Clinical Study Report

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Study of the Safety and Efficacy of LY2623091 in Chronic Kidney Disease Patients

Investigational Medicinal Product: LY2623091
Indication Studied: Chronic kidney disease (CKD)
PAREXEL Study Number: 203297
Sponsor Study Number: I4M-MC-MRAC
Development Phase: Phase IIa
Company/Sponsor Signatory: [redacted]
Vice President Chorus, [redacted]
Eli Lilly and Company
[redacted]
United States of America (USA) [redacted]

Coordinating Investigator Name and Address: [redacted]
South Africa, 9300

Study Duration: 09 September 2011 to 20 March 2013
Date of Report: Final 1.0, 10 March 2014

This study was conducted in compliance with International Conference on Harmonisation Good Clinical Practice guidelines and the Declaration of Helsinki. The essential documentation related to this study has been retained by relevant parties.

2 SYNOPSIS

Title of Study:	Study of the Safety and Efficacy of LY2623091 in Chronic Kidney Disease Patients	
Study Numbers:	[redacted].: PXL203297 Sponsor Study No.: I4M-MC-MRAC	
Investigational Medicinal product:	LY2623091	
Development Phase:	Phase IIa	
Sponsor:	[redacted] Indianapolis, Indiana 46285 United States of America	
Coordinating Investigator:	[redacted]	
Study Center(s):	• [redacted] South Africa • [redacted] South Africa • [redacted] South Africa [redacted] • [redacted] South Africa • [redacted] Bulgaria • [redacted] Macedonia	
Publication:	None	
Studied Period:	**First patient screened:**	09 September 2011
	Last patient completed:	20 March 2013

Study Objective(s):

Primary Objective:

- To investigate the effect of LY2623091 on change from baseline in proteinuria after 3 weeks of daily oral dosing in patients with chronic kidney disease (CKD).

Secondary Objectives:

- To investigate the effect of LY2623091 on potassium clearance following an oral potassium challenge in patients with CKD,
- To investigate the safety and tolerability of LY2623091 in patients with CKD,
- To explore the pharmacokinetic (PK) profile of LY2623091 after multiple oral dosing in patients with CKD.

Study Design:

This was a Phase IIa, multiple dosing, double blind, positive control, 2 period incomplete cross over study that enrolled men and women of non-childbearing potential diagnosed with CKD. The study consisted of the following 4 treatment arms: 1) 0.2 mg LY2623091, 2) 1.5 mg LY2623091, 3) 10 mg LY2623091, and 4) 50 mg eplerenone (EPL), all once daily (QD). Patients participated in 2 treatment arms, separated by a wash out period; this schedule was considered a treatment sequence. Patients were randomly assigned to one of 12 possible treatment sequences.

Methodology:

Chronic kidney disease patients who were enrolled in the study participated during 2 treatment

periods. Each period included 21 days of drug administration, with a minimum wash-out period of 28 days between dosing in treatment periods 1 and 2. The study drug was administered QD in a fed state with dosing days numbered 1 to 21 in each of the treatment periods, except on Day 21 when dosing occurred in a fasted state because an oral potassium challenge was scheduled on that day, 1 hour post dose. Screening was performed within the 28 days prior to the first dose of study drug. A follow-up visit occurred approximately 7 to 10 days after the last dose of study drug in treatment period 2.	
Study Patients: Patients with a diagnosis of CKD	
Planned for inclusion:	48 patients
Enrolled and randomized:	42 patients
Excluded:	Zero (0) patients were excluded from the safety population One (1) patient was excluded from the pharmacodynamic (PD) population One (1) patient was excluded from the PK population
Analyzed:	Forty-two (42) patients in the safety population Forty-one (41) patients in the PD intent-to-treat population (ITT) Thirty-nine (39) patients in the PK ITT population (2 patients withdrew consent after being dosed with EPL, but prior to receiving any dosings with LY2623091 and were therefore not included in this population)
Diagnosis and Inclusion Criteria: Men and women (18–75 years of age) previously diagnosed with CKD (including diabetic kidney disease [DKD] and chronic glomerulonephritis) were eligible for enrolment onto the study – only if they were of non-childbearing potential, had an estimated glomerular filtration rate (eGFR) between 30 and 70 mL/min/1.73m^2 and had been taking an angiotensin converting enzyme (ACE) inhibitor and/or angiotensin II receptor blocker (ARB), for at least 3 months, and at a stable dose for ≥ 2 months prior to randomization.	
Protocol Deviations: Minor protocol deviations that mostly related to the recording of incorrect urine weight and volumes occurred during the study period. One protocol deviation related to exclusion criteria (use of verapamil in 1 patient).	
Test Product, Dose and Mode of Administration, Batch Number:	
Test product:	LY2623091
Presentation:	Capsule
Mode of administration:	Oral
Dose:	0.2, 1.5, and 10 mg QD
Reference Product, Dose and Mode of Administration, Batch Number:	
Reference product:	Eplerenone
Presentation:	Capsule
Mode of administration:	Oral
Dose:	50 mg QD (standard dose)

