2. BPAE Synopsis

Clinical Study Report Synopsis: Study I1A-MC-BPAE

Title of Study: A Phase 2 Clinical Study to Evaluate Daily Oral Doses of LY500307 for 24 weeks in Men with Lower Urinary Tract Symptoms (LUTS) and Prostatic Enlargement Secondary to Benign Prostatic Hyperplasia (BPH)	
Number of Investigators: This multicenter study included - 80 principal investigators.	
Study Center(s): This study was conducted at 80 study centers in 8 countries.	
Publication(s) Based on the Study: None at this time.	
Length of Study: Date of first patient enrolled: 24 May 2010 Date of last patient completed entire study: 18 October 2011	**Phase of Development:** 02

Objectives: The primary objective of this study was to compare the effect of LY500307 once daily for 24 weeks versus placebo treatment in improving the International Prostate Symptom Score (IPSS) in men with LUTS and prostatic enlargement secondary to BPH.

The secondary objectives of this study include the following:

- To compare the effect of 24 weeks of LY500307 versus placebo treatment on the total prostate volume (TPV) as measured by trans-rectal ultrasound (TRUS)
- To evaluate the effect of 24 weeks of LY500307 versus placebo treatment on peak urinary flow rate (Q_{max})
- To evaluate the effect of 24 weeks of LY500307 versus placebo treatment on
  - BPH-related quality of life (QoL) assessed by IPSS-QoL Index; and
  - IPSS storage, voiding, and nocturia subscores
- To evaluate the effect of 24 weeks of LY500307 versus placebo treatment on prostate specific antigen (PSA)
- To evaluate LY500307 pharmacokinetic (PK) and factors affecting LY500307 exposure
- To evaluate the relationship between LY500307 exposure and clinical efficacy as well as safety measures
- To assess the safety of LY500307 once daily for 24 weeks in the treatment of men with LUTS and prostatic enlargement secondary to BPH

Study Design: Study I1A-MC-BPAE (BPAE) was an outpatient, multicenter, randomized, double-blinded, placebo-controlled, parallel, Phase 2 dose-finding study in 414 male subjects with LUTS and documented prostate enlargement secondary to BPH. Patients were randomized to placebo or to 1 of 4 LY500307 treatment arms (1-, 3-, 10-, or 25-mg LY500307 doses). Randomization was stratified by country and according to baseline statin use.

Number of Subjects:

- Planned: 575
- Randomized: 414
- Treated (at least 1 dose): 85 subjects received placebo; 83 subjects received 1 mg LY500307; 80 subjects received 3 mg LY500307; 82 subjects received 10 mg LY500307; and 84 subjects received 25 mg LY500307.
- Completed: 36 subjects receiving placebo; 39 subjects receiving 1 mg LY500307; 37 subjects receiving 3 mg LY500307; 37 subjects receiving 10 mg LY500307; and 40 subjects receiving 25 mg LY500307

Diagnosis and Main Criteria for Inclusion: Male patients with a history of BPH and moderate-to-severe LUTS due to prostate enlargement defined as baseline IPSS score ≥13 and TPV ≥30 mL, who are at least 45 years of age and who have given informed consent, were eligible to participate in this study. Only BPH patients with total testosterone concentration of ≥300 ng/dL were enrolled into this study.

LY500307, Dose, and Mode of Administration:

LY500307 doses of 1, 3, 10 or 25 mg, given orally once a day as capsules in strengths of 1, 5, and 25 mg. To maintain the blind, each test product dose consisted of 3 capsules as follows:

- LY500307 1-mg dose = 1 LY500307 1-mg capsule and 2 placebo capsules
- LY500307 3-mg dose = 3 LY500307 1-mg capsule and 0 placebo capsules
- LY500307 10-mg dose = 2 LY500307 5-mg capsules and 1 placebo capsule
- LY500307 25-mg dose = 1 LY500307 25-mg capsule and 2 placebo capsules

Reference Therapy, Dose, and Mode of Administration: Identical-in-appearance placebo capsules to be taken once a day in the morning before breakfast. Each dose consisted of 3capsules.

Duration of Treatment:

Placebo Lead-in Period: 4 weeks; Active Treatment Period: 24 weeks; Follow-up Period: up to 8 weeks.

Variables:

Efficacy: IPSS; TPV by TRUS of prostate; uroflowmetry; IPSS storage, voiding, nocturia subscores and the QoL index score; and PSA

Safety: Adverse events (AEs); serious adverse events (SAEs); AEs of special interest including all fatal and non-fatal cardiovascular events (deep vein thrombosis, retinal vein thrombosis, cerebral venous thrombosis, superficial venous thrombosis requiring anticoagulation, nonfatal pulmonary embolism, and major cardiovascular events including myocardial infarction [MI], unstable angina, stroke, and transischemic attack [TIA]); electrocardiograms (ECGs); weight, blood pressure and pulse rate; biomarkers of iatrogenic hypogonadism (total and free testosterone, dihydrotestosterone [DHT] and sex-hormone binding globulin [SHBG]); gynaecomastia; fasting lipid profiles; and routine hematology and clinical chemistry tests.

