1. GACB Abbreviated Clinical Study Report

Safety, Tolerability, Pharmacokinetics and Pharmacodynamics of LY2245461 after Multiple Oral Administrations in Healthy Postmenopausal Women

LY2245461

A multicenter, randomized, double-blind, placebo-controlled, parallel design, 28-day multiple-dose, inpatient/outpatient study to evaluate 4 escalating doses of LY2245461 in healthy postmenopausal women.

Chorus, a division of Eli Lilly and Company
Protocol I2B-MC-GACB
Phase 1
First subject entered (signed informed consent): 13 May 2008
Last subject completed: 23 February 2009
Date of report: 05 June 2009

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Eli Lilly and Company

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2. GACB Synopsis

Clinical Study Report Synopsis: Study I2B-MC-GACB

Title of Study: Safety, Tolerability, Pharmacokinetics and Pharmacodynamics of LY2245461 after Multiple Oral Administrations in Healthy Postmenopausal Women	
Number of Investigators: This multicenter study included 3 principal investigators.	
Study Centers: This study was conducted at 3 study centers in 3 countries.	
Publications Based on the Study: None at this time.	
Length of Study: First subject enrolled: 13 May 2008 Last subject completed: 23 February 2009	**Phase of Development:** 1
Objectives: Primary: To investigate the safety and tolerability of multiple oral doses of LY2245461 in healthy postmenopausal women. Secondary: • To characterize the pharmacokinetics (PK) of LY2245461 administered as multiple doses given daily for 28 days in healthy postmenopausal women. • To characterize the pharmacodynamic (PD) effects of LY2245461 administered daily for 28 days in healthy postmenopausal women. • To characterize the PK/PD dose and/or exposure response relationships.	
Study Design: Study I2B-MC-GACB was a double-blind, multicenter, placebo-controlled, parallel design, 28-day multiple dose, inpatient/outpatient study evaluating 4 escalating doses (25, 100, 500, and 1000 mg) of LY2245461 in healthy postmenopausal or perimenopausal women.	
Number of Subjects: Planned: 52; 13 per treatment group (10 active treatment, 3 placebo). Randomized: 53; 41 LY2245461, 12 placebo Treated (at least 1 dose): 53; 41 LY2245461, 12 placebo Completed: 50; 38 LY2245461, 12 placebo	
Diagnosis and Main Criteria for Inclusion: Healthy, postmenopausal (naturally or surgically) females, 12 months without a menstrual period or perimenopausal women 6 months without a menstrual period and follicle stimulating hormone (FSH) >40 IU/L, aged 45 to 65 years, inclusive, and body mass index (BMI) between 20 and 40 kg/m^2, inclusive. Subjects had a history of ≥3 self-reported hot flashes/day and a hot flash frequency (HFF) of >5 hot flashes/day (24 hours) as indicated by Biolog (UFI model 3991 SCL, Morro Bay, California) hot flash event marker (EM) or Biolog hot flash monitor skin conductance recording (SCR).	
Study Drug, Dose, and Mode of Administration: 1 of 4 doses (25, 100, 500, or 1000 mg) of LY2245461 given orally as capsules once daily.	
Reference Therapy, Dose, and Mode of Administration: Matching placebo given orally as capsules once daily.	
Duration of Treatment: 28 consecutive days of LY2245461 or placebo.	

Variables:

Safety: Adverse events (AEs), clinical laboratory evaluations, vital signs, physical examinations, 12-lead electrocardiograms (ECGs), and concomitant medications.

Pharmacokinetic: Maximum (peak) observed plasma LY2245461 drug concentration (C_{max}), time of maximum drug concentration (t_{max}), terminal elimination rate constant (λz), terminal elimination half-life ($t_{1/2}$), area under the concentration-time curve from time 0 to time t where t was the time of the last measurable concentration, (AUC[0-tz]), AUC from time 0 extrapolated to infinite time (AUC[0-∞]), and apparent clearance of drug from plasma (CL/F). In addition to the parameters specified in the protocol, the following ratios were calculated for analysis of dose proportionality:

- C_{max}/Dose
- AUC(0-tz)/ Dose
- AUC(0-∞)/ Dose

Pharmacodynamic: Subjective HFF recorded on Biolog EM, objective HFF detected by slope monitoring method of Biolog SCR, and subjective Visual Analog Scale (VAS) of the Hot Flash Related Daily Interference Scale (HFRDIS); hormone levels including estradiol (E2), FSH, and luteinizing hormone (LH); serum osteocalcin and serum CrossLaps™; fasting lipid panel including triglycerides, high-density lipoprotein (HDL), low-density lipoprotein (LDL), and total cholesterol; transvaginal ultrasound (TVU) and vaginal maturation index.

