2. CLINICAL STUDY SYNOPSIS

Name of Company: Eli Lilly and Company
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Name of Active Ingredient(s): LY2428757

Title of Study: A 12-Week, Double-Blind, Placebo-Controlled Trial of LY2428757 in Patients with Type 2 Diabetes Mellitus

Protocol Number: I1I-MC-GECD

Study Period:
Phase of Development: 2
Date of first enrollment: 09 Dec 2008
Date of last completed: 14 Jan 2010

Investigator(s): Health and research centers.

Study Center(s): 60 active sites (i.e., sites that enrolled at least 1 patient) in 11 countries.

Publication(s): None.

Objectives:

Primary Objective

To test the hypothesis that once-weekly injections of LY2428757 given to patients with type 2 diabetes mellitus (T2DM) inadequately controlled with diet and exercise alone, or metformin monotherapy, produces a significant decrease in the mean hemoglobin A1c (HbA1c), defined as glycosylated fraction of haemoglobin A, from baseline to endpoint at 12 weeks as compared to placebo.

Secondary Objectives

- To evaluate the safety and tolerability of LY2428757 given once-weekly for 12 weeks in patients with T2DM.
- To evaluate and compare the percentage of patients requiring study discontinuation due to treatment failure for both LY2428757 and placebo. Treatment failure was defined as uncontrolled hyperglycemia.
- To establish the dose-response relationship for change in HbA1c in patients with T2DM given once-weekly LY2428757 with or without metformin.
- To evaluate and compare the effects of LY2428757 and placebo on change in weight from baseline to endpoint.
- To evaluate and compare the effects of LY2428757 and placebo on fasting and postprandial plasma glucose levels and insulin secretory response.
- To evaluate the population pharmacokinetics (popPK) and pharmacodynamics (PD) of LY2428757.
- To evaluate the frequency and consequences of immune reactions to LY2428757.
- To evaluate and compare the effects of LY2428757 and placebo on fasting lipid and lipoprotein values.
- To evaluate and compare the effects of LY2428757 and placebo on the impact of weight loss on physical functioning, self-esteem, and the overall impact on weight-related quality of life as measured by the patient-reported outcomes questionnaire and Impact of Weight on Quality of Life-Lite (IWQoL-Lite).
- To evaluate and compare the effects of LY2428757 and placebo on health status as measured by the Eurpoean Quality of Life-5 Dimensions (EuroQoL – 5 Dimensions [EQ-5D]) patient-reported outcomes questionnaire.
- To evaluate and compare the effects of LY2428757 and placebo on diabetes symptoms (e.g., cognitive, hypoglycemia, neuropathic, and psychological).

Study Design: This was a multicenter, multinational, randomized, double-blind, placebo-controlled study.

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Number of Patients (planned and analyzed):
Planned
300 patients to be enrolled (allocated to 6 treatment groups, each consisting of 50 patients) with 210 completers (at least 35 patients per group).
Actual
Overall, 247 patients were randomized (intention-to-treat [ITT] population), of whom 244 (98.8%) patients were included in the safety population, 241 (97.6%) patients to the modified ITT (mITT) population and 205 (83.0%) patients to the per-protocol (PP) population.

Diagnosis and Main Criteria for Inclusion:
Men or women (aged 18 to 70, inclusive) with T2DM for at least 6 months before entering the study who were being treated with diet and exercise alone or in combination with a stable dose of at least 1000 mg/day of metformin for at least 2 months, and who had an HbA1c value of 7% to 10%, inclusive, at Visit 1 and a fasting glucose of ≤15 mmol/L (270 mg/dl) at Visit 2.

Test Product, Dose and Mode of Administration, and Lot Number(s):
Test Product
LY2428757 supplied in 5 mg lyophilized powder in vials.
Dose and Mode of Administration
Once weekly subcutaneous injections of 0.5 mg, 2 mg, 6.2 mg, 12 mg, or 17.6 mg.
Lot Number(s)
[redacted], [redacted], [redacted] and [redacted].

