2 SYNOPSIS

Title of Study: A Proof-of-Concept Study of the Effects of LY2828360 in the Treatment of Patients With Osteoarthritic Knee Pain

Name of Sponsor: [redacted], Lilly Research Laboratories, a Division of Eli Lilly and Company

Name of Investigational Product: LY2828360

Principal Investigator/Investigators: [redacted], MD

Study Center(s): Single center in [redacted], Denmark

Publication (reference): None

Study Period: 14 Mar 2011 to 13 Sep 2011

Phase of Development: Phase 2a

OBJECTIVES

Primary:

- To assess the safety and efficacy of 80 mg daily administration of LY2828360 compared to placebo on the change from baseline of pain severity (average pain scores [APS])

Secondary:

- To evaluate the efficacy of 80 mg LY2828360 once a day (QD) versus placebo during the 4-week treatment phase on the change from baseline of secondary efficacy measures
- To assess the safety of 80 mg LY2828360 QD versus placebo during the treatment phase
- To assess the pharmacokinetics of LY2828360 in osteoarthritis (OA) patients
- To investigate the relationship between exposure of LY2828360 and efficacy

METHODS

Number of Subjects: 39 patients enrolled and 32 completed the study

Planned: Up to 44 patients to obtain 30 completers

Diagnosis and Main Criteria for Inclusion: Males or females of nonchildbearing potential between 40 and 75 years of age and body weight greater >40 kg and <120 kg with a body mass index (BMI) between 19 to 35 kg/m^2 inclusive. Patient with unilateral or bilateral OA of knee diagnosed according to the American College of Rheumatology (ACR) criteria based on clinical and radiographic evidence.

Test Product, Dose and Mode of Administration, Lot/Batch Number:

Study Drug	Dose Strength	Mode of Administration	Drug Product Lot Number
LY2828360	20 mg	Oral	[redacted]

Duration of Treatment: 28 days of once daily dosing of 80 mg LY2828360 (4 capsules of 20 mg) and 28 days of once daily dosing with matching LY2828360 placebo (4 capsules)

Reference Therapy, Dose and Mode of Administration, Lot/Batch Number:

Study Drug	Study Dose	Mode of Administration	Drug Product Lot Number
Placebo for LY2828360	Not applicable	Oral	[redacted]

Criteria for Evaluation:

Efficacy: Change from baseline of pain severity as measured by the weekly mean of the daily 24-hour APS, night pain and worst daily pain, Chronic Pain Sleep Inventory (CPSI), Brief Pain Inventory (BPI), Western Ontario and MacMaster (WOMAC) OA physical function, time and pain intensity from the 40-m self-paced walk test, time and pain intensity from the 11-step stair climb test, Pittsburgh Sleep Quality Index (PSQI), Investigator and Patient Global Assessment of Changes (IGAC and PGAC), and DoloTest®.

Pharmacokinetic/Pharmacodynamics: Relationship between exposure of LY2828360 and efficacy.

Safety: Discontinuation rates, treatment emergent adverse events (TEAEs), rescue medication, laboratory assessments, vital signs (VS), electrocardiograms (ECGs), Subjective Liking Visual Analogue Scales (SL-VAS), Addiction Research Center Inventory (ARCI) and Subjective questionnaire (Columbia-Suicide Severity Rating Scale [C-SSRS]).

Statistical Methods:

Efficacy: Both primary and secondary efficacy measures were analyzed using Mixed-Effects Model Repeated Measures (MMRM) approach and including covariates as described in the statistical analysis plan.

Pharmacokinetic Measures: Plasma concentration-time profiles for LY2828360 were analyzed using standard noncompartmental methods of analysis.

Pharmacodynamics: Analysis of change from baseline of pain severity as measured by the weekly mean of the daily 24-hour APS, night pain and worst daily pain, CPSI, BPI, WOMAC OA (physical function, pain, and stiffness subscales), time and pain intensity from the 40-m self-paced walk test, time and pain intensity from the 11-step stair climb test, PSQI, IGAC and PGAC, SL-VAS, ARCI, and DoloTest. These tests were listed and summarized using standard descriptive statistics. Additional analyses were performed if warranted upon review of the data.

Safety Measures: Summary statistics were provided on the safety parameters such as VS, ECGs, clinical laboratory results, subjective questionnaire (C-SSRS). Exploratory statistical analyses may have been performed as appropriate.

SUMMARY OF RESULTS

Subject Disposition: 39 enrolled and included in the safety analysis; 37 included in pharmacokinetic (PK) analysis, 39 included in pharmacodynamic (PD) analysis.

Demographics: Gender: 25 males and 14 females; Race: 39 (100%) White;
Mean age ± standard deviation (SD): 63.3 ± 6.9 years; Median Age: 64.0 years (min - max: 48 - 74 years).

Efficacy/Pharmacodynamic Results:

There were no statistically significant differences for any of the primary or secondary analyses. Any statistically significant analyses for the exploratory analyses for treatment effect on Exploratory Pain Models (EPMs) and biomarkers were considered not clinically relevant. There were no significant correlations between the treatment difference (LY2828360 - placebo) in the weekly mean daily APS change from baseline at Week 4 and any of the PK parameters.

Pharmacokinetic Results:

Pharmacokinetic data from Study CCAC were very similar to those determined after 2 weeks of treatment in the 85 mg cohort of Study CCAB. This corroborates the fact that steady state already is reached after 2 weeks. The variability of the pharmacokinetic parameters was also similar. The C_{max} geometric mean at the 80 mg dose after 4 weeks of administration in patients was 439.2 ng/mL and moderate interindividual variability was observed (geometric percentage coefficient of variation [%CV] = 35%). Mean pharmacokinetic parameters were higher in women than in men, and the variability in each gender was slightly lower than the overall variability.

Safety Results: Of the 39 patients who were randomized to receive LY2828360 or placebo, a total of 32 completed the study. Five randomized patients prematurely discontinued from the study due to adverse events (AEs) or use of forbidden concomitant medication. Four of these 5 patients prematurely discontinued because of medical reasons (ongoing pain) or use of forbidden concomitant medication to relief pain symptoms. The fifth patient reported an episode of rash after having received 14 doses of LY2828360. The AE in this fifth patient was considered by the investigator to be possibly related to study drug because the AE occurred during the dosing period; however, the event may have been related to patient use of expired sunburn cream. Two other patients did not complete the study (1 withdrew consent for personal reasons and 1 was prematurely discontinued after receiving the wrong study treatment).

A total of 57 TEAEs were reported by 24 patients. All TEAEs were mild to moderate in intensity except one back pain event that was severe but it was not evaluated as study drug related. Fifteen patients reported 26 TEAEs that were judged as study drug related by the investigator. There was no clear relationship between the dose and the type or the number or the frequency of TEAEs.

There were no notable trends in change from baseline for neither laboratory values nor ECG parameters within patients.

CONCLUSIONS:

- There were no statistically significant differences for any of the primary or secondary analyses. Any statistically significant analyses for the exploratory analyses for treatment effect on EPM and biomarkers were considered not clinically relevant.
- Pharmacokinetic data from Study CCAC obtained after 4 weeks of daily administration of 80 mg were very similar to those determined after 2 weeks of treatment in the 85 mg cohort of Study CCAB. This corroborates the fact that steady state is reached after 2 weeks of daily administration of LY2828360. Mean exposure (ie, $AUC_{0\text{-}8h}$) was slightly higher in women (3283 ng*h/mL) than in men (2428 ng*h/mL).
- LY2828360 at 80 mg QD for 4 consecutive weeks were well tolerated by patients with OA knee pain. There was no clear relationship between administrations of LY2828360 and the type or number of TEAEs. Review of VS and ECG data did not reveal any clinically significant safety concerns.

Date of Report: Final – 3 January 2012