Duration of Treatment:

There were 2 treatment periods, each with a 21-day duration of drug administration. A minimum wash-out period of 28 days between the 2 treatment periods was required. An oral potassium challenge was scheduled after dosing on the last treatment day in each period (Day 21). Screening was performed within 28 days prior to the first dose of study drug. A follow-up visit occurred approximately 7 to 10 days after the last dose of study drug in the second treatment period.

Treatment Compliance:

2 patients each missed 2 dosing days.

Criteria for Evaluation:

Efficacy: The primary evaluation of efficacy was change from baseline in 24-hour proteinuria after 3 weeks of daily oral dosing in CKD patients.

Pharmacodynamics: 24-hour protein: creatinine ratios (PCR) for Day -1 and Day 21 [urine collection started at -26 h (Day -2 or Day 20) and ended 2 hours prior to the oral potassium challenge on Day -1 or Day 21]; PCR of the first morning urine sample on Days -2, -1, 1, 7, 14, 20, 21, 22; Potassium clearance following oral potassium challenge; urine aldosterone and serum potassium.

Pharmacokinetics: Plasma LY2623091 concentrations on Day 20 of each treatment period.

Safety: Adverse events (AEs, including severity), clinical laboratory tests (including clinical chemistry, hematology, urinalysis, and serology), vital signs, physical examination, and electrocardiograms (ECGs).

Statistical Methods:

All efficacy analyses were conducted on the PD ITT population.

Efficacy: The difference between 24-hour proteinuria values obtained at baseline (Day -2/-1) and that obtained after 21-days of treatment were calculated for each patient after each treatment period. The difference between baseline and post-treatment values were considered the change from baseline in 24-hour proteinuria. Differences in the change from baseline in 24-hour proteinuria, following the different treatments, were compared using non-parametric tests because the data did not have a normal distribution. In addition, since the data violated the normality assumptions, the 24-hour proteinuria data were log-transformed and the absolute as well as the percentage changes from baseline were calculated using the log-transformed results. A graphical display of the change from baseline and percentage change from baseline in 24-hour proteinuria were presented on the log-transformed data and visual inspection of the 24-hour proteinuria data identified 4 extreme values from 2 patients. Sensitivity analyses were then conducted on the absolute as well as percentage change from baseline in 24-hour proteinuria after removal of the 24-hour proteinuria data for the 2 patients who had extreme values. For each patient, the 24-hour proteinuria data for the entire treatment period in which the extreme value(s) occurred, were removed.

Pharmacodynamics: The change from baseline in 24-hour PCR was compared between the treatments using a linear mixed effects analysis of variance (ANOVA) with treatment and treatment period included as fixed effects and patient included as a random effect. A sensitivity analysis on 24-hour PCR data was also conducted after removal of 24-hour PCR data for the patient from the entire treatment period in which the extreme 24-hour proteinuria value(s) was identified. Since the data violated the normality assumptions, the 24-hour PCR results were log-transformed and the planned analyses, including the sensitivity analysis, were repeated using the log-transformed data.

The average of the mean PCR values from first morning urine samples of Days -2, -1 and 1 (pre-dose), and the average of the mean PCR values of Days 20, 21 and 22 (end of treatment) in each treatment period were calculated; the change from baseline was calculated by subtracting the average pre-dose mean from the average end of treatment mean per treatment period. The change from baseline in oral potassium challenge parameters (Day -1 to Day 20) were compared between the treatments using a linear mixed effects analysis of covariance (ANCOVA) with treatment and treatment period included as fixed effects and patient included as a random effect. Since the data violated the normality assumptions, the PCR values for pre-dose and end of treatment were log-transformed and the planned analyses were repeated using the log-transformed data.

