SYNOPSIS

NAME OF SPONSOR/COMPANY: Ortho-McNeil Janssen Scientific Affairs, LLC (OMJSA) NAME OF FINISHED PRODUCT: Levofloxacin NAME OF ACTIVE INGREDIENT(S): Levofloxacin	INDIVIDUAL STUDY TABLE REFERRING TO PART OF THE DOSSIER Volume: Page:	(FOR NATIONAL AUTHORITY USE ONLY)

Protocol No.: LEVOINI1002

Title of Study: A Randomized, Open-label Study Comparing Levofloxacin Once-daily 750 mg PO for 5 Days and Azithromycin Once-daily 500 mg PO on Day 1 and Then 250 mg on Days 2 Through 5 in a Microbiologic Evaluation for Emergence of Bacterial Resistance in the Oropharyngeal Flora of Healthy Subjects

Investigator: David R. Mathews, M.D. – Quintiles Phase I Services, Lenexa, Kansas

Publication (Reference): Not applicable to this study.

Study Initiation/Completion Dates:	**Phase of development: 1**
First Subject Enrolled: 26 June 2006	
Last Subject Completed: 11 October 2006	

Objectives:

The planned primary objective of this study was to evaluate the changes in the minimum inhibitory concentration and the numbers and types of any bacterial species cultured from the oropharyngeal flora of healthy adults from initiation through 6 weeks after treatment with either levofloxacin 750 mg once daily for 5 days or azithromycin 500 mg once daily on Day 1 and 250 mg on Days 2 through 5 for a total of 5 days.

The planned study hypothesis was that there would be significantly less four-fold increases in MICs seen with the levofloxacin regimen than with the azithromycin regimen.

Following review of preliminary data, the objective of the study was modified to include an analysis of rates of resistance at baseline. Because the crieteria of a four-fold increase in MIC cannot be applied to baseline isolates, resistance was based on central laboratory interpretation of MIC results and was applied to all study visits.

Methodology:

This was a randomized, open-label, single center, exploratory, Phase 1 study that explored changes and resistance patterns of bacteria in the oral flora of healthy male and female adult subjects.

Subjects were randomized to receive 1 of the following treatments:

Levofloxacin: 750-mg tablet daily for 5 days
Azithromycin: 500 mg (two 250-mg tablets) on Day 1 and 250-mg tablet on Days 2 through 5

Microbiologic testing (throat swab) was performed before dosing and following dosing to determine the emergence of bacterial resistance in the oropharyngeal flora.

Number of Subjects (planned and analyzed):

Planned: 140 subjects; 70 subjects to receive levofloxacin; 70 subjects to receive azithromycin.

Analyzed: A total of 143 subjects were enrolled in this study, including 71 subjects in the levofloxacin regimen and 72 subjects in the azithromycin regimen. One hundred thirty-six (136) subjects completed the study according to the protocol and 7 subjects were prematurely withdrawn.

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Diagnosis and Main Criteria for Inclusion:

Male or female healthy subjects, 18 years or older.

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

Test Product:	Levofloxacin
Dose:	750 mg
Mode of Administration:	Oral
Batch Number:	6CG815

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

Reference Product:	Azithromycin
Dose:	250 mg
Mode of Administration:	Oral
Batch Number:	4HP094F

Duration of Treatment:

Five days of study drug treatment followed by 6 weeks of observation.

Criteria for Evaluation:

Microbiological Findings:

Primary Endpoint – The primary endpoint was the emergence of bacterial resistance in the oropharyngeal flora starting prior to the initiation of study drug through a 6-week observation period. Microbiologic testing (throat swab) was conducted prior to dosing on Day 1 and following dosing on Days 5, 19, 33, and 47.

Analytical Methodology:

Microbiologic testing (throat swab) was conducted prior to and following dosing. Samples were analyzed by Physicians Reference Laboratory, Lenexa, Kansas.

Safety:

Safety assessments were conducted prior to drug administration, during study drug treatment, and at the end-of-therapy visit. These included clinical laboratory evaluations, vital signs, physical examinations, pregnancy testing, and collection of adverse events. Serious adverse events were to be collected for 30 days following the last dose of study drug.

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Statistical Methods:

Categorization of Sensitive to antibiotic, Intermediate resistance, or Resistant to antibiotic was based on central laboratory assessments of minimum inhibitory concentration results and was utilized to determine emergence of bacterial resistance. The proportion of subjects with emergence of bacterial resistance through the 6-week interval in the 2 treatment groups were analyzed by the 2-sided Fisher's exact test at the 5% significance level. Analyses were also conducted to compare the proportion of subjects at each post-therapy visit with emergence of bacterial resistance. All analyses were based on an intent-to-treat population which included all subjects who received at least 1 dose of study drug.

SUMMARY - CONCLUSIONS

MICROBIOLOGICAL FINDINGS:

At study entry, 69% (50/72) of subjects randomized to azithromycin treatment were colonized by an azithromycin-resistant organism. In contrast, only 1.4% (1/71) of the subjects randomized to levofloxacin treatment were colonized by a levofloxacin-resistant organism at study entry. The majority of baseline resistant organisms in the azithromycin treatment group were streptococcal organisms. In this treatment group, 45% (53/117) of the streptococcal organisms isolated at baseline were resistant to azithromycin. In the levofloxacin treatment group, none of the 121 streptococcal organisms isolated at baseline were resistant to levofloxacin. The most common colonizing organism isolated at baseline in both treatment groups was *Streptococcus mitis*. In the azithromycin treatment group, 55% (27/49) of the *Streptococcus mitis* organisms isolated at baseline were resistant to azithromycin. In the levofloxacin treatment group, none of the 45 *Streptococcus mitis* organisms isolated at baseline was resistant to levofloxacin.