Pharmacokinetic: Absorption constant (ka); apparent oral clearance (CL/F); apparent distribution volume at steady state (Vss/F); area under the concentration-time curve during a daily dosing interval at steady state (AUC_{SS}); and terminal half-life ($t_{1/2}$). Other PK parameters (for example, maximal plasma concentration [C_{max}] and time of C_{max} [t_{max}]) may also be reported as deemed appropriate.

Statistical Evaluation Methods:

Efficacy: The primary efficacy endpoint for this study is the IPSS total score change from baseline (Visit 3) after 24 weeks (Visit 8) of LY500307 treatment. Assuming, compared with placebo, a treatment effect of 2-point reduction with a standard deviation (SD) of 6 in the IPSS total score change from baseline, 82 patients per treatment arm were required to complete 24 weeks of treatment to provide 80% power with a 1-sided alpha of 0.1 or 68% power with a 2-sided alpha of 0.1. Assuming a 29% drop-out rate for the study, 115 patients were randomized to each treatment arm; a total of approximately 575 patients were randomized for this study. Efficacy analyses were conducted for the Active-Treatment Period on the modified intent-to-treat (mITT) population. Efficacy analyses for the variables of IPSS total score change from baseline and TPV were also conducted on the per-protocol population. Safety analyses were conducted on the intent-to-treat (ITT) population. All efficacy variables were summarized by descriptive statistics for each treatment group during the treatment period (Visit 1 or Visit 2 or Visit 3 through Visit 8). For continuous variables, summary statistics include the number of observations, mean, median, minimum, maximum, and SD. For categorical variables, counts and percentages were tabulated for each category. Unless otherwise specified, all statistical comparisons were at the 2-sided, 0.1 statistical significance level although the study is only powered at the 1-sided 0.1 alpha level. No adjustment of type-1 error for multiple comparisons was made.

Pharmacokinetic/Pharmacodynamic: Plasma LY500307 concentration data were analyzed via a population PK approach implemented with the program nonlinear mixed-effect model (NONMEM). No covariate search was conducted.

The relationship between LY500307 exposure and efficacy measurements (IPSS and TPV) as well as PD/safety biomarker (TT) were evaluated graphically, where LY500307 exposure parameters (AUC_{SS}) in individual patients were used.

Safety: Adverse events (AEs) are classified according to the Medical Dictionary for Regulatory Activities (MedDRA) and reported at the MedDRA system-organ class and preferred-term levels. Treatment-emergent adverse events (TEAEs) and SAEs are listed by treatment group. Counts and proportions of TEAEs and SAEs are reported by treatment group and compared among treatment groups by Fisher l exact/Pearson treatment group, and vital signs, including systolic blood pressure, diastolic blood pressure, pulse rate (PR), and weight were listed and summarized by treatment group and visit. A mixed-model for repeated measures (MMRM), with baseline response measurement, treatment, visit, and treatment-by-visit as independent variables, were used to analyze vital signs and weight. Least-squares (LS) means are reported by treatment and visit. LS mean differences, 90% confidence intervals (CI), and p-values are reported for treatment comparisons. Electrocardiogram (ECG) data will be listed and summarized by treatment and visit.

LY500307 effect on total and free testosterone and DHT concentrations was tested using an analysis of covariance model with predose measurements as a covariate and the Visit 8 measurement as a response variable.

LY500307 effect on LDL-C was analyzed with MMRM. Statin use was added ovariate in the LDL-C analysis. In addition, a maximum-effect model may be carried out to further assess the dose-safety response and exposure-safety response relationships. Exposure to each study treatment was calculated for each patient and summarized by treatment group.

Interim Analyses: A Data Assessment Committee (DAC) was established prior to the interim analyses to control the dissemination of the findings. Only the DAC is authorized to evaluate unblinded interim efficacy, safety, and PK analyses.

Summary:

Study BPAE was designed to test the hypothesis that LY500307, a selective ERβ agonist, is efficacious in reducing TPV and relieving LUTS in men with BPH at an "androgen-sparing" dose. The primary endpoint of the study, IPSS total score, is the standard measurement of efficacy and is an FDA-required clinical endpoint for drugs that are aimed at the treatment of LUTS due to BPH. A key secondary endpoint, the change in TPV from baseline, is a commonly tested endpoint in clinical trials of α-reductase inhibitors (ARI) that aim at slowing the clinical progression of BPH.

The patient population and study duration are also comparable to those selected in Phase 2 trials for ARIs. These considerations make it possible to compare the effect of LY500307 with the published results of our comparator, dutasteride and finasteride (the 2 ARIs marketed for the same indication).

The analysis of the interim data from Study BPAE met the a priori determined futility criteria which, therefore, led to the early termination of the trial. At the conclusion of the study, no clinically and statistically significant changes in IPSS score were achieved after 6 months of treatment. None of the IPSS subscores indicated any therapeutic benefit in storage or obstructive symptoms, or BPH-related QoL. All treatment groups experienced reduction in the IPSS score throughout the trial, and none of the LY500307-treated groups demonstrated any statistically or clinically meaningful separation from placebo group. While marked placebo response could be one of the underlying reasons for the lack of separation of active treatment from placebo, the placebo response observed in this trial (IPSS change from baseline of -3.44 ± 6.82) was comparable with other clinical trials of similar design (McConnell et al. 2003) (Roehrborn et al. 2004). In addition, unlike ARIs, LY500307 also demonstrated a lack of treatment effect in the Q_{max}. Both parameters suggested that the therapeutic efficacy for LY500307 is inadequate for the treatment of LUTS in BPH patients.

Preclinical animal models and pathological examination of prostate tissues from BPH patients suggested that ERβ pathway plays an important role in the apoptotic process in prostate epithelial and stromal tissues (Weihua et al. 2002) (onso-Magdalena et al. 2009). The preclinical pharmacology model supported this hypothesis. Animals treated with LY500307 demonstrated more rapid reduction in prostate volume, and apoptosis was observed in both epithelial and stromal tissue. Study BPAE is the first clinical trial to test this hypothesis in patients with LUTS due to enlarged prostate. Results from this trial revealed no clinically and statistically significant reduction in TPV after 6 months of treatment, while the expected effect from ARI treatment for similar duration would have been between 15% to 17% (Roehrborn et al. 2004). The observed variability of TPV measurement was less than the assumed variability for sample-size calculation; therefore, Study BPAE is adequately powered to detect any clinically relevant reduction in prostate volume. A 6.6% reduction in TPV was observed in patients randomized into placebo treatment, which is not consistent with the observation from large randomized controlled trials suggesting that in BPH patients, TPV increases over time (McConnell et al. 2003). In smaller trials, similar degree of reduction in TPV has been reported (Bent et al. 2006). Regardless of the placebo response observed in Study BPAE, the percentage changes of TPV from baseline in the LY500307-treated groups were much less than the ARIs. In addition, no clear dose response was observed.

LY500307 was in general well tolerated in BPH patients up to 25 mg once daily for 24 weeks. The incidence rate of SAEs, early termination due to AE, AESI, and TEAEs, was comparable between patients randomized to LY500307 and placebo. In addition, at the dose testing, there were no clinically significant androgen suppression, alteration in fasting lipid profile, and routine laboratory testing (complete blood counts, liver and renal functions). There were no clinically significant changes in vital signs and weight in patients randomized to LY500307. There was no increased incidence of sexual dysfunction as reported by patients in Study BPAE, or significant change in sexual dysfunction as measured by IIEF and MSHG-EjD questionnaires.

The PK profile of LY500307 in BPH patients was similar to the profile of healthy males and exceeds the exposure of LY500307 in the preclinical pharmacology studies.

One question remains as to whether LY500307 would be beneficial if administered at a higher dose. Based on the Phase 1 data, it has been anticipated that up to 12% suppression in total testosterone concentration could be observed in patients randomized to a 25-mg LY500307 dose. In Study BPAE, no testosterone suppression was observed at any active dose. This discrepancy could be attributed to the age difference between the Phase 1 studies (age range 20 to 60 years) and Study BPAE (median age for the treatment groups is between 63.55 and 67.47 years). It is well known that as men age, their hypothalamus-pituitary-gonadal sensitivity to estrogen suppression decreases (Veldhuis and Iranmanesh 2005); therefore, it follows that BPH patients could tolerate a higher dose of LY500307 than healthy young men. However, health inspection of the efficacy results from Study BPAE failed to indicate any dose-response in any of the efficacy endpoints. In addition, at the highest dose, the exposure of LY500307 is approximately 8 times that of the effective dose in the preclinical animal model, which should adequately bridge any interspecies differences.

Conclusion:

- LY500307, a selective ERβ agonist, was well tolerated in patients with LUTS due to BPH at doses up to 25 mg for 24 weeks, as measured by incidences of AEs, vital signs, routine laboratory tests, hormonal and fasting lipid profiles.
- The efficacy of LY500307 at doses up to 25 mg once daily for 24 weeks in relieving LUTS as measured by IPSS scores in mean with LUTS due to enlarged prostate was inadequate to support future development of LY500307 for the treatment of symptoms and signs of BPH.
- No clinically relevant and statistically significant reduction in total prostate volume was observed in patients with LUTS due to prostate enlargement.
- Changes in Q_{max} in LY500307-treated patients cannot be differentiated from patients randomized to placebo.
- The PK parameters observed in Study BPAE were consistent with those observed in Phase 1 trials.

References

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