Reference Therapy, Dose and Mode of Administration, and Lot Number(s):
Reference Product
Sterile saline, 0.9% for injection.
Dose and Mode of Administration
Once weekly subcutaneous injections with 5 volumes (0.2, 0.4, 0.7, 2.4 and 2.0 ml, respectively) to match the volumes used in the LY2428757 groups.
Lot Number(s)
Not applicable because the placebo could be supplied locally.

Duration of Treatment: A total of 12 weeks (7 days apart for each injection).

Criteria for Evaluation:
Efficacy
Primary
The change in HbA1c from baseline (measurement at Visit 3) to endpoint (measurement at Visit 9).
Secondary
- Changes in glucose tolerance and insulin secretory response by oral glucose tolerance test (OGTT).
- Seven-point blood glucose profiles measured by self-monitoring of blood glucose (SMBG) values before and after each meal and at bedtime.
- Fasting plasma glucose and lipids (triglycerides, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, and total cholesterol).
- Body weight and waist circumference.
- Degree of recent appetite and satiety by horizontal visual analog scales (VAS).

Safety
Adverse events (AEs), degree of nausea by VAS, vital signs, electrocardiograms (EKGs), and laboratory evaluations.

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Health Outcome/Quality of Life (QoL) Measures

- IWQoL-Lite – an obesity-specific, self-report instrument designed to assess respondent's perceived effect of their weight on their quality of life.
- EQ-5D – A patient-rated questionnaire used to evaluate health status.

Diabetes Symptom Checklist (revised version) (DSC-R) – assessed the presence and perceived burden of diabetes-related symptoms.

Pharmacokinetic/Pharmacodynamics (PK/PD) Analyses

Drug concentration data were collected and analyzed.

Statistical Methods:

Efficacy: Efficacy analyses were conducted on the mITT population. The primary efficacy endpoint was the change from baseline in HbA1c. A Mixed-effects Model for Repeated Measures (MMRM) was used for the primary analysis. The lease square (LS) means estimates of each treatment, the 95% confidence intervals (CIs), and the p-values from the comparisons at each visit were reported. The primary efficacy endpoint was also analyzed using analysis of covariance (ANCOVA) for the change from baseline to endpoint. Missing endpoints were imputed using last observation carried forward (LOCF). Secondary efficacy endpoints (glucose, insulin and glucagon endpoints, weight, and VAS) were analyzed using an MMRM model. LS means were obtained from this model for each treatment group and visit. Fasting lipids were analyzed using an ANCOVA model. Treatment comparisons included the treatment difference LS means, the 95% CIs, and the p-values. Subgroup analyses were performed examining the interaction of the treatment groups and the subgroup effect using the change from baseline to endpoint. The subgroups included: gender, age (< 65, ≥ 65 years old), baseline HbA1c ($< 8.5\%$, $\geq 8.5\%$), country, ethnicity (Caucasian, Non-Caucasian), metformin use (yes or no), and baseline body mass index (BMI) (< 33 kg/m^2, ≥ 33 kg/m^2). The interaction effect was evaluated using a significance level of 0.10.

Safety: Safety analyses were performed on the population of randomized patients who received at least one administration of study drug. Treatment-emergent adverse events (TEAEs) were summarized using the numbers and percentages of patients by treatment group, system organ class and preferred terms. Clinical laboratory, vital sign (systolic blood pressure, diastolic blood pressure, and heart rate), waist circumference, and EKG measurements and VAS values for nausea were summarized using descriptive statistics. For the laboratory analytes, a change-from-baseline-to-endpoint (Visit 9 with LOCF) analysis was performed using an analysis of variance (ANOVA). The numbers and percentages of patients who had abnormally low or abnormally high laboratory values were summarized. Vital sign and waist circumference measurements and VAS values for nausea were analyzed using the MMRM model. Treatment comparisons included the treatment difference LS means, the 95% CIs, and the p-values. An MMRM was used to analyze the change from baseline in QT interval, Fridericia corrected QT (QTcF) interval, Bazett corrected QT (QTcB) interval and PR intervals. Weight change was further analyzed by patients experiencing AEs of nausea versus those who did not. Summary statistics are provided for HbA1c and body weight for all subgroups.