At the conclusion of 5 days of therapy, 96% (69/72) of the azithromycin treated subjects were colonized by an azithromycin-resistant organism. By comparison, 47% (33/71) of the levofloxacin treated subjects were colonized by a levofloxacin-resistant organism. The majority of the resistant colonizers isolated at the end of treatment with azithromycin or levofloxacin were streptococcal organisms. In the azithromycin treatment group, 84% (118/141) of the streptococcal organisms isolated at the end of treatment were resistant to azithromycin. In the levofloxacin treatment group, 48% (35/73) of the streptococcal organisms isolated at the end of treatment were resistant to levofloxacin. As was observed at baseline, the most common colonizing organism isolated at the end of treatment was *Streptococcus mitis*. In the azithromycin treatment group, the number of *Streptococcus mitis* organisms isolated prior to and at the end of treatment remained essentially unchanged, 49 and 50, respectively. However, the number of isolates resistant to azithromycin increased from 27 to 38. In the levofloxacin treatment group, the number of *Streptococcus mitis* organisms isolated at the end of treatment was 18 compared to 45 at baseline. However, the number of isolates resistant to levofloxacin increased from 0 at baseline to 13 at the end of treatment.

Two weeks after therapy, 96% (69/72) of the azithromycin treated subjects were colonized by an azithromycin-resistant organism. Six weeks after therapy, 86% (62/72) of the azithromycin treated subjects were still colonized by an azithromycin-resistant organism. By comparison, the number of levofloxacin treated subjects colonized by a levofloxacin-resistant organism fell to 5.6% (4/71) 2 weeks after therapy and remained at this level 6 weeks following therapy. Subjects administered azithromycin were found to have a significantly (p-value <0.0001) greater number of resistant isolates compared to subjects administered levofloxacin for all visits. Six weeks after therapy, 142 and 162 streptococcus organisms were isolated in the azithromycin and levofloxacin treatment groups, respectively.

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In subjects treated with azithromycin, the rate of azithromycin-resistance observed in these streptococcal organisms was 85% (120/142). In subjects treated with levofloxacin, the rate of levofloxacin-resistance observed in these streptococcal organisms was 2% (3/162). Again, the most common colonizing organism isolated at this time point was *Streptococcus mitis*.

In the azithromycin treatment group, 77% (30/39) of the *Streptococcus mitis* organisms isolated 6 weeks after therapy were resistant to azithromycin. In the levofloxacin treatment group, 2% (1/41) of the *Streptococcus mitis* organisms isolated 6 weeks after therapy was resistant to levofloxacin.

SAFETY RESULTS:

There were no deaths or serious adverse events during the course of this study through the 6-week observation period. One subject was prematurely discontinued from the study due to an adverse event of diarrhea of moderate intensity following a single 500 mg dose of azithromycin on Day 1.

During the treatment phase of the study, a total of 70 subjects (49.0%) experienced at least 1 treatment-emergent adverse event, including 32 subjects (45.1%) administered levofloxacin and 38 subjects (52.8%) administered azithromycin.

The most frequently reported adverse events during treatment with levofloxacin were nausea, abdominal pain, and headache reported by 15 (21.1%), 5 (7.0%), and 5 (7.0%) subjects, respectively. During treatment with azithromycin, the most frequently reported adverse events were nausea, abdominal pain, diarrhea, and headache reported by 8 (11.1%), 10 (13.9%), 10 (13.9%), and 5 (6.9%) subjects, respectively.

No trends or clinically meaningful changes were observed in clinical laboratory assessments, vital signs, or physical examinations during the treatment phase of the study.

CONCLUSIONS:

- Nearly 70% of subjects randomly assigned to receive azithromycin were colonized with an azithromycin-resistant organism prior to study entry. In contrast, only 1.4% of subjects randomly assigned to receive levofloxacin were colonized with a levofloxacin-resistant baseline organism.
- After 5 days of therapy, nearly all of the azithromycin treated subjects were colonized with an azithromycin-resistant organism while approximately 50% of the levofloxacin treated subjects were colonized with a levofloxacin-resistant organism.
- Six weeks after therapy, 86% of the azithromycin treated subjects were still colonized by an azithromycin-resistant organism compared to 6% of the levofloxacin treated subjects colonized with a levofloxacin-resistant organism.
- The most common colonizing organism at each evaluation time point was *Streptococcus mitis*. The rate of azithromycin-resistance in this streptococcal species 6 weeks after azithromycin treatment was 77% compared to a 2% rate of levofloxacin-resistance 6 weeks after levofloxacin treatment.
- Levofloxacin 750 mg administered orally for 5 days and azithromycin 500 mg administered orally on Day 1 followed by 250 mg on Days 2 to 5 were well tolerated during this study. No clinically important differences were noted between treatments.

Date of the report: Final: 16 June 2008

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