2. EIAF Synopsis

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Clinical Study Report Synopsis: Study I1V-MC-EIAF

Title of Study: A Phase 2 Efficacy and Safety Study of LY2484595 Alone and in Combination with Atorvastatin, Simvastatin, and Rosuvastatin in Patients with Hypercholesterolemia or Low HDL-C

Number of Investigators: This multicenter study included 57principal investigators.

Study Centers: This study was conducted at 57 study centers in 6 countries.

Publication Based on the Study: Nicholls SJ, Brewer HB, Kastelein JJ, Krueger KA, Wang MD, Shao M, Hu B, McErlean E, Nissen SE. Effects of the CETP Inhibitor Evacetrapib Administered as Monotherapy or in Combination With Statins on HDL and LDL Cholesterol: A Randomized Controlled Trial. *JAMA.* 2011;306(19):2099-109.

Length of Study:	**Phase of Development:** 2
Date of first patient enrolled: 19 May 2010 Date of last patient completed the study: 27 June 2011	

Objectives: The primary objective of this study was to determine whether LY2484595, administered in combination with atorvastatin for 12 weeks to patients with hypercholesterolemia or low high-density lipoprotein cholesterol (HDL-C), significantly increases mean HDL-C and decreases mean low-density lipoprotein cholesterol (LDL-C) from baseline to endpoint, compared to atorvastatin alone.

The secondary objectives of the study were as follows:

- To demonstrate whether LY2484595 administered as monotherapy significantly increases mean HDL-C and decreases mean LDL-C compared to placebo.
- To evaluate the additive pharmcodynamic (PD) effects of LY2484595 administered in combination with simvastatin or rosuvastatin on mean HDL-C and LDL-C.
- To evaluate the pharmacokinetic (PK) of LY2484595 in the presence of atorvastatin, simvastatin, and rosuvastatin.
- To evaluate the effect of LY2484595 on plasma cholesteryl ester transfer protein (CETP) activity and mass in the presence of statins.
- To evaluate the effect of LY2484595 on the PK/PD profile of atorvastatin, simvastatin, and rosuvastatin.
- To evaluate the dose-response, exposure-response, and time-response relationships for HDL-C and LDL-C over a 12-week time course for LY2484595 as monotherapy and in combination with atorvastatin, simvastatin, and rosuvastatin.
- To assess for interactions between baseline characteristics (e.g., HDL-C, LDL-C, triglycerides [TG]) and lipid response to therapy.
- To evaluate the effects of LY2484595 as monotherapy and in combination with statins on safety and tolerability.
- To evaluate the incidence and severity of rashes with LY2484595 and potential relationship to study drug.
- To evaluate the effect of LY2484595 on blood pressure, aldosterone, plasma renin activity, plasma potassium, serum sodium, and serum bicarbonate compared with placebo, and to assess for a correlation between LY2484595 exposure and blood pressure or measures of mineralocorticoid activity.
- To assess whether LY2484595 has an effect on the incidence of statin-related safety concerns, including myopathy and liver injury.
- To evaluate the effects of LY2484595 on exploratory biomarkers associated with the risk of atherosclerosis (e.g., high-sensitivity C-reactive protein [hsCRP], myeloperoxidase [MPO]).
- To examine test-retest stability of patient-reported outcomes instrument EuroQol-5 dimensions (EQ-5D) and mean change in baseline utility score at end of study. The Visual Analog Scale (VAS) and overall utility score were the primary variables of interest.

Study Design: This was an outpatient, multicenter, randomized, double-blind, double–dummy, parallel group, placebo- and active-controlled, Phase 2 efficacy and safety study.

Number of Patients:

Planned: 400 (40 patients in each of the 10 treatment groups)

Randomized: 40 LY30, 39 LY100, 42 LY500, 41 ATO20, 35 ATO20+LY100, 42 SIM40, 40 SIM40+LY100, 40 ROS10, 41 ROS10+LY100, 38 placebo

Treated (at least 1 dose): 40 LY30, 38 LY100, 40 LY500, 41 ATO20, 35 ATO20+LY100, 41 SIM40, 40 SIM40+LY100, 39 ROS10, 41 ROS10+LY100, 38 placebo

Completed: 35LY30, 34 LY100, 32 LY500, 35 ATO20, 30 ATO20+LY100, 34 SIM40, 33 SIM40+LY100, 34 ROS10, 32 ROS10+LY100, 36 placebo

Diagnosis and Main Criteria for Inclusion: Male or female patients with hypercholesterolemia or low HDL-C who were 18 years of age or older and had given informed consent were eligible to participate in this study.