PK/PD Analyses: Drug concentration data were combined with dosing information, demographics, clinical laboratory, vital signs, and efficacy data to produce a NONMEM dataset for population PK/PD analysis. The concentration-time data were fit to provide estimates of the PK parameters and error terms.

Inter-patient variability was assessed separately on each of the PK parameters using an exponential error structure (i.e., log-normal distribution of individual parameter values). Covariance between the inter-patient variability terms were assessed by application of the omega block. Proportional, additive, and combined proportional and additive error structures were evaluated for the residual error.

The effect of patient factors was assessed. For the continuous covariates, a variety of linear and nonlinear models were tested. The validity of the final model was tested by a number of means, which included but were not limited to objective function mapping, leverage analysis, and posterior predictive check.

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Health Outcomes/QoL Analyses: The mITT patient population was used in all health outcome analyses.

- Summary statistics of the raw and change from baseline values for total IWQoL-Lite and all scale scores were computed for each treatment and protocol-specified visit. Scores were calculated using Kolotkin and Crosby's standard method. Treatment differences of change in each domain and for the total score from baseline to Endpoint (Visit 9 LOCF) were assessed using an ANCOVA model.
- Frequency counts and percentages by categorical outcomes (e.g., no pain, moderate pain, and extreme pain) are presented for each of the 5 dimensions of the EQ-5D. Summary statistics and change from baseline for the VAS score (continuous variable) are provided by visit and treatment group.
- Summary statistics, including change from baseline, are provided for each visit by treatment group for DSC-R. Summaries are provided for each of the 8 subdomains and the overall DSC-R score. Change from baseline to endpoint (Visit 9 with LOCF) was analyzed using an ANCOVA model. Separate ANCOVA analyses were conducted for each of the 8 subdomain scores and for the overall DSC-R score.

Efficacy Results:

The means of HbA1c decreased after baseline in the 5 LY2428757 treatment groups already after 2 weeks of treatment, reaching the maximum decrease after 10 weeks of treatment. The mean decreases between baseline and Visit 9 (12 weeks of treatment) in HbA1c displayed a dose-response relation ship between the 0.5 mg treatment group and the 12.0 mg treatment group, but the mean HbA1c values did not decrease any further in the 17.6 mg treatment group.

The comparisons of the LS mean differences in the baseline to endpoint change in HbA1c values between the placebo group and the LY2428757 treatment groups by an MMRM analysis showed superiority ($p < 0.05$) for all doses of LY2428757 compared to placebo. These differences were -0.47% (0.5 mg), -0.67% (2.0 mg), -1.11% (6.2 mg), -1.28% (12.0 mg) and -1.24% (17.6mg). Compared to placebo, statistically significant differences in HbA1c change were observed as early as 2 weeks of treatment (Visit 4) for doses of LY2428757 $\geq$ 2.0 mg.

At the endpoint (Visit 9 with LOCF), the proportion of patients who reached HbA1c values $\leq$ 7.0% was statistically significantly ($p < 0.05$) higher in patients treated with doses of LY2428757 $\geq$ 2.0 mg compared to the placebo group. Differences compared to placebo were also statistically significant ($p < 0.05$) for the 6.2 mg, 12 mg, and 17.6 mg treatment groups for the proportion of patients with endpoint HbA1c $\leq$ 6.5% and < 6.0%.

In the mITT population, the interaction term was statistically significant ($p < 0.10$) for the overall treatment by subgroup interactions regarding change from baseline in HbA1c values according to the subgroup ANCOVAs at Endpoint (Visit 9 with LOCF) accounting for baseline HbA1c value (< 8.5% versus $\geq$ 8.5%), but not for the remaining subgroup analyses.

Treatment with LY2428757 produced dose-dependent reductions in pre- and post-challenge plasma glucose values, glucose total area under the curve (AUC) during OGTTs at Visits 4 and 9, and glucose incremental AUC during the OGTT at Visit 4. Changes in fasting plasma glucose measured at multiple visits, and in 7-point glucose profiles recorded in patients diaries were consistent with the OGTT results. The plateau of LS mean differences in mean decreases in fasting plasma glucose was already reached at Visit 4 (Week 2) in the 6.2, 12.0 and 17.6 mg treatment groups (-28.22, -31.08 and -42.69 mg/dl, respectively). The LS mean differences between placebo and the 6.2, 12.0 and 17.6 mg treatment groups in 7-point SMBG were statistically significant ($p < 0.05$) at almost all visits at all times of the day.

