PriCara™, Unit of Ortho McNeil, Inc.

Clinical Study Report

A MULTICENTER, DOUBLE-BLIND PHASE 3B STUDY TO COMPARE THE SAFETY AND CLINICAL EFFICACY OF LEVOFLOXACIN 750 MG FOR 2 WEEKS AND LEVOFLOXACIN 750 MG FOR 3 WEEKS TO THAT OF LEVOFLOXACIN 500 MG FOR 4 WEEKS IN THE TREATMENT OF CHRONIC PROSTATITIS

Protocol CR012103; Phase 3B

RWJ-25213-097 (levofloxacin)

PRINCIPAL INVESTIGATOR:
Multi-center

DATE STUDY INITIATED:
27 November 2006

DATE STUDY COMPLETED:
03 September 2008

Issue Date: 09 January 2009
Prepared by: PriCara, Unit of Ortho-McNeil, Inc.
Department: Medical Affairs
Document No.: EDMS-USRA-11065176:2.0

SYNOPSIS

NAME OF SPONSOR/COMPANY:
PriCara
Unit of Ortho-McNeil, Inc.

INDIVIDUAL STUDY TABLE REFERRING TO PART OF THE DOSSIER

(FOR NATIONAL AUTHORITY USE ONLY)

NAME OF FINISHED PRODUCT:
LEVAQUIN®

Volume:

NAME OF ACTIVE INGREDIENT(S):
Levofloxacin

Page:

Protocol No.: LEVOINI3002, CR012103

Title of Study: A Multicenter, Double-Blind Phase 3B Study to Compare the Safety and Clinical Efficacy of Levofloxacin 750 mg for 2 Weeks and Levofloxacin 750 mg for 3 Weeks to that of Levofloxacin 500 mg for 4 Weeks in the Treatment of Chronic Prostatitis

Principal Investigator: 38 investigators enrolled subjects (see Appendix 1.4.1).

Publication (Reference): Paglia M, Peterson J, Fisher AC, Nicholson S. A double-blind, Phase 3B study to evaluate the safety and efficacy of 2- and 3-week dosing of levofloxacin 750 mg once daily to that of 4-week dosing of levofloxacin 500 mg once daily in the treatment of chronic bacterial prostatitis (CBP). Poster presented at: 48th Annual Meeting of the Interscience Conference on Antimicrobial Agents and Chemotherapy; October 25-28, 2008; Washington, DC.

Study Initiation/Completion Dates: 27 November 2006 – 03 September 2008 **Phase of development:** 3B

Objectives: The objective of this study was to compare the safety and efficacy of levofloxacin 750 mg administered orally (p.o.) once-a-day (q24h) for 2 weeks and levofloxacin 750 mg p.o. q24h for 3 weeks to levofloxacin 500 mg p.o. q24h for 4 weeks in the treatment of chronic prostatitis.

Methodology: This was a multicenter, randomized, double-blind, Phase 3B non-inferiority study of levofloxacin 750 mg administered for 2 or 3 weeks compared with levofloxacin 500 mg administered for 4 weeks conducted in the United States involving outpatient adult males with chronic prostatitis. Subjects were randomized in a ratio of 1:1:1 to receive 1 of the following drug regimens:

- Regimen A: Levofloxacin 750 mg p.o. q24h for 14 days, followed by placebo p.o. q24h for 14 days;
- Regimen B: Levofloxacin 750 mg p.o. q24h for 21 days followed by placebo p.o. q24h for 7 days; or
- Regimen C: Levofloxacin 500 mg p.o. q24h for 28 days.

Screening and admission took place on Study Day 1. An On-therapy Telephone Contact took place on Study Day 7-10. Subjects were evaluated at the study site at 3 Weeks (Visit 2, Study Day 19-22), 4 Weeks (Visit 3, Study Day 26-29), and at the Posttherapy Visit (Visit 4, Study Day 33-36). Subjects who were cured or improved at Visit 4 were followed for the occurrence of relapse at the 6-Week, 3-Month, and 6-Month Poststudy Telephone Contacts.

Efficacy evaluations included assessment of clinical response at the Posttherapy Visit and relapse assessments at 6-weeks, 3-months, and 6-months poststudy.

Safety evaluations included incidence of treatment-emergent adverse events (TEAEs) that began on-therapy through Visit 4 (posttherapy evaluation). Serious adverse events (SAEs) were followed for up to 30 days after the last dose of study medication. Safety was also assessed by changes in the physical findings, vital signs, and laboratory results from baseline through Visit 4 (post-therapy evaluation).

