2. BIAC Synopsis

Approval Date: 09-Jan-2012 GMT

Clinical Study Report Synopsis: Study 12R-MC-BIAC

Title of Study: A Phase 2 Study of LY2605541 Compared with Insulin Glargine in the Treatment of Type 2 Diabetes Mellitus

Number of Investigators: This multicenter study included 31 principal investigators.

Study Centers: This study was conducted at 31 study centers in 7 countries.

Publications Based on the Study: None at this time.

Length of Study:
Date of first patient enrolled: 02 Feb 2010
Date of last patient completed: 10 Jan 2011

Phase of Development: 2

Objectives:

The primary objective of Study BIAC was to test the hypothesis that in patients with type 2 diabetes mellitus (T2DM) who were treated with basal insulin and continuing their prestudy therapeutic regimen of oral antihyperglycemic medications (OAMs), LY2605541 injected once daily in the morning would result in lower fasting blood glucose (FBG) levels at endpoint compared with insulin glargine injected once daily in the morning for up to 12 weeks.

The secondary objectives of the study were as follows:

- To compare the change from baseline of FBG levels at endpoint between LY2605541 and insulin glargine.
- To assess the 2 LY2605541 dose algorithms.
- To assess the safety and tolerability of LY2605541, including generation of antibodies to LY2605541.
- To compare the proportion of patients experiencing hypoglycemia and the rate of hypoglycemia, adjusted per 30 days, between LY2605541 and insulin glargine.
- To compare the 8-point self-monitored blood glucose (SMBG) profiles (blood glucose [BG] measurements before and 2 hours after the start of the morning, midday, and evening meals, at bedtime, and at 0300 hours) between LY2605541 and insulin glargine.
- To characterize within-patient and between-patient variability of FBG for patients receiving LY2605541.
- To compare the baseline to endpoint change in hemoglobin A_{1c} (HbA_{1c}) (to assess glycemic control) between LY2605541 and insulin glargine.
- To compare the daily basal insulin dose between LY2605541 and insulin glargine.
- To evaluate the pharmacokinetics (PK) of LY2605541 after multiple doses in patients with T2DM.

Some exploratory objectives of the study were:

- To compare the absolute body weight from baseline to endpoint between LY2605541 and insulin glargine.
- To evaluate the specified health outcomes instruments with regard to expected effect size changes and correlation to clinical outcomes for potential use in future studies.

Study Design: Study BIAC was a Phase 2, multicenter, multinational, open-label, randomized, 3-arm, parallel, outpatient study comparing 2 different dosing algorithms of LY2605541 to insulin glargine in patients with T2DM.

Number of Patients:
Planned Number to be Screened: 434
Randomized: 289 Total, 93 insulin glargine, 98 LY2605541 Algorithm 1, 98 LY2605541 Algorithm 2
Treated (at least 1 dose): 288 Total, 93 insulin glargine, 98 LY2605541 Algorithm 1, 97 LY2605541 Algorithm 2
Completed: 267Total, 91 insulin glargine, 85 LY2605541 Algorithm 1, 91 LY2605541 Algorithm 2

Diagnosis and Main Criteria for Inclusion: Male or female patients with type 2 diabetes who were at least 18 years of age and had an $HbA_{1c} \leq 10.5\%$; a body mass index (BMI) between 19 and 45 kg/m^2, inclusive; and had been treated with metformin and/or a sulfonylurea in combination with once daily neutral protamine Hagedorn (NPH) insulin or insulin glargine for at least 3 months could be considered for participation in this study.

Test Product Dose, and Mode of Administration:
LY2605541 was administered subcutaneously (SC) once daily in the morning (at approximately the same time each morning prior to breakfast) using a syringe with needle. Doses were adjusted using 1 of 2 dosing algorithms based on the patient's BG.

Reference Therapy, Dose, and Mode of Administration:
Insulin glargine was administered SC once daily in the morning (at approximately the same time each morning prior to breakfast) using a syringe with needle. The dose was adjusted using a dosing algorithm based on the patient's BG levels. Insulin glargine was administered in accordance with the product labeling for each patient's country.

Concomitant Therapy, Dose and Mode of Administration:
The patient's prestudy OAMs (metformin and/or sulfonylurea) were administered in accordance with the product labeling for the country in which treatment occurred. Regardless of the insulin arm they were assigned to, patients had to continue to use their stable prestudy dosage regimen for the OAM(s) throughout the study.

Duration of Treatment:
Screening to randomization: Up to 5 weeks
Treatment period: 12 weeks
Follow-up: 4 weeks following completion of treatment

Variables:
Efficacy: 8-point SMBG profiles with measures prior to and 2 hours after each meal, at bedtime, and at 0300 hours (fasting BG at endpoint was the primary measure); FBG by laboratory; HbA_{1c}; and daily basal insulin dose.
Safety: Hypoglycemic episodes, adverse events (treatment emergent [TEAEs] and serious [SAEs]), vital signs (systolic blood pressure, diastolic blood pressure, pulse rate), body weight, laboratory measures, LY2605541 antibody titers.
Health Outcomes: Insulin Treatment Satisfaction Questionnaire, Diabetes Symptom Checklist – revised, and Adult Low Blood Sugar Survey
Pharmacokinetics/Pharmacodynamics (PK/PD): LY2605541 concentration in blood, FBG from laboratory sample.

Statistical Evaluation Methods:

Statistical:

Assuming a randomization ratio of 1:1:1 (LY2605541 Dosing Algorithm 1: LY2605541 Dosing Algorithm 2: insulin glargine), a mean difference of 1.0 mmol/L, and a standard deviation of 2.45 mmol/L, 240 completers (80 completers in each treatment arm) would provide 90% of statistical power to detect a significant difference in fasting glucose between insulin glargine and the pooled LY2605541 arms. This power estimation was based on a 2-sample t-test at alpha = 0.10. For all efficacy and safety analyses, patients from the 2 LY2605541 dosing algorithms were pooled such that the LY2605541 group was compared to the insulin glargine group.

All statistical analyses were based on a slightly modified intent-to-treat principle (full analysis set). All randomized patients taking at least 1 dose of randomized study medication were included in the full analysis set.

Primary Analysis:

The primary efficacy measure was FBG, as measured by the 8-point SMBG profiles at study endpoint for the full analysis set. FBG was summarized and analyzed using a Mixed-Effect Model Repeated Measure (MMRM) approach. The model included fixed effects of treatment (LY2605541 Algorithm 1, LY2605541 Algorithm 2, insulin glargine); conversion (pre-interim analysis [IA], post-IA); stratification variables (country, baseline daily basal insulin dose group, and baseline HbA_{1C} group); visit; interaction between visit and treatment; and a random effect for patient.

Additional analyses were completed for the primary analysis that accounted for baseline differences in the model. Therefore, the model included fixed effects for treatment (LY2605541 Algorithm 1, LY2605541 Algorithm 2, insulin glargine); conversion (pre-IA, post-IA); stratification variables (country, baseline daily basal insulin dose group, and baseline HbA_{1C} group); baseline fasting blood glucose; visit; interaction between visit and treatment; and a random effect for patient.

Originally, only summarization was planned for FBG by laboratory. As a result of a request by the FDA, the lab measured FBG was analyzed in the same manner as the primary endpoint to support the primary analysis.

Secondary Analyses:

The secondary continuous variables with repeated measures were analyzed for the full analysis set using a MMRM model similar to the one described for the primary analysis.

Unless otherwise specified, these variables were compared at baseline, each visit, and change from baseline to each visit.

The following secondary categorical variables were analyzed using logistic regression to ensure the results of the analyses were not biased due to the conversion change, since the guidance on the initial conversion to LY2605541 was changed after the IA:

- Proportion of patients with HbA_{1C} <7.0% at endpoint (last observation carried forward [LOCF])
- Proportion of patients with HbA_{1C} ≤6.5% at endpoint (LOCF)

The model included treatment (LY2605541 Algorithm 1, LY2605541 Algorithm 2, insulin glargine) as the fixed effect and conversion (pre-IA, post-IA) as strata.

Health Outcomes:

Specific health outcome instruments were evaluated with regard to expected effect size changes and correlation to clinical outcomes for potential use in future studies. The health outcome scores with repeated measures were summarized and analyzed using an analysis of covariance (ANCOVA) model, with the following fixed effects: treatment (LY2605541 Algorithm 1, LY2605541 Algorithm 2, insulin glargine); stratification variables (country, baseline daily basal insulin dose group, and baseline HbA_{1C} group); and a covariate for baseline of the score of interest.

Pharmacokinetics/Pharmacodynamics (PK/PD):

A PK/PD model that links concentrations to fasting and SMBG glucose was used to link dosing algorithms to changes in glucose.

Summary:

- Of the 350 patients who entered the study, 289 were randomly assigned to treatment, 288 received at least one dose of study drug, 267 (92.7%) completed the study, and 21 (7.3%) did not complete the study. The reasons for early discontinuation were: physician decision 6 (2.1%), protocol violation 4 (1.4%), subject decision 5 (1.7%), adverse event 4 (1.4%), and sponsor decision 2 (0.7%), none of which were statistically significant when comparing patients treated with insulin glargine with patients treated with LY2605541.
- The mean patient age was 59.5 years, with the majority of patients (72.2%) being <65 years old. The majority of patients were white (93.1%); 46.9% were female, and 53.1% were male. The mean body weight at baseline was 90.25 kg, and the mean BMI was 32.04 kg/m^2. The mean waist circumference was 106.3 cm, mean hip circumference was 110.5 cm, and the mean waist to hip ratio was 0.96. The mean HbA_{1C} at baseline was 7.77%, with 75.7% of patients having an HbA_{1C} ≤8.5% and 24.3% of patients having an HbA_{1C} >8.5%. The mean duration of diabetes was 11.9 years; 62.4% of patients were taking a daily basal insulin dose ≤0.4 U/kg, and 37.6% were taking a daily basal insulin dose >0.4 u/kg. There were no statistically significant differences in demographics at baseline when comparing the insulin glargine group with the combined LY2605541 group.
- The primary objective of the study was to test the hypothesis that LY2605541 could be titrated to achieve a superior lowering of fasting blood glucose (as measured by SMBG) at endpoint compared with insulin glargine when both were administered before breakfast to patients with T2DM previously treated with basal insulin (NPH or insulin glargine). This study failed to prove this hypothesis and furthermore showed similar overall glycemic control as assessed by HbA_{1C}, fasting glucose (as measured by laboratory), and mean daily blood glucose as measured by 8-point SMBG profile.
- Seven patients reported SAEs during the treatment period: 5 (2.6%) patients treated with LY2605541 and 2 (2.2%) patients treated with insulin glargine. In addition, 2 patients reported SAEs during the follow-up period. None of the SAEs was considered by the investigators to be related to study drug, study procedure, or study device. Fifteen patients reported TEAEs that were considered by the investigators to be possibly related to study drug: 13 (6.7%) in the LY2605541 combined group and 2 (2.2%) in the insulin glargine group. There were no statistically significant differences between the LY2605541 combined group and the insulin glargine group in the percentage of patients reporting TEAEs for any system organ class or overall. Four patients treated with LY2605541 discontinued due to the following adverse events: non-severe hypoglycemia, VIIth nerve paralysis, injection site reaction, and myocardial ischemia.

Conclusions:

In patients with T2DM previously treated with basal insulin in combination with metformin and/or sulfonylurea, morning administration of LY2605541 compared with insulin glargine, in combination with these oral antihyperglycemic medications, was well tolerated and resulted in:

- no statistically significant difference between the combined LY2605541 treatment groups and insulin glargine for fasting blood glucose at endpoint (Week 12).
- A statistically significant lower mean BG for LY2605541 Algorithm 2 compared with insulin glargine at the morning postmeal and mid-day premeal time points. When the analysis was adjusted for baseline, significantly lower mean BG was observed for several time points during the 8-point profile with the individual LY2605541 algorithms or the combined LY2605541 treatment groups.
- lower nocturnal hypoglycemia rate when adjusting for baseline despite similar overall hypoglycemia rate for the combined LY2605541 treatment groups compared with insulin glargine. As an ultra-long-acting basal insulin, LY2605541 did not increase the risk of severe or protracted hypoglycemia.

- no difference between the LY2605541 combined treatment groups and insulin glargine in the change from baseline to 12 weeks for HbA_{1c}.
- less within-patient glycemic variability for LY2605541 combined treatment groups than for insulin glargine.
- mean increases in alanine aminotransferase and aspartate aminotransferase for patients treated with LY2605541 with the observed mean values remaining within the normal range.
- Triglycerides were similar at baseline for LY2605541 and insulin glargine treatment groups and did not change significantly from baseline to any postbaseline time point for either treatment group. However, at Week 12, the mean triglyceride level was significantly higher for patients treated with LY2605541 than for patients treated with insulin glargine. LDL-C and HDL-C did not change significantly from baseline to any postbaseline time point for either treatment and the levels were similar for both treatments at Week 12.
- no statistically significant differences in TEAEs or SAEs between LY2605541 and insulin glargine.
- no deaths during the study.
- Based on similar endpoint (Week 12) glycemic control between groups, endpoint insulin doses (in nmol/kg) were used to refine estimates of relative potency of LY2605541 and insulin glargine. When adjustments were made for HbA1c at endpoint, FBG(SMBG) from the week preceding endpoint, and FBG(Lab) at endpoint, these adjustments yielded similar estimates of equipotent doses of LY2605541 to insulin glargine (approximately 1.5:1 on a molar basis).
- no apparent immunogenicity differences between LY2605541 and insulin glargine after 12 weeks of therapy.

The typical value of clearance after accounting for bioavailability was 2.02 L/hr, which was much lower than hepatic blood flow (81 L/hr), indicating low extraction across the liver. No significant covariates were identified.