Increases in plasma insulin and C-peptide responses to OGTT were also observed at some doses of LY2428757, however these changes were not seen at all time points and the dose response for these effects was not consistent. The ratio of change in insulin (0 to 30 minutes) to change in plasma glucose (0 to 30 minutes) in the OGTT did not increase.

There was no obvious effect of LY2428757 treatment on either fasting glucagon, or the change in glucagon during an OGTT.

There were no relevant changes in the means of the lipid profiles (neither for all patients nor stratified by intake of lipid lowering medications).

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The mean decrease in fasting weight was largest in the 6.2 and 17.6 mg treatments group (exceeding 2 kg in the 17.6 mg treatment group at Visits 6 to 9 and Endpoint [Visit 9 with LOCF] and in the 6.2 mg treatment group at Visits 8, 9 and Endpoint [Visit 9 with LOCF]), while there was only a slight mean decrease in the remaining treatment groups. In the mITT population, statistically significantly ($p < 0.05$) more patients had lost ≥ 1 kg in fasting weight in the 2.0, 6.2, 12.0 and 17.6 mg treatment groups than in the placebo group at Endpoint (Visit 9 with LOCF), while statistically significantly ($p < 0.05$) more patients had lost ≥ 5 kg in fasting weight in the 17.6 mg treatment group than in the placebo group at Endpoint (Visit 9 with LOCF). There was a significant ($p < 0.10$) treatment by subgroup interaction regarding change from baseline in body weight based on an ANCOVA at Endpoint (Visit 9 with LOCF) accounting for country, but not for the remaining interaction terms.
Regarding changes from baseline in waist circumference, none of the differences ($p \geq 0.05$) between the LY2428757 treatment groups and the placebo group were statistically significant.
The VASs for hunger, appetite and feeling of satiety did not indicate a consistent difference between the LY2428757 treatment groups and the placebo group.

Safety Results:

The mean number of doses of study drug was 10.9 doses and the median duration of treatment was 78.0 days; there were no relevant differences between the treatment groups.
Overall, 145 (59.4%) of the patients reported 1 or more TEAEs, 7 (2.9%) patients reported serious TEAEs and 91 (37.3%) patients reported possibly study drug-related TEAEs. Severe TEAEs were reported by 12 (4.9%) in the 5 LY2428757 treatment groups and no patient in the placebo group. No patient died during the study. There were no relevant differences between the LY2428757 treatment groups or a dose-response relationship regarding the proportions of patients who reported TEAEs, serious TEAEs or severe TEAEs, whereas the proportions of patients who reported possibly study drug-related TEAEs were higher in the 12.0 and 17.6 mg treatment groups (51.2% and 55.8%, respectively) than in the remaining treatment groups.
In terms of system organ classes (SOCs), gastrointestinal disorders were reported by 89 (36.5%) patients, followed by infections and infestations (37 [15.2%] patients), nervous system disorders (32 [13.1%] patients), and general disorders and administration site conditions (30 [12.3%] patients); TEAEs of the remaining SOCs were reported by fewer than 10% patients overall. There were not relevant differences between the treatment groups except for:

- The proportions of patients with gastrointestinal disorders, which were reported most often in the 17.6 mg treatment group (23 [53.5%] patients) and least often in the 0.5 mg treatment group (4 [11.1%] patients), compared to 10 (25.0%) patients reported in the placebo group.
- The proportions of patients with general disorders and administration site conditions, which were reported most often in the 17.6 mg treatment group (11 [25.6%] and least often in the 2.0 mg treatment group (3 [7.1%] patients), compared to 4 (10.0%) patients in the placebo group.

Nausea was reported by the largest proportion of patients (51 [20.9%] patients), followed by diarrhea (23 [9.4%] patients), headache (18 [7.4%] patients) and vomiting (13 [5.3%] patients). TEAEs of the remaining preferred terms (PTs) were reported by fewer than 5% patients overall. The proportions of patients reporting nausea, vomiting, dyspepsia and constipation suggest a dose-response relationship within the 5 LY2428757 treatment groups.
The proportions of patients reporting possibly study drug-related TEAEs suggest a dose-response relationship within the 5 LY2428757 treatment groups. Possibly study drug-related TEAEs of gastrointestinal disorders were reported by 69 (28.3%) patients, followed by general disorders and administration site conditions (16 [6.6%] patients) and metabolism and nutrition disorders (15 [6.1%] patients); possibly study drug-related TEAEs of the remaining SOCs were reported by fewer than 5% of the patients overall. Gastrointestinal disorders were reported most often in the 17.6 mg

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treatment group (22 [51.2%] patients) and least often in the 0.5 mg treatment group (1 [2.8%] patients). The possibly study drug-related TEAE nausea was reported by the largest proportion of patients (46 [18.9%] patients), followed by diarrhea (12 [4.9%] patients), vomiting (11 [4.5%] patients), dyspepsia (10 [4.1%] patients) and constipation (8 [3.3%] patients). Possibly study drug-related TEAEs of the remaining PTs were reported by fewer than 3% patients overall. The proportions of patients reporting possibly study drug-related TEAEs of nausea and vomiting suggest a dose-response relationship within the 5 LY2428757 treatment groups.

Overall, 7 (2.9%) patients experienced a total of 7 serious TEAEs, of which only atrial fibrillation in the 6.2 mg treatment group was considered to be drug-related by the investigator. There was no apparent dose-response relationship for the occurrence of serious TEAEs.

Overall, 7 (2.9%) patients experienced TEAEs leading to study drug discontinuation, the most frequent of which were gastrointestinal disorders (overall, 3 [1.2%] patients, 1 [2.4%] in the 12.0 mg treatment group and 2 [4.7%] in the 17.6 mg treatment group).

There was 1 report of acute pancreatitis, which occurred in the 2.0 mg treatment group. There were no apparent differences between placebo and LY2428757 treatment groups in amylase or lipase abnormalities. No patients in the placebo group or the 0.5 mg treatment group had TEAEs of increased lipase or amylase values or one or both of the lipase and amylase values was $\geq$ 2 times the ULN on 2 consecutive tests.

Hypoglycemic events were experienced by 17 patients between Week 1 and Week 12. None of the hypoglycemic events occurred in the placebo group, but there was no dose-response relationship for the hypoglycemic events among LY2428757 treated patients. There was 1 event of severe hypoglycemia reported in a patient that had received a single dose of short-acting insulin on the day of the event as treatment for hyperglycemia during an OGTT.

There were no relevant differences between the treatment groups regarding clinical chemistry, hematology values or specified laboratory parameters. Results of vital signs and 12-lead EKG parameters were not suggestive of a treatment effect with LY2428757.

Conclusions:

- Treatment with once-weekly injections of LY2428757 given to patients with T2DM was superior over placebo regarding decrease in the mean HbA1c from baseline to endpoint at 12 weeks.
- The mean reduction in HbA1c blood concentrations exceeded 1% in the 6.2, 12.0 and 17.6 mg treatment groups.
- The maximum mean reduction in HbA1c blood concentrations was already seen in the 12.0 mg treatment group.
- Superiority of LY2428757 over placebo is supported by the secondary variables including reductions in fasting and postprandial glucose and body weight.
- LY2428757 concentration increased with doses from 0.5 to 17.6 mg.
- The PK of LY2428757 in patients with type 2 diabetes in Study GECD is consistent with previous Phase 1 studies in patients with diabetes.
- The covariate effects of dose and body weight on PK parameters are within acceptable range of population PK variability and are not considered clinically meaningful.
- The safety and tolerability of LY2428757 observed in this study is consistent with previous observations and in line with what has been reported for other glucagon-like peptide-1 receptor agonists.
- No safety issues were identified that would preclude the continued clinical development of LY2428757 for the treatment of T2DM.

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