Statistical Evaluation Methods:

Safety: Safety data were summarized, tabulated, and listed by treatment and dose group.

Pharmacokinetic: Plasma concentrations of free (not conjugated) LY2245461 were analyzed using liquid chromatography with tandem mass spectrometric detection (LC/MS/MS). Noncompartmental pharmacokinetic parameters were calculated from plasma concentration-time data using WinNonlin® Professional version 5.2.1 (Pharsight Corp, Mountain View, CA).

Plasma LY2245461 concentrations were summarized using descriptive statistics including N, mean, standard deviation (SD), median, minimum, maximum and coefficient of variation (CV%), for each treatment.

Pharmacodynamics: Determinations of hot flash incidence and frequency were made using proprietary software supplied with the Biolog. Analysis of the effect of LY2245461 on HFF were performed using a Generalized Linear Model (GLM) analysis with change in HFF from baseline as the response and treatment (active and placebo), baseline HFF, and duration (7 or 28 days) as main effects (model delta HFF = treatment, baseline HFF, duration, baseline HFF x treatment, baseline HFF x duration, treatment x duration). The effect with the highest p-value (excluding treatment) was removed and the model was run again until all effects were significant. Treatment remained in the model regardless of significance. If treatment was significant in the final model, a least squares mean analysis was run to analyze active treatment versus placebo. A similar modeling process was performed with change in HFF from baseline as the response and dose (dose = 0 for placebo), baseline HFF, and duration (7 or 28 days) as main effects (model delta HFF = dose, baseline HFF, duration, baseline HFF x dose, baseline HFF x duration, dose x duration). The effect of LY2245461 on HFRDIS scores were analyzed in a similar fashion. Pharmacodynamic measures, including hormone levels, bone biomarkers, lipids, endometrial thickness and ovarian cysts (measured by TVU) were analyzed using the GLM method.

Summary: No deaths or other serious adverse events occurred during the study. One subject discontinued due to an AE of mild paraesthesia that was assessed as possibly related to LY2245461 by the investigator. The following treatment-emergent adverse events (TEAEs) occurred in more than 5% of LY2445461-treated subjects and at a frequency greater than in placebo-treated subjects: headache, nasopharyngitis, hot flush, constipation, back pain, nausea, pain in extremity, and pyrexia. There were no clinically significant abnormalities in laboratory evaluations or ECGs attributable to LY2245461. No clinically significant changes were observed in vital signs or gynecological examinations, including TVU and vaginal maturation index.

C_{max} values for the 25- through 500-mg dose levels increased less than proportional to the increase in dose on all days, but the increase over a 2-fold increase in dose (between 500 and 1000 mg) appeared to be reasonably dose proportional. AUC values displayed a similar pattern to $C_{max.}$ The power estimates for the relationship with dose were 0.5114 and 0.5268 for Day 28 C_{max} and AUCτ, respectively. Average t_{max} values ranged from 1.2 to 2.3 hours on all days, indicating relatively rapid absorption following oral administration. t_{max} appeared to be independent of LY2405319 dose. Mean CL/F values were quite high, many fold larger than total cardiac plasma output, at all dose levels, suggesting that LY2245461 may have a low bioavailability. Additionally, there was a significant increase (4 to 5-fold) in apparent clearance with increase in dose. The lowest average CL/F was 845 L/h for the 25-mg dose on Day 28 and the highest was 7032 L/h for the 500 mg dose on Day 1. The apparent volume of distribution (Vz/F), based on terminal phase data, was exceedingly large and increased with increasing dose but also decreased somewhat during multiple dosing. The smallest average Vz/F was 25173 L for the 25-mg dose on Day 28 and the largest was 216025 L for the 1000-mg dose on Day 1. There was modest accumulation of LY2245461 during the 28-day dosing regimen as indicated by accumulation ratios (R_{acc}) ranging from 1.6 to 2.1, on average. This is to be expected on the basis of the relatively long half-life and the 24-hour dosing interval. The fluctuation was relatively low, ranging from 149% to 176% on Day 28.