Test Product, Dose, and Mode of Administration:

This study involved comparisons of the following treatments administered orally once daily:

Monotherapy:

LY2484595 30 mg/day, given orally as one 30-mg tablet once daily

LY2484595 100 mg/day, given orally as one 100-mg tablet once daily

LY2484595 500 mg/day, given orally as five 100-mg tablets once daily

Placebo

Combination Therapy:

LY2484595 (100 mg/day) + atorvastatin 20 mg/day, given orally as one 20-mg capsule once daily

LY2484595 (100 mg/day) + simvastatin 40 mg/day, given orally as one 40-mg capsule once daily

LY2484595 (100 mg/day) + rosuvastatin 10 mg/day, given orally as one 10-mg capsule once daily

atorvastatin 20 mg capsule once daily

simvastatin 40 mg capsule once daily

rosuvastatin 10 mg capsule once daily

Duration of Treatment:

Patient total participation could range between 19 and 41 weeks:

Diet Lead-in/Washout Phase: approximately 2-18 weeks

Treatment Phase: 12 weeks

Follow-up Phase: 4-6 weeks

Variables:

Efficacy: Primary measures included: HDL-C and LDL-C. Secondary measures included: TG, total cholesterol, non-HDL cholesterol (non-HDL-C), very-low-density lipoprotein (VLDL) cholesterol, apolipoprotein panel (Apo A-I, Apo A-II, Apo C-II, Apo C-III, Apo E, Apo B-total), lipoprotein particle size and number by nuclear magnetic resonance (NMR), and inflammatory biomarkers (hsCRP, MPO).

Safety: Treatment-emergent adverse events (TEAEs), serious adverse events (SAEs), assessment and management of patients developing rash, vital signs and physical examinations including systolic and diastolic blood pressure and pulse rate, centrally adjudicated cardiovascular events, electrocardiograms, glucocorticoid activity, mineralocorticoid activity, muscle injury, liver injury, and additional laboratory measurements.

Bioanalytical: Plasma samples were assayed for LY2484595, statin parent, and statin metabolites using a validated liquid chromatography - mass spectrometry and liquid chromatography - tandem mass spectrometry (LC/MS/MS) method.

Pharmacokinetic/Pharmacodynamic: Venous blood samples were obtained to measure the plasma concentrations of LY2484595 and the following statin parent and statin metabolites: atorvastatin, o-hydroxyatorvastatin, p-hydroxyatorvastatin, rosuvastatin, rosuvastatin lactone, N-desmethyl rosuvastatin, simvastatin, and simvastatin acid. Venous blood samples were collected also to measure CETP activity and mass.

Health Outcomes: EQ-5D.

Evaluation Methods:

Efficacy: The primary efficacy variables were the percent change from baseline in HDL-C and LDL-C. Efficacy analyses were conducted for the Active Treatment Phase on the modified intent-to-treat (mITT) population. Per-protocol analysis was also conducted for the primary efficacy variables. Summary statistics (mean, standard deviation [SD], median, min, max) of HDL-C and LDL-C and their percent changes from baseline were tabulated by treatment and visit. The primary analysis applied mixed model repeated measures, and a nonlinear mixed effects model was used as a secondary analysis. Lipids, CETP activity, lipid NMR measures, and their percent changes from baseline during the Treatment Phase are summarized by visit and treatment. CETP mass, hsCRP, MPO, and the respective change from baseline during the Treatment Phase are summarized by visit and treatment. The percent changes or changes were analyzed using mixed effects models with region, baseline measurement, and treatment as fixed effects. For lipids, CETP mass, and CETP activity, visit and treatment by visit interaction also were included in the model as fixed effects to model within-patient repeated measures at multiple visits.

