

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**21-721**

**MEDICAL REVIEW(S)**

## CLINICAL REVIEW

<u>Application Type</u>	NDA 21-721
<u>Reviewer Name</u>	Carl N. Kraus, M.D.
<u>Review Completion Date</u>	August 20, 2004
<u>Established Name</u>	Levaquin™
<u>(Proposed) Trade Name</u>	Levaquin™
<u>Therapeutic Class</u>	Fluoroquinolone
<u>Applicant</u>	J&JPRD
<u>Priority Designation</u>	S
<u>Formulation</u>	Oral Solution (25mg/ml)
<u>Dosing Regimen</u>	250 mg/500mg/750mg once daily

### Indication(s)

1. Complicated and uncomplicated urinary tract infections
2. Acute pyelonephritis
3. Chronic bacterial prostatitis
4. Complicated and uncomplicated skin and skin structure infections
5. Nosocomial pneumonia
6. Acute maxillary sinusitis
7. Acute bacterial exacerbation of chronic bronchitis
8. Community-acquired pneumonia (including that due to penicillin-resistant *Streptococcus pneumoniae*)

Intended Population Adult

## CLINICAL REVIEW

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### ABBREVIATIONS

J&JPRD	Johnson & Johnson Product Research and Development
AE	Adverse Event
BE	Bioequivalence
RBC	Red Blood Cell
WBC	White Blood Cell
BUN	Bloods Urea Nitrogen
ALT	Alanine Transferase
AST	Aspartate Amino Transferase

## 1 EXECUTIVE SUMMARY

NDA 21-721 was submitted to the FDA on December 19, 2003 to secure approval of an oral solution of the Levaquin™, a broad spectrum antimicrobial initially approved by the FDA in 1996. Four clinical studies were submitted by Johnson & Johnson Product Research Development for evaluation of this oral solution formulation of levofloxacin. Two of these studies included systemic exposure to the antibiotic (LOFBO-PHI-116 and LOFBO-PHI-117) and two were taste comparison studies that did not include systemic exposure to the antibiotic (LOFBO-LSTT-002 and LOFBO-LSTT-003).

The primary goal of the two studies with systemic exposure to the investigational formulation was to insure that the new formulation was bioequivalent to a currently approved and marketed formulation as well as characterize any food effect on the pharmacokinetics of the new formulation. The levofloxacin oral solution (25 mg/ml) met the criteria for bioequivalence to the 500 mg oral tablet. Specifically, key pharmacokinetic variables of the investigational formulation were found to fall within the standard accepted range of 80%-125% of an approved formulation. The food effect study revealed that the maximal attained concentration of the investigational oral formulation was diminished with meals. There was a noted food effect for the solution which resulted in a decrease in C<sub>max</sub> leading to a recommendation that the oral solution should be provided either 1 hour prior to meals or 2 hours after meals.

The subjects evaluated in the two studies with systemic levofloxacin exposure were 96 in number. Since over — subjects have been previously exposed to systemic levofloxacin in clinical trials the goals of safety data collection in this submission were to evaluate the character and severity of events specific to the oral solution. There were no unlabeled adverse events captured and no increase in the relative severity of clinically concerning adverse events in the oral solution exposed subjects compared to the approved oral tablet formulation.

Concern regarding the use of levofloxacin in children is related to the pre-clinical safety signal present in juvenile dogs as well as other species in which articular cartilage damage occurs at an alarming frequency. The availability of an oral levofloxacin solution may indirectly promote the use of this quinolone in children. Conversely, the approval of an oral solution will benefit severely ill patients on ventilatory support or for whom oral medications may not be an option due to aspiration risks, obstructions, or other debilitating illnesses.

The submitted data for approval of an oral solution formulation of levofloxacin has met the requirements of bioequivalence to the 500 mg marketed oral tablet. The benefit of marketing such a formulation outweighs the potential risks and is therefore approvable from a clinical perspective. The levofloxacin oral solution will be approved for all the marketing indications of the tablet and intravenous formulations.

### Recommendation on Post-marketing Actions

All adverse events captured in the two studies with adequate patient exposure to levofloxacin oral solution (LOFB-PHI-116 and LOFB-PHI-117) are currently present in the Levaquin™ label. There were no unexpected or more severe adverse events reported in these studies. No further risk management activity is recommended.