Mean HFF, measured by Biolog EM, decreased from baseline at Day 7 and Day 28 in all treatment groups, including placebo. At Day 28, the decrease in mean HFF from baseline was greater in the placebo treatment group compared to all LY2445461 treatment groups. Mean HFF, measured by Biolog SCR, decreased from baseline to Day 7 in all treatment groups, including placebo. From baseline to Day 28, mean HFF decreased in the 25-mg, 1000-mg, and placebo treatment groups whereas mean increases were observed in the 100- and 500-mg treatment groups. At Day 28, the magnitude of decrease in mean HFF was greater in the placebo treatment group compared to the 25- and 100-mg treatment groups. Improvement was seen on all items of the HFRDIS for all treatment groups, including placebo, with the exception of leisure activities and overall quality of life in the 500-mg treatment group. Overall, mean improvement on the HFRDIS was greater in the placebo treatment group compared to all LY2445461 treatment groups.

From baseline to Day 28, FSH increased (median percent) in the 1000-mg treatment group and LH increased in the placebo treatment group; median percent decreases in E2, FSH, and LH were observed in all other treatment groups. Serum osteocalcin decreased (median percent) from baseline to Day 28 in all treatment groups with the exception of an increase in the 500-mg treatment group and in the placebo treatment. Serum CrossLaps increased from baseline in the 25-mg, 100-mg, and placebo treatment groups and decreased in the 500- and 1000-mg treatment groups. Triglycerides, HDL, LDL, and total cholesterol decreased (median percent) from baseline to Day 28 in all treatment groups with the exception of a median percent increase from baseline in triglycerides in the 25-mg treatment group.

Conclusions:

- Daily oral doses up to 1000 mg of LY2245461 for 28 days were well tolerated by healthy postmenopausal women.
- There were no clear-cut patterns of TEAE occurrence or laboratory abnormalities that suggested a causal association with LY2245461 based upon dose-relationship. Nausea occurred at a higher frequency at the highest dose of 1000 mg LY2245461, but the overall frequency of 9.8% for all LY2245461 dosed subjects was not remarkably higher than placebo (8.3%). The incidence of hot flush was highest for the 1000-mg LY2245461dose, and taken together with the overall increase in all LY2245461 dosed subjects and the pharmacology of the drug, a causal relationship with LY2245461 is possible.
- Absorption after oral administration of LY2245461 appears to be relatively rapid with mean t_{max} of 1.2 to 2.3 hours.
- Both C_{max} and AUCτ increased less than proportionally to the increase in dose between 25 and 500 mg.
- Total subject variability in C_{max} (range: 22% to 67%) and AUC (range: 14% to 63%) was generally moderate.
- Both CL/F and Vz/F were large, with values for each increasing with increasing dose.
- Modest accumulation of LY2245461 occurred on daily administration (1.58- to 2.10-fold), whereas fluctuation was relatively low (149% to 176%) on Day 28.
- Decreases in mean HFF (Biolog EM and SCR) were greater in the placebo treatment group compared to LY2445461 treatment groups. Overall, greater mean improvement was observed on the HFRDIS in the placebo treatment group compared to LY2445461 treatment groups.
- Hormone levels (E2, FSH, and LH) decreased in all treatment groups with the exceptions of increases in FSH in the 1000-mg treatment group and LH in the placebo treatment group. Serum osteocalcin decreased in all treatment groups with the exception of an increase in the 500-mg group and in the placebo treatment. Serum CrossLaps increased at lower LY2245461 doses (25 and 100 mg) and placebo and decreased in the 500- and 1000-mg treatment groups. Fasting lipids (triglycerides, HDL, LDL, and total cholesterol) decreased in all treatment groups with the exception of an increase in triglycerides in the 25-mg treatment group.