Pharmacokinetics: Standard non-compartmental methods were used to assess pharmacokinetics in the PK population. The primary parameters were peak concentrations as well as the area under the curve during the dosing period on Day 20.

Safety: All randomized patients received the study drug and were included in the safety analyses (safety population). Sensitivity analyses were performed to exclude extreme values from the potassium results using the same definition of extreme values as above for efficacy analysis.

Results:

The effect of LY2623091 on proteinuria

The change in 24-hour proteinuria (absolute values with percentage change in parenthesis) for the different treatments were as follows: -98.9 mg/24-hrs (2.28%) for 0.2 mg, -19.7 mg/24-hours (2.50%) for 1.5 mg, 119.4 mg/24-hrs (-1.91%) for 10 mg LY 2623091, and 273.7 mg/24-hours (38.42%) for 50 mg EPL. There were no significant reductions in proteinuria by LY2623091 or by EPL treatments based on the full analysis set. Analysis of the log-transformed data showed a non-statistically significant trend for a reduction in the percentage change in proteinuria, from a low to a high dose of LY2623091 (-1.06% for the 0.2 mg dose, -1.47% for the 1.5 mg dose and -2.28% for the 10 mg dose).

The sensitivity analysis, which excluded 2 patients from the treatment period in which they had 1 or more extreme value, showed a non-statistically significant trend for a reduction in proteinuria from a low to a high dose of LY2623091, although the reduction in 24-hour proteinuria following treatment with the intermediate dose level (1.5 mg) was smaller than expected for this trend. The trend for a reduction in the percentage change of log-transformed 24-hour proteinuria values was also evident in the results of the sensitivity analysis (-1.10% for the 0.2 mg dose, -1.47% for the 1.5 mg dose and -2.77% for the 10 mg dose).

Protein:creatinine ratio (PCR) from 24-hour urine samples: Analysis of the full data set showed a non-statistically significant reduction in PCR following the 10 mg treatment dose (-287 mg/g) and analysis of the sensitivity set, in which 2 patients were excluded from the treatment period in which they had 1 or more extreme value, showed a statistically significant reduction in the absolute and percentage 24-hour PCR change from baseline results following this dose level (-416 mg/g and -18.8%, respectively). There was a non-statistically significant trend for a reduction in mean 24-hour PCR values although the intermediate dose level (1.5 mg) did not result in a reduction in this parameter and it therefore did not fit this trend. Log-transformation of the sensitivity data set also showed this trend for a reduction in mean 24-hour PCR, with the intermediate dose level not following this trend.

Protein:creatinine ratio from first morning urine samples: Analysis of the full analysis set showed a non-statistically significant reduction in PCR from baseline to end of treatment following the 10 mg treatment dose (-141 mg/g). For this analysis, baseline was defined as the average of the

values from Days -2, -1, and 1, and the end of treatment value was defined as the average of the values from Days 20, 21, and 22. There were no extreme values among the PCR results from first morning urine samples and no sensitivity analyses were thus conducted.

Urine creatinine: There were no significant changes in urine creatinine after treatment with the study drug, nor were there significant differences in such across treatments.

Urine aldosterone: There was an increasing trend in urine aldosterone from low to high dose of LY2623091, and also an increase in urine aldosterone following EPL treatment. The trend was not obvious for the middle dose level of LY2623091 (1.5 mg). None of the changes were statistically significant within a treatment or across treatments.

Potassium clearance

Change in serum potassium over the course of treatment: LY2623091 had a dose-related effect on serum potassium. There was a small reduction in serum potassium over time following the lower LY2623091 doses (0.2 and 1.5 mg) and an increase over time following the 10 mg dose. The change in serum potassium levels following treatment with 0.2 mg LY2623091 was statistically significantly lower than that following 10 mg LY2623091 on Day 14 (P = 0.022), with a trend for lower changes in potassium levels on Day 20 (P = 0.058). Treatment with EPL resulted in an increase in serum potassium which was similar to or slightly lower, but not statistically different, than that after treatment with the 10 mg dose. The change in serum potassium following 0.2 mg LY2623091 was significantly lower than that following EPL (P = 0.034, Day 20).