The study sample size was selected primarily to ensure sufficient power to detect desired changes in both HDL-C and LDL-C in patients receiving LY2484595 in combination with atorvastatin. For patients treated with LY2484595 or placebo on background of atorvastatin, the SDs of percent changes in HDL-C and LDL-C were expected to be 30% and 15%, respectively, and Pearson's correlation coefficient between the changes is 0.4. Considering a 2-sided 0.1 significance level by a 2-sample t test, it was expected that 35 patients per group would provide 87% power to simultaneously detect a 40% increase from baseline in HDL-C and a 10% decrease from baseline in LDL-C in patients treated with LY2484595, as compared to placebo, in combination with atorvastatin. Assuming a 15% dropout rate of enrolled patients, approximately 40 patients were needed to be randomized to each treatment group.

Safety: Safety analyses were conducted on the intent-to-treat (ITT) population. Numbers of patients who experienced TEAEs and drug-related TEAEs are summarized by system organ class, preferred term, and treatment. Incidence rates of TEAEs, and drug-related TEAEs were compared across treatment groups using a chi-square test. Laboratory measurements and their changes from baseline (for numerical tests) or status ("abnormal" or "normal") are listed and summarized by treatment and visit. For continuous laboratory tests, changes from baseline in laboratory measurements were analyzed by mixed-effects repeated measures (MMRM), with region, baseline measurement, visit, treatment, and treatment by visit interaction as fixed effects. For categorical laboratory tests, a chi-square test or Fisher's exact test was applied to compare treatment-induced changes from baseline to last observed value among treatments. For each laboratory test, abnormalities are summarized by treatment, and frequency of abnormality was compared between treatments using a chi-square test or Fisher's exact test. Vital signs, including pulse rate, SBP, DBP and their changes from baseline are listed and summarized by visit. Mixed effects models were used to analyze changes from baseline in vital signs, where region, baseline measurement, treatment, visit, and treatment by visit interaction included as fixed effects. Within-patient repeated measures was modeled with the previously described covariance structure selection principle.

Bioanalytical: Serum and plasma samples were stored for possible future research on LY2484595.

Pharmacokinetic/Pharmacodynamic: Analysis was performed using a nonlinear mixed-effect modeling approach. Population PK analyses were performed to characterize the PK of LY2484595 in the presence and absence of atorvastatin, simvastatin, and rosuvastatin. Population PK analyses were also performed to characterize the PK of atorvastatin, simvastatin, rosuvastatin and their respective metabolites in the presence and absence of LY2484595. Population PK/PD analyses were conducted to evaluate the relationship between LY2484595 concentrations and/or dose and HDL-C and LDL-C, and the longitudinal response of these lipid biomarkers.

Health Outcomes: A utility score was calculated from EQ-5D using a published algorithm. Changes from baseline in the utility score and VAS of EQ-5D were analyzed by an analysis of covariance (ANCOVA) model applying last-observation-carried-forward, with baseline utility score/VAS as a covariate and treatment as an independent variable.

Summary:

- A total of 398 patients were randomized and 335 patients (84.2%) completed the study. For the total of 63 patients who discontinued, the most common reasons for discontinuation were adverse event (33.3%), subject decision (27.0%), protocol violation (19.0%), and abnormal lab/ECG result (11.1%). Demographic and baseline characteristics, including LDL-C, HDL-C, and triglycerides, were well-balanced across treatment groups.
- LY2484595 treatment for 12 weeks in patients with hypercholesterolemia or low HDL-C resulted in statistically significant, dose-related increases in HDL-C and decreases in LDL-C. All primary and secondary efficacy objectives of this study were met.
- The mean change in HDL-C from baseline to Week 12 with LY monotherapy compared to placebo was 56.7%, 97.6%, and 131.9% for the LY30, LY100, and LY500 groups, respectively. LY2484595 100 mg in combination with atorvastatin compared to atorvastatin alone increased HDL-C by 78.5%. Similar changes were seen with the other statins.
- The mean change in LDL-C from baseline to Week 12 with - monotherapy compared to placebo was -17.6%, -26.2%, and -39.8% for the LY30, LY100, and LY500 groups, respectively. Decreases in LDL-C with LY2484595 100 mg in combination with atorvastatin compared to statin alone was -13.9%, with similar changes when LY was combined with simvastatin and rosuvastatin.
- A statistically significant -20.1% mean decrease in fasting triglycerides (TG) was observed in the LY500 group compared with placebo. TG decreases seen with the other monotherapy doses and statin combination were not statistically significant.
- Statistically significant increases in APO A1, APO A2 and APO C3 were observed with all LY2484595 monotherapy and statin combination groups compared to controls. APO C2 and APO E increases were statistically significant with all LY100 (monotherapy and statin combination) and LY500 groups. APO B decreases were statistically significant with all LY2484595 monotherapy groups.
- Dose-related decreases in corrected CETP activity (-49.5% to -89.1%) and increases in CETP mass (63.9% to 136.7%) were observed with LY2484595, consistent with lipid changes.
- Mean changes from baseline to endpoint (LOCF) in biomarkers (CRP and MPO) were variable across treatment groups and no statistically significant differences were observed between monotherapy treatment groups and placebo.
- Statistically significant decreases in LDL particle concentration and increases in LDL and HDL particle size were observed with all LY2484595 monotherapy and statin combination groups compared to controls.
- The magnitude of differences across treatment groups in EQ-5D index score and VAS health status score was below the minimal important difference commonly used in the quality-of-life evaluation literature .
- The clearance of LY2484595 was found to increase with dose of LY2484595, ranging from 13.1 L/hr at 30 mg to 25.4 L/hr at 500 mg. LY2484595 clearance tended to increase with CGCL, with the model-predicted mean CL/F value 10% lower at 50 mL/min than at 100 mL/min. No other covariates were found to significantly impact the PK of LY2484595.
- Coadministering atorvastatin, simvastatin, and rosuvastatin with LY2484595 resulted in mean AUC ratios of 0.861, 1.25, and 1.27, respectively, relative to administering the statin alone. Only the increase in simvastatin exposure with LY2484595 was statistically significant
- Based on exposure-response modeling, baseline HDL was found to significantly impact the HDL response with LY2484595, where patients with lower baseline HDL values had a larger HDL increase from baseline. The theoretical maximum effect (Emax)of LY2484595 on HDL was 177% change from baseline, and the AUC that produced half of the maximum effect was 5380 ng*hr/ml.
- Baseline ApoA1 was found to have a significant impact on the LDL response with LY2484595, where patients with lower baseline ApoA1 values had larger LDL reductions from baseline. The theoretical maximum effect (Emax) of LY2484595 on LDL was -44.1% change from baseline, and the AUC that produced half of the maximum effect was 4230 ng*hr/ml.

- Model based analyses indicate that the LDL response produced by coadministering atorvastatin, simvastatin, or rosuvastatin with LY2484595 was equal to the sum of the LDL responses produced by the statins and LY2484595 when administered alone.
- The results from this study show that 12-week therapy with daily doses of LY2484595 up to 500 mg as monotherapy or daily doses of LY2484595 100 mg in combination with a statin was safe and well tolerated in patients with hypercholesterolemia or low HDL-C.
- In all treatment groups, the majority of patients experienced at least 1 TEAE during the Active Treatment Phase of the study (65.4% overall). The most commonly reported TEAEs (≥3% overall) included Nasopharyngitis (10.7%), Diarrhea (4.1%), Nausea (4.1%), Arthralgia (3.6%), and Headache (3.6%). Most TEAEs were mild or moderate in severity. There were a total of 13 patients, evenly distributed across active treatment groups, that reported 1 or 2 TEAEs that were considered severe.
- Adverse Events reported during the Follow-Up Phase were not substancially different from those observed during active treatment.
- There were no deaths reported during the study. A total of 6 treatment-emergent SAEs were reported during the Active Treatment Phase in a total of 4 patients. No event was deemed related to study drug by either the investigator or the Sponsor.
- Discontinuations due to AE occurred in 7.17% of patients in LY groups and 2.48% of patients in non-LY groups. Although there were statistically more patients who discontinued due to an AE in the pooled LY vs. non-LY group, there was no pattern in the type of AEs prompting discontinuation.
- The only AE that was reported more frequently in the pooled LY vs. non-LY group was Dizziness. None of the reports of Dizziness occurred with the highest LY dose (LY500) or were associated with increases in blood pressure.
- LY did not produce any adverse effects on blood pressure.
    - Based on the planned analysis of blood pressure change from Visit 3 baseline, there were statistically significant differences between the pooled LY and non-LY group in SBP and between the SIM40+LY100 compared with the SIM40 group in DBP. There was no dose-related effect of LY monotherapy (doses ranging from 30 mg to 500 mg) on SBP or DBP change and there was no relationship between LY2484595 exposure (AUC) and change in SBP. This analysis did not account for the differences in blood pressure between the LY and non-LY groups prior to the initiation of therapy.
    - Based on analyses that controlled for pre-treatment differences in blood pressure between LY and non-LY groups, there was a statistically significant increase in DBP change in the SIM40+LY100 compared with the SIM40 group (LS mean difference: 4.5±1.5 mmHg, p=.003), that was not seen with atorvastatin and rosuvastatin or with SBP change with any statin combination. There was no effect of LY monotherapy on DBP or SBP. In the absence of an exposure-related effect of LY on blood pressure, it would not be biologically plausible to observe an increase in DBP with SIM40+LY100, but not with LY500.
    - Based on analyses that controlled for pre-treatment differences in blood pressure between LY and non-LY groups, LY did not increase the proportion of patients who had SBP or DBP higher than the selected thresholds at any visit or sustained over 2 or more visits. LY did not increase the proportion of patients who became hypertensive on treatment.
    - Although there was a statistically significant difference in the incidence of Blood Pressure Systolic Increased overall, no such difference was observed in comparison of incidence of this AE with the pooled LY group versus non-LY group, or in analyses where all blood pressure increase-related events (Blood Pressure Systolic Increase, Blood pressure increase, and Hypertension) were pooled. Thus, the statistically significant finding in the incidence overall was not considered clinically relevant because there was no consistent evidence of a signal of increased blood pressure. No blood pressure increase-related AEs were reported in the LY500 group.
- • LY2484595 did not have any adverse effects on mineralocorticoid or glucocorticoid measures.