Number of Subjects (planned and analyzed):

	Levofloxacin 750 mg x 2 weeks	Levofloxacin 750 mg x 3 weeks	Levofloxacin 500 mg	Total
Planned:	80	80	80	240
Enrolled:	81	81	80	242
Analyzed:				
Clinically evaluable population	59	57	64	180
Intent-to-treat population (ITT)	81	80	80	241
Modified intent-to-treat population (mITT)	73	74	75	222
Safety evaluable population	81	81	80	242

Diagnosis and Main Criteria for Inclusion: Adult men, 40 years of age and older, with a history of clinical signs and symptoms suggestive of chronic prostatitis and current clinical signs and symptoms of chronic prostatitis were eligible for the study provided they met all of the inclusion criteria and none of the exclusion criteria. Chronic prostatitis was defined as prostatitis that had been diagnosed in at least 1 previous episode in the last 12 months. Investigators were to enroll subjects from their practices.

SYNOPSIS (CONTINUED)

NAME OF SPONSOR/COMPANY:	INDIVIDUAL STUDY TABLE REFERRING TO PART OF THE DOSSIER	(FOR NATIONAL AUTHORITY USE ONLY)
PriCara™ Unit of Ortho-McNeil, Inc.		
NAME OF FINISHED PRODUCT: LEVAQUIN®	Volume:	
NAME OF ACTIVE INGREDIENT(S): Levofloxacin	Page:	

Test Product, Dose and Mode of Administration, Batch No.:

Levofloxacin 750 mg capsules (Lot Nos. PD2172, PD2389, PD2499) were supplied by PriCara as over-encapsulated 750 mg levofloxacin commercial tablets. Placebo capsules (Lot Nos. PD2170, PD2387, PD2501) were included in the medication kits.

Reference Therapy, Dose and Mode of Administration, Batch No.:

Levofloxacin 500 mg capsules (Lot Nos. PD2171, PD2388, PD2500) were supplied by PriCara as over-encapsulated 500 mg levofloxacin commercial tablets.

Duration of Treatment: 28 days for all subjects. Subjects in the levofloxacin 750 mg treatment groups received active therapy for either 14 or 21 days, followed by 14 or 7 days of placebo treatment. Subjects in the levofloxacin 500 mg treatment group received 28 days of active therapy.

Criteria for Evaluation:

Efficacy:

Clinical endpoints were evaluated in this trial.

Primary Endpoint:

The primary efficacy endpoint was resolution or improvement of signs and symptoms at the Posttherapy Visit for the mITT population. Subjects were categorized clinical successes (cure or improvement) or clinical non-successes (failure or unable to evaluate). The Posttherapy visit which occurred within the specified Posttherapy window, 33-36 days after the first dose of active study drug, was used; however, for clinical failures, the Posttherapy Visit was not required to have occurred within the specified window.

Secondary Endpoints:

Secondary efficacy endpoints include: 1) Clinical cure rates at the Posttherapy Visit for the clinically evaluable and mITT evaluable populations. 2) Clinical success rates at the Week 3 (Visit 2) and Week 4 (Visit 3) evaluations for the clinically evaluable and mITT evaluable populations. 3) Clinical response rates at the 6-Week, 3-Month, and 6-Month Poststudy telephone contacts for subjects in the mITT evaluable population who were cured or improved at the Posttherapy visit and were successfully contacted. 4) Proportion of subjects in the clinically evaluable and mITT evaluable populations with resolution or improvement of each of the clinical signs and symptoms at Week 3 (Visit 2), Week 4 (Visit 3) and the Posttherapy Visit (Visit 4). 5) National Institutes of Health-Chronic Prostatitis Symptom Index (NIH-CPSI) domain scores at each visit for the clinically evaluable and mITT evaluable populations. 6) Daily Symptom Index Scores for the clinically evaluable and mITT evaluable populations. 7) Time to Symptom Resolution for the clinically evaluable population.

Safety: Occurrence of TEAEs during the study; changes from admission to Posttherapy in clinical laboratory test results, physical examination findings, and vital signs.

Statistical Methods: The primary efficacy variable was clinical success at the Posttherapy Visit in the mITT population. Two-sided 95% confidence intervals (CIs; normal approximation to the binomial as given in Blackwelder[1]) around the difference (comparator minus test group) in clinical success rates were computed to evaluate noninferiority of the test group(s) to the comparator. To conclude that a test group is at least as efficacious as the comparator, a CI upper bound of 20% was used. The assessment of non-inferiority on the primary endpoint was carried out in the mITT, clinically evaluable, and ITT populations.