Serum potassium post oral potassium challenge

LY2623091 treatment had a dose-related effect on serum potassium levels following the oral potassium challenge: There was a small reduction from baseline following the 0.2 mg LY2623091 dose and progressive increases from baseline following the 1.5 mg and 10 mg doses. Serum potassium levels also increased following treatment with EPL, with the magnitude of the increase between that evoked by the 1.5 mg and 10 mg doses of LY2623091. The serum potassium area under the curve for the 6 hours post challenge (AUC_{0-6}) following the 0.2 mg LY2623091 dose was significantly lower and the AUC_{0-6} following the 10 mg LY2623091 dose was significantly higher than that following treatment with EPL (P = 0.003 for both 0.2 and 10 mg LY2623091 vs. EPL).

Renal potassium clearance

There was a trend for reduction in renal potassium clearance post potassium challenge as the dose level for LY2623091 increased; however, significance was not reached. The change from baseline in renal potassium clearance following treatment with 0.2, 1.5 and 10 mg LY2623091 did not differ significantly from that following EPL.

Serum potassium:urine potassium to sodium ratio

The change from baseline (Day -1) at Day 21 in serum potassium:urine potassium to sodium ratio post oral potassium challenge, represented by a change in AUC_{0-6}, did not differ significantly from that following treatment with EPL, nor across LY2623091 dose levels. There was a tendency for the ratio to increase from a low to a high dose of LY2623091 (mean change in serum potassium:urine potassium to sodium ratio following the 0.2 and 10 mg dosings were -0.617 and 1.289 h*mmol/L, respectively, P = 0.525). EPL resulted in a change in the same range as the 10 mg LY2623091 dosing (0.957 h*mmol/L).

Pharmacokinetic results

The peak concentration of LY2623091 occurred at approximately 2 to 4 hours after each of the 3 treatments followed by a slow decline over the next 20 hours. Mean plasma concentration at peak was 1.84, 1.91 and 1.88 fold that at trough for the 0.2, 1.5 and 10 mg LY2623091 dosages,

respectively. The LY2623091 geometric mean, peak plasma concentration ($C_{max,ss}$) and area under the plasma concentration time curve within the dosing interval ($AUC_{0-\tau}$, τ = 24 hours) increased in a dose proportional manner over the 0.2 mg to 10 mg dose range. The median time of maximum observed plasma concentration ($t_{max,ss}$) following the 0.2 mg dose was 2.99 hours, whilst the median $t_{max,ss}$ following 1.5 mg and 10 mg doses was 2.00 hours. Moderate variability in PK parameters was observed with geometric coefficient of variation percentage (GCV%) of 31% to 44% for the $C_{max,ss}$ and $AUC_{0-\tau}$ parameters across the dose levels.

Safety Results:

The number and percentage (in parenthesis) of patients with at least one treatment-emergent adverse events (TEAE) in the different treatment groups were as follows: 9 (42.9%) in 0.2 mg LY2623091, 9 (40.9%) in 1.5 mg LY2623091, 8 (47.1%) in 10 mg LY2623091 and 10 (47.6%) in EPL. In total, 65 TEAEs were reported during the study period by 36 patients. Four (4) serious adverse events (SAEs), of which 1 leading to death, were reported in 3 patients. None of these SAEs were assessed by the reporting Investigator as related to study drug and none of the study patients discontinued from the study due to SAEs.

Ten (10) of the 65 TEAEs were considered related to treatment: 6 of these were related to gastrointestinal disorders, 1 to elevated blood potassium levels, 1 to insomnia and 2 to vascular disorders and none were considered severe. During the 28-day wash-out period between treatment periods 1 and 2, a total of 15 AEs were reported: 4 related to gastrointestinal disorders (4 participants), 5 to infections and infestations (5 participants), 2 to metabolic and nutritional disorders (2 participants), 1 to musculoskeletal and connective tissue disorders, and 3 to nervous system disorders (2 participants). The highest LY2623091 dose reduced mean systolic blood pressure (BP) by about 8 mm/Hg and diastolic BP by about 2 mm/Hg. There was no physiologically meaningful change in the heart rate of patients in the different treatment groups over the course of treatment.