  - There were no differences between the pooled LY and non-LY groups in mean change in aldosterone, plasma renin activity (PRA), serum sodium, serum and plasma potassium, serum chloride and serum bicarbonate, or in salivary cortisol. Although there was a statistically significant increase in aldosterone with ROS10+LY100 group compared with the ROS10 group; this was not observed with LY in combination with the other statins, with the highest dose of LY monotherapy, or with other measures of mineralocorticoid activity.
  - LY2484595 treatment did not increase mineralocorticoid-related AEs (i.e. Hypokalemia, Hypernatremia, and Blood Potassium Decreased). No mineralocorticoid-related AEs were observed at the highest dose of LY (LY500).
- There was no evidence of an increased risk of severe cutaneous reactions (as determined by the incidence of adjudicated high-risk rash and by the incidence of pooled AEs under pre-specified SMQs) associated with LY monotherapy or in combination with statin. Two rashes were adjudicated as high risk rashes (one with ROS10+LY100 in a patient that also reported a low risk rash earlier in the study, and one with SIM40). Two other rashes were adjudicated to be low risk rashes (one with ROS10+LY100 and one with SIM40+LY100). The incidence of high risk rash associated with LY therapy is low, similar to what observed with statins and unrelated to LY dose.
- There was no evidence of any adverse effect of LY2484595 on hepatic safety as monotherapy or in combination with statins. There were no statistically or clinically significant effects of LY2484595 on mean change from baseline in ALT or AST. There were no treatment group differences in the reporting of drug-related hepatic disorder adverse events. No subjects on LY monotherapy reported any hepatic-related TEAE.
- LY2484595 had no adverse effects on muscle safety when administered as monotherapy or in combination with statins. There were no statistically or clinically significant mean changes from baseline in creatine phosphokinase (CK). No patients on LY2484595 monotherapy or combination therapy with simvastatin demonstrated CK increases >5-fold ULN. There were no treatment group differences in the reporting of muscle-related TEAEs.
- There was no evidence of any adverse effect of LY2484595 on CV safety. There were no positively adjudicated CV events in any LY or other treatment group.
- There was no evidence of a risk of a QT prolonging effect with LY monotherapy or statin combination therapy based on AE reporting.
- LY as monotherapy or in combination with statins did not produce clinically important adverse effects on any of the clinical chemistry analytes or hematology parameters.

Conclusions:

In conclusion, the results from this study show that 12-week therapy with daily doses of LY2484595 up to 500 mg or daily doses of LY2484595 100 mg in combination with a statin was more effective in increasing HDL-C and lowering LDL-C compared with placebo and statin alone. Further treatment with LY2484595 as monotherapy or in combination with statins was safe and well tolerated in patients with hypercholesterolemia or low HDL-C.