### Summary of Clinical Findings

NDA 21-721 was submitted to the FDA on December 19, 2003 to secure approval of an oral solution of the Levaquin™, a broad spectrum antimicrobial initially approved by the FDA in 1996. As a means of securing regulatory approval the sponsor conducted one study evaluating the bioequivalence of the investigational solution formulation to the 500 mg oral tablet initially approved under NDA 20-634 and 20-635. The sponsor also submitted a food effect study in which the pharmacokinetic profile of the investigational oral solution was evaluated with and without food. Two taste preference studies were also conducted but were evaluated solely for safety.

The bioequivalence study established that the investigational oral solution formulation met the regulatory requirement for bioequivalence. Specifically, the confidence intervals for the  $C_{max}$  and  $AUC_{0-\infty}$  between the solution and tablet formulations were 98%-108% and 99%-103%, respectively. The  $C_{max}$  for subjects evaluated for food effect was 74% that of the fasting state and this decrease in  $C_{max}$  will be reflected in the Levaquin™ label.

The safety of the investigational levofloxacin oral solution formulation as evaluated in the submitted studies was found to be similar in character to that of the approved 500 mg tablet. There was a noted elevation in reports of headache and dizziness in the oral solution arm that was concentrated in the food effect study conducted in Europe. Given the possible attribution of such events to a fasting state as well as the difficulties of evaluating a study without a comparator conducted in a foreign population, these events were not considered to be of clinical concern. Overall, there was no increase in the incidence or severity of the observed labeled events and there were no observed events absent from the current Levaquin™ label.

### Brief Overview of Clinical Program

Four studies were submitted by J&JPRD under NDA 21-721. Study LOFBO-PHI-116 was a 3 way crossover trial evaluating the bioequivalence of three oral formulations of levofloxacin (tablet, — and solution) in healthy men and women (N=36) between 18 and 55 years of age. Study LOFBO-PHI-117 was a single dose, 2 way crossover food effect study in healthy men and women (N=24) between 18 and 55 years of age. Study LOFBO-LSTT-002 was an open label crossover taste and palatability studying healthy men and women between 18 and 30 years of age. Six flavors

— of the oral levofloxacin solution were evaluated (N=120). LOFBO-LSTT-003 was a single-blind 2 way crossover taste and palatability study in healthy men and women between 18 and 30 years of age (N=72).

In LOFB-PHI-116 and LOFB-PHI-117 systemic exposure was limited to a single oral dose (either 500 mg tablet, 500 mg — or 500 mg in an oral

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solution). There was no systemic exposure to levofloxacin in the taste and palatability studies (LOFBO-LSTT-002 and LOFBO-LSTT-003).

*Efficacy*

The submitted levofloxacin oral solution was shown to have similar pharmacokinetic parameters to the marketed 500 mg tablet. The regulatory requirements for bioequivalence have been met and the conducted food effect study revealed a significant decrease in the levofloxacin pharmacokinetic profile when given with food that will be reflected in the Levaquin™ label.

*Safety*

The current Levaquin™ label details the key safety concerns related to its use. These concerns include a warning for use in pediatric patients under the age of 18 years, pregnant women and nursing mothers. Other recognized concerns include central nervous system events (e.g., convulsions, psychoses, confusion, depression, and anxiety), hypersensitivity events (e.g., angioedema, anaphylactic reactions, urticaria, pruritis, and rash), musculoskeletal events (arthralgias, arthritis, myalgias, tendonitis and tendon rupture) as well as gastrointestinal events (e.g., nausea, diarrhea, abdominal pain, taste perversion, and dyspepsia).

The approved Levaquin™ label incorporates data from all submitted clinical trials as well as post-marketing adverse events reporting submitted to the FDA's Adverse Events Reporting System. The number of subjects that have been evaluated in clinical trials with systemic exposure to levofloxacin now exceeds \_\_\_\_\_ and the number of worldwide prescriptions of levofloxacin is in excess of \_\_\_\_\_.

The current studies submitted that captured safety data from systemic levofloxacin exposure (LOFBO-PHI-116 and LOFBO-PHI-117) included a total of 96 healthy subjects between 18 and 55 years of age. Of the 96 subjects enrolled, 3 were withdrawn early, one of which was not related to an adverse event. The adverse events noted from the remaining 95 subjects were equally distributed between the tablet, \_\_\_\_\_ and solution study arms save an increase in headache and dizziness in the oral solution arm. The headache and dizziness reports were concentrated in the food effect study conducted in Belgium. Given the lack of a biologic plausible explanation for the event, the possible attribution to a fasting state as well as the confounder of a disparate foreign subject population without a comparator arm, these events were not considered to be of clinical concern.