Discussion:

There is evidence to support the inhibition of mineralocorticoid (aldosterone) receptors as a therapeutic modality for CKD. However, currently available aldosterone antagonists are associated with the development of hyperkalemia at the doses administered to achieve desired efficacy. The focus of this study was to determine what, if any, therapeutic index exists for LY2623091 for improvement in renal function of a CKD population. The effects on proteinuria and on potassium handling were evaluated across a dose range of LY2623091, and compared to treatment with EPL.

Efficacy

24-hour Proteinuria: There was a non-significant trend for a reduction in 24-hour proteinuria from low to high doses of LY2623091 that was evident from analyses of log-transformed data and the sensitivity data set. For the sensitivity analyses, 2 patients were excluded from the treatment period in which they had 1 or more extreme value. EPL treatment resulted in a reduction in proteinuria analogous in magnitude to that of the lowest dose of LY2623091, albeit not statistically significant.

Pharmacodynamics

PCR: The trend for a reduction in proteinuria, from a low to a high dose of LY2623091, observed in the analysis of 24-hour proteinuria data, was also evident in the change from baseline analyses of 24-hour PCR as well as first morning urine PCR values. However, the intermediate dose level (1.5 mg LY2623091) did not fit this trend.

Serum potassium: LY2623091 treatment resulted in a dose-related change in serum potassium, with a small reduction following a dose of 0.2 mg and progressive increases following 1.5 and 10 mg

doses. The effect of 10 mg LY2623091 on serum potassium levels appeared similar to that of EPL within the study.

Potassium clearance post oral potassium challenge: LY2623091 treatment also resulted in a dose-related effect on serum potassium following the oral potassium challenge, with a reduction in serum potassium after administration of 0.2 mg LY2623091 and progressive increases as the LY2623091 dose increased. Treatment with EPL increased serum potassium levels post challenge, with a magnitude of effect that fell within that across the LY2623091 dose range (between 1.5 and 10 mg).

Pharmacokinetics

Pharmacokinetic profile: The PK of LY2623091 in CKD patients in this study was generally consistent with the PK in healthy subjects as reported in a previous study (MRAB). LY2623091 exposure in both populations was dose-proportional; a comparison of the dose-normalized mean Day 6 and Day 20 $AUC_{0-\tau}$ and $C_{max,ss}$ values in healthy subjects and CKD patients, respectively, indicated slightly lower exposures in the CKD population (approximately 30% lower than those in healthy subjects for both parameters). The overlap between the range of dose-normalized $AUC_{0-\tau}$ and $C_{max,ss}$ values for CKD patients (n=20 per group) and healthy volunteers (n=8 per group) was large. Such small mean differences across studies are common, and cannot be interpreted as a true PK difference between patients and healthy subjects. However, it was noted that variability of $C_{max,ss}$ and $AUC_{0-\tau}$ in this study appear to be larger than those reported in healthy subjects in study MRAB, where coefficient of variation percentage (CV%) was approximately 2 to 3 fold lower. Larger datasets and cross-study population PK modeling can be used to estimate the difference in PK if it exists.

Safety

Sixty-five (65) TEAEs were reported during the study period by 36 patients. Four (4) SAEs, of which one leading to death, were reported by 3 patients. None of these SAEs were assessed by the reporting Investigator as related to study drug and study patients did not discontinue from the study due to SAEs.

Conclusions:

Efficacy and Pharmacodynamics

- The LY2623091 dose required for a reduction in proteinuria and that which showed an effect on potassium handling were not substantially different.
- There was no evidence of an improved therapeutic index for LY2623091 compared to EPL.

Pharmacokinetics

- The LY2623091 PK parameters $C_{max,ss}$ and $AUC_{0-\tau}$ increased in proportion to dose over the tested dose range.
- The PK of LY2623091 in CKD patients in this study was generally consistent with the PK in healthy patients (MRAB), with slightly lower exposures and higher variability in patients.

Safety

- All doses of LY2623091 administered in this study (0.2, 1.5 and 10.0 mg) appeared safe and were generally well tolerated by CKD patients when considering the clinical observations and vital signs of patients.
- The highest LY2623091 dose reduced BP parameters to a similar extent as EPL, while there were no meaningful changes in heart rate across treatments.
- Serum potassium increased in a dose-related manner for LY2623091.

Date of Report: Final 1.0, 10 March 2014
This study was conducted in compliance with International Conference on Harmonisation Good Clinical Practice guidelines and the Declaration of Helsinki.