 12 weeks of treatment. The majority of patients in both treatment groups were exposed to study drug for ≤4 weeks. Prior to discontinuation, 12 of 16 patients (75%) treated with LY2599506 were receiving a total daily dose of 400 mg or less; in the glyburide group, 15 of 22 patients (68.2%) received a total daily dose of 10 mg or less.
- One serious adverse event (acute hepatitis) was reported by a patient treated with LY2599506 and was considered to be related to study drug. No patients discontinued due to an AE.
- The incidence of TEAEs was slightly higher in the LY2599506 group than the glyburide group, with 5 (31.3%) patients in the LY2599506 group and 5 (22.7%) patients in the glyburide reporting at least 1 TEAE; the most frequent TEAE was headache. All TEAEs were mild or moderated in severity.
- The incidence of hypoglycemia was lower during treatment with LY2599506: 3 (18.8%) patients reported hypoglycemia compared to 9 (40.9%) patients reporting hypoglycemia during treatment with glyburide. No episodes of severe hypoglycemia were noted.
- Elevations of alanine aminotransferase ≥3 times the ULN were noted in 3 of the 16 patients (18.8%) treated with LY2599506, with no concomitant elevation in bilirubin. Serum cholesterol levels decreased over the course of the study for patients in the LY2599506 group and a <20% increase in fasting triglycerides was observed. 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 23.2 L/hr (46.1%) and 431 L (71.3%), respectively. Moderate to high variability in PK was observed. Pharmacokinetics were generally consistent with observations from previous studies.