The secondary efficacy endpoints included clinical cure rates at Posttherapy and clinical success rates at Week 3 (Visit 2) and Week 4 (Visit 3). Clinical cure rates (cure vs. other categories combined) at Posttherapy are presented for subjects in the clinically evaluable and mITT populations. Two-sided 95% CIs on differences (comparator minus each test group) in clinical cure rates were computed and are also presented graphically to compare the 2 populations.

Clinical response rates at the 6-Week, 3-Month, and 6-Month Poststudy Telephone Contacts were analyzed for subjects who were cured or improved at Posttherapy Visit 4, had not previously relapsed, and could be contacted. Additional analyses were the proportion of subjects with resolution or improvement of each of the prostatitis symptoms by visit as well as NIH-CPSI domain scores by visit and Daily Symptom Index Scores collected via diary.

Descriptive statistics were used to summarize TEAEs and pretherapy to posttherapy changes in laboratory test results and vital signs. Two-sided 95% CIs were calculated for the difference between the treatment groups and the rates of TEAEs overall and within each body system.

SYNOPSIS (CONTINUED)

NAME OF SPONSOR/COMPANY: PriCara™ Unit of Ortho-McNeil, Inc.	INDIVIDUAL STUDY TABLE REFERRING TO PART OF THE DOSSIER	(FOR NATIONAL AUTHORITY USE ONLY)
NAME OF FINISHED PRODUCT: LEVAQUIN®	Volume:	
NAME OF ACTIVE INGREDIENT(S): Levofloxacin	Page:	

EFFICACY RESULTS:

Primary efficacy analysis:

At the Posttherapy Visit assessment, occurring 33-36 days after the first dose of active study drug (unless subject was a clinical failure), rates of clinical success for the mITT population were 63.0% for the levofloxacin 750 mg x 2 weeks group, 64.9% for the levofloxacin 750 mg x 3 weeks group, and 69.3% for the comparator group. The 95% CI upper bound was less than 20% for the difference between the comparator and levofloxacin 750 mg x 3 weeks groups, indicating that levofloxacin 750 mg x 3 weeks was noninferior to the comparator. The 95% CI upper bound was greater than 20% for the difference between the comparator and levofloxacin 750 mg x 2 weeks groups, however, indicating that levofloxacin 750 mg x 2 weeks was not noninferior to the comparator.

Secondary efficacy analyses:

Clinical Success at Posttherapy

For the clinically evaluable population, rates of clinical success at the Posttherapy Visit were 66.1% for the levofloxacin 750 mg x 2 weeks group, 68.4% for the levofloxacin 750 mg x 3 weeks group, and 73.4% for the comparator group. The 95% CI around the difference between the levofloxacin 750 mg x 2 weeks group and the comparator group was (-8.9, 23.5). The 95% CI around the difference between the levofloxacin 750 mg x 3 weeks group and the comparator group was (-11.2, 21.2).

Clinical Success Rates at Week 3 and Week 4

At Week 3, the clinical response rate of cured in the mITT population was 8.2% for the levofloxacin 750 mg x 2 weeks group, 5.4% for the levofloxacin 750 mg x 3 weeks group, and 9.3% for the comparator group. The clinical response rate of improved was 69.9% in the levofloxacin 750 mg x 2 weeks group, 73.0% in the levofloxacin 750 mg x 3 weeks group, and 73.3% in the comparator group.

At Week 4, the clinical response rate of cured in the mITT population was 11.0% for the levofloxacin 750 mg x 2 weeks group, 17.6% for the levofloxacin 750 mg x 3 weeks group, and 22.7% for the comparator group. The clinical response rate of improved was 54.8% for the levofloxacin 750 mg x 2 weeks group, 54.1% for the levofloxacin 750 mg x 3 weeks group, and 53.3% for the comparator group.

Clinical Response during the Poststudy Phase

At the 6-Week Poststudy Telephone Contact, the clinical response of non-relapse in the mITT population was 82.6% for the levofloxacin 750 mg x 2 weeks group, 66.7% for the levofloxacin 750 mg x 3 weeks group, and 84.6% for the comparator group. At the 3-Month Poststudy Telephone Contact, the clinical response of non-relapse in the mITT population was 64.4% for the levofloxacin 750 mg x 2 weeks group, 50.0% for the levofloxacin 750 mg x 3 weeks group, and 73.1% for the comparator group. At the 6-Month Poststudy Telephone Contact, the clinical response of non-relapse in the mITT population was 41.3% for the levofloxacin 750 mg x 2 weeks group, 39.6% for the levofloxacin 750 mg x 3 weeks group, and 59.6% in the comparator group.