The sponsor's goal in the currently submitted NDA was to obtain regulatory approval that the levofloxacin oral solution is bioequivalent to the currently marketed 500 mg tablet. The number of subjects evaluated were of sufficient number to evaluate bioequivalence but is severely limited to provide a reasonable characterization of safety since an evaluation of 95 subjects will capture events that occur at a very high frequency (roughly one in thirty-two, or a frequency of approximately 3%). It is therefore reassuring that there are no unexpected or severe events present in the submitted studies and there should be recognition that these studies cannot provide the characterization of safety already reflected in the Levaquin™ label. With the acknowledgement of this

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limitation, the current oral levofloxacin solution appears as safe for use as the currently marketed 500 mg tablet.

*Special Populations*

As stated in the current Levaquin™ label, “The safety and efficacy of levofloxacin in pediatric patients, adolescents (under the age of 18 years), pregnant women, and nursing women have not been established.” The oral levofloxacin solution will necessarily carry the same warning for marketing.

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## 2 INTRODUCTION AND BACKGROUND

### Product Information

Levofloxacin is the L-isomer of ofloxacin and is a fluoroquinolone with a broad spectrum of activity including gram positive, gram negative and atypical pathogens. Levofloxacin has been marketed since 1996 under the trade name Levaquin™ by Johnson & Johnson Pharmaceutical Research & Development, LLC (J&JPRD). Current FDA approved indications are for the treatment of complicated and uncomplicated urinary tract infections, acute pyelonephritis, chronic bacterial prostatitis, complicated and uncomplicated skin and skin structure infections, and respiratory infections including nosocomial pneumonia, acute maxillary sinusitis, acute bacterial exacerbation of chronic bronchitis, and community-acquired pneumonia (including that due to penicillin-resistant *Streptococcus pneumoniae*). The approved formulations that carry these indications are the levofloxacin tablets (250 mg, 500 mg, and 750 mg strengths) as well as the 25 mg/ml intravenous solution. The sponsor has submitted NDA 21-721 in support of a Levaquin™ oral solution for an initial evaluation in community-acquired pneumonia.

### Important Issues with Pharmacologically Related Products

Key safety concerns related to the fluoroquinolones as a drug class include QT prolongation with a consequent elevated risk of torsades de pointes (TdP), musculoskeletal adverse events such as tendinopathy and arthralgias, as well as peripheral neuropathy. Preclinical safety studies in dogs, rabbits, marmosets and rats have revealed the potential for articular cartilage damage that has precluded their routine use in patients younger than 18 years. There have been a number of case reports reflecting this safety concern<sup>1</sup>. Appropriate use in children is currently reflected in the Levaquin™ product label with denotation of these safety issues in the Warnings section. The currently submitted oral levofloxacin solution (25 mg/ml) will therefore carry similar labeling to ensure the continued appropriate safe use of levofloxacin.

### Pre-submission Regulatory Activity

Per the sponsor's introduction to study LOFBO-PHI-116, \_\_\_\_\_  
\_\_\_\_\_  
\_\_\_\_\_

In the "Guidance for Industry: Bioavailability and Bioequivalence Studies for Orally Administered Drug Products – General Considerations," a recommendation for single-dose pharmacokinetic studies as well as a food effect studies that includes a two period, two treatment crossover is outlined to assist sponsors in their submission to the FDA. In accordance with this guidance, J&JPRD has submitted two studies in NDA 21-

<sup>1</sup> Cuzzolin L, Fanos V., Safety of Fluoroquinolones in paediatrics. Expert Opin Drug Saf. 2002 Nov;1(4):319-24.

721 to support the bioequivalence of this oral solution to the currently approved and marketed 500 mg tablet.

## Study Design

### *LOFBO-PHI-116*

LOFBO-PHI-116 was randomized, open-label, single-center, single-dose, 3-way crossover, definitive bioequivalence study of 3 oral formulations of levofloxacin (500 mg tablet, \_\_\_\_\_, and 25 mg/ml solution) in healthy men and women. Thirty-six subjects between the ages of 18 and 55 years, inclusive, were to be enrolled and randomly assigned to 1 of 6 treatment-sequence groups (6 subjects each, 3 men and 3 women) according to a computer-generated randomization schedule (Appendix 2.1, Sponsor's Study Report). If more than 1 subject withdrew from a treatment-sequence group, additional subjects were to be enrolled to ensure that at least 5 subjects, and at least 2 subjects of each sex, completed the study in each treatment-sequence group.