Prostatitis Signs and Symptoms

The prostatitis sign or symptom that resolved in ≥40.0% of subjects in the levofloxacin 750 mg x 2 weeks, levofloxacin 750 mg x 3 weeks, and comparator groups by Week 3 was painful ejaculation. Prostatitis signs and symptoms that improved in ≥15.0% of subjects in all treatment groups by Week 3 were suprapubic discomfort, perineal discomfort, frequency, and urgency.

The prostatitis sign or symptom that resolved in ≥40.0% of subjects in all treatment groups by Week 4 was perineal tenderness or pain. There were no prostatitis signs and symptoms that were considered improved in ≥15.0% of subjects in all treatment groups by Week 4.

The prostatitis signs and symptoms that resolved in ≥40.0% of subjects in all treatment groups by Posttherapy were dysuria, suprapubic discomfort, painful ejaculation, low back pain, perineal discomfort, urgency, hesitancy, decreased urinary stream, urinary retention, pain on DRE, perineal tenderness or pain, chills, and fever. The prostatitis signs and symptoms that improved in ≥15.0% of subjects in all treatment groups by Posttherapy were perineal discomfort, frequency, urgency, hesitancy, and pain on DRE.

National Institutes of Health-Chronic Prostatitis Symptom Index

With respect to NIH-CPSI scores in the mITT population, the mean (standard deviation) total score was 11.8 (5.43) for the levofloxacin 750 mg x 2 weeks group, 12.0 (5.74) for the levofloxacin 750 mg x 3 weeks group, and 12.9 (5.76) for the comparator group at Screening/Admission. After Screening/Admission, total score for all treatment groups improved, with the levofloxacin 750 mg x 2 weeks, levofloxacin 750 mg x 3 weeks, and comparator groups experiencing changes in mean total score of -6.3 (5.52), -6.8 (5.90), and -8.5 (6.41), respectively, by Posttherapy. Results were similar in the clinically evaluable population.

SYNOPSIS (CONTINUED)

NAME OF SPONSOR/COMPANY:	INDIVIDUAL STUDY TABLE REFERRING TO PART OF THE DOSSIER	(FOR NATIONAL AUTHORITY USE ONLY)
PriCara™ Unit of Ortho-McNeil, Inc.		
NAME OF FINISHED PRODUCT: LEVAQUIN®	Volume:	
NAME OF ACTIVE INGREDIENT(S): Levofloxacin	Page:	

Secondary efficacy analyses (continued):

Daily Symptom Index

Regarding Daily Symptom Index scores in the mITT population, mean score decreased from Day 1 through Day 28 for all 7 items for all treatment groups; there were generally no appreciable differences between groups.

SAFETY RESULTS:

Levofloxacin was generally safe and well-tolerated in all treatment groups. There were no deaths for subjects enrolled in the study. SAEs were experienced by 2 subjects in the levofloxacin 750 mg x 2 weeks group (syncope, coronary artery disorder) and 1 subject in the levofloxacin 750 mg x 3 weeks group (depression, hallucination, suicidal ideation). None of these SAEs was assessed as related to study drug. No SAEs were experienced by subjects in the comparator group.

Thirteen subjects in the levofloxacin 750 mg x 2 weeks group, 9 subjects in the levofloxacin 750 mg x 3 weeks group, and 3 subjects in the comparator group experienced TEAEs that resulted in early discontinuation of study drug.

The incidence of treatment-emergent markedly abnormal laboratory values was similar across treatment groups. No clinically significant changes from study entry to posttherapy were observed in vital signs in any treatment group.

CONCLUSION:

Levofloxacin at doses of 750 mg p.o. administered once daily for 3 weeks was noninferior to levofloxacin at doses of 500 mg p.o. q24h for 4 weeks. Levofloxacin 750 mg p.o. q24h for 2 weeks, however, was not noninferior to levofloxacin at doses of 500 mg p.o. q24h, administered for 4 weeks. Levofloxacin was consistently safe and well-tolerated across treatment groups.

Date of the report: 09 January 2009

Disclaimer

Information in this posting shall not be considered to be a claim for any marketed product. Some information in this posting may differ from, or not be included in, the approved labeling for the product. Please refer to the full prescribing information for indications and proper use of the product.