The subjects were to receive each of the following treatments (1 formulation per period) in the sequence assigned to their treatment-sequence group:

- Levofloxacin 500 mg as 1 Levaquin™ 500-mg marketed tablet
- Levofloxacin 500 mg as a / / /
- Levofloxacin 500 mg as a single 20-mL dose of oral solution formulation (125 mg/5 mL).

Patients were ineligible for study enrollment if they were taking any medication or therapies other than hormonal contraceptive within 14 days of study participation. Subjects entered the study site on Day 0 of each open-label treatment period and remained there through the collection of the 48-hour blood sample for pharmacokinetic evaluations. Study drug was administered on Day 1 of each period, and each Day 1 was separated by at least 4 days. The schedule of study events is outlined in Table 1 below (page 23, Clinical Study Report).

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**Table 1 LOFBO-PHI-116 Time and Events Schedule**

	Study Phase:	Open-Label Treatment <sup>b</sup>				Posttreatment Early Withdrawal <sup>c</sup>
	Screening <sup>a</sup>	Periods I, II, and III				
Day:	-14	0	1	2	3	
<b>Screening Procedures</b>						
Informed consent	X					
Medical History	X					
Height	X					
Weight	X					X
HIV; hepatitis B and C screen	X					
Drugs of abuse/alcohol screen	X	X				
Creatinine clearance	X					
12-lead electrocardiogram	X					
<b>Open-label Procedures</b>						
Admission to study unit		X <sup>d</sup>				
Confinement		X	X	X	X	
Randomization		X <sup>e</sup>				
Study drug administration <sup>f</sup>			X			
Discharge from study unit					X	X
<b>Pharmacokinetic procedures</b>						
Blood samples collected <sup>g</sup>			X	X	X	X <sup>h</sup>
<b>Safety Procedures</b>						
Vital signs	X		X <sup>i</sup>		X <sup>i</sup>	X <sup>i</sup>
Physical examination	X					X
Hematology, serum chemistry	X		X <sup>j</sup>		X <sup>j</sup>	X <sup>j</sup>
Urinalysis	X		X <sup>j</sup>		X <sup>j</sup>	X <sup>j</sup>
Pregnancy test <sup>k</sup>	X <sup>l</sup>	X <sup>m</sup>				
Monitor adverse events <sup>n</sup>	X	X	X	X	X	X

**LOFBO-PHI-117**

LOFBO-PHI-117 was an open-label, randomized, 2-way crossover, single-dose, single-center, food-effect study in healthy men and women between the ages of 18 and 55 years, inclusive with the objective of evaluating the effect of food on the single-dose pharmacokinetics of the oral solution (25 mg/ml) of levofloxacin. This study was conducted in Belgium. Twenty-four subjects were enrolled and randomly assigned to 1 of 2 treatment sequence groups. Twelve subjects (6 men and 6 women) were enrolled into each treatment sequence group. In each treatment period, subjects were admitted to the study unit the evening of Day 0, before administration of study drug on Day 1, and housed through 48 hours after dosing with study drug (i.e., until Day 3). Subjects received study drug as a single oral dose under both fed (within 10 minutes after completion of a high-fat, high-calorie breakfast) and fasted (10-hour overnight fast) conditions according to their randomized treatment sequence:

- Fed treatment: 500 mg of levofloxacin as a single dose of the oral solution formulation (125 mg/5 mL) following a high-fat, high-calorie breakfast (see below) consumed after a 10-hour overnight fast. Subjects had to consume the breakfast within a 30-minute period and had to be dosed within 10 minutes after completion of the meal.

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- Fasted treatment: 500 mg of levofloxacin as a single dose of the oral solution formulation (125 mg/5 mL) following a 10-hour overnight fast.

A Time and Events schedule for this study is provided below in Table 2 (page 26, Clinical Study Report).

**Table 2 LOFBO-PHI-117 Time and Events Schedule**

Study Phase: Study Day:	Screening <sup>a</sup> -14	Open-Label Treatment <sup>b</sup> Periods I and II				Posttreatment/ Early Withdrawal <sup>c</sup>
		0	1	2	3	
<b>Screening Procedures</b>						
Informed consent	X					
Medical history	X					
Height	X					
Weight	X					X
HIV - hepatitis B and C screen	X					
Drugs of abuse/alcohol screen	X	X				
Creatinine Clearance	X					
12-lead ECG	X					
<b>Open-label Procedures</b>						
Admission to study unit		X <sup>d</sup>				
Confinement		X	X	X	X	
Randomization			X <sup>e</sup>			
Study drug administration <sup>f</sup>			X			
Discharge from study unit					X	X <sup>g</sup>
<b>Pharmacokinetic Procedures</b>						
Blood samples <sup>h</sup>			X	X	X	X <sup>i</sup>
<b>Safety Procedures</b>						
Vital signs	X		X <sup>j</sup>		X <sup>j</sup>	X <sup>j</sup>
Physical examination	X					X
Hematology, serum chemistry	X		X <sup>k</sup>		X <sup>k</sup>	X <sup>k</sup>
Urinalysis	X		X <sup>k</sup>		X <sup>k</sup>	X <sup>k</sup>
Pregnancy test <sup>l</sup>	X <sup>m</sup>	X <sup>n</sup>				
Monitor adverse events <sup>o</sup>	X					X

**LOFBO-LSTT-002**

LOFBO-LSTT-002 was a single-center, open-label, randomized, 6-sequence, 6-period, crossover, taste and palatability study consisting of 3 phases: Prerandomization, Taste Evaluation, and Postevaluation. Subjects who met the eligibility criteria in the Prerandomization Phase were entered into the Taste Evaluation Phase and randomized to 1 of 6 flavor sequence groups (20 subjects per group). In each Taste Evaluation Period, subjects tasted, without swallowing, up to 2 mL of the assigned flavor. After each tasting, subjects expelled the full contents of their mouth, and rated 9 taste and palatability attributes (Overall Liking, Aftertaste, Taste/flavor, "Mouthfeel", Bitterness, Grittiness,

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Flavor Level, Sweetness, and Thickness) using 5- and 7-point categorical scales. The time and events schedule is outlined in Table 3 below (page 36, Clinical Study Report).

**Table 3 LOFBO-LSTT-002 Time and Events Schedule**

	Prerandomization <sup>a</sup>	Taste Evaluation Testing Days <sup>b</sup>	Postevaluation
<b>Procedures</b>			
Medical history	X		
Inclusion/Exclusion Criteria	X	X <sup>c,d</sup>	
Physical examination	X		
Vital signs: sitting blood pressure, pulse rate, respiratory rate, and oral temperature	X	X <sup>e</sup>	
Urine pregnancy test <sup>f</sup>	X	X <sup>d</sup>	
Taste evaluation <sup>g</sup>		X <sup>h</sup>	
Adverse events <sup>i</sup>	X	X	X

**LOFBO-LSTT-003**

LOFBO-LSTT-003 was a single-center, single-blind, randomized, 2-sequence, 2-period, crossover, taste and palatability study consisting of 3 phases: Prerandomization, Taste Evaluation, and Postevaluation. Subjects who met the eligibility criteria in the Prerandomization Phase were entered into the Taste Evaluation Phase and randomized to 1 of 2 treatment sequence groups (36 subjects per group). The Taste Evaluation Phase consisted of 1 testing day with 2 taste evaluation periods. In each taste evaluation period, subjects tasted, without swallowing, up to 2 mL of the assigned formulation. Before tasting each formulation, subjects rinsed their mouth with water, ate an unsalted cracker, and rinsed their mouth again with water. After each tasting, subjects expelled the full contents of their mouth, and rated 9 taste and palatability attributes (Overall Liking, Aftertaste, Taste/flavor, "Mouthfeel", Bitterness, Grittiness, Flavor Level, Sweetness, and Thickness) using 5- and 7-point categorical scales. The time and events schedule is outlined in Table 4 below (page 36, Clinical Study Report).

**Table 4 LOFBO-LSTT-003 Time and Events Schedule**

Phase Visit	Prerandomization <sup>a</sup>	Taste Evaluation <sup>b</sup>	Postevaluation <sup>c</sup>
	1	2	3
Informed consent	X		
Medical history	X	X <sup>d,e</sup>	
Inclusion/exclusion criteria	X	X <sup>d,e</sup>	
Physical examination	X		
Randomization		X	
Taste evaluation <sup>f</sup>		X <sup>g</sup>	
Vital signs <sup>h</sup>	X	X <sup>i</sup>	
Urine pregnancy test <sup>j</sup>	X	X <sup>e</sup>	
Adverse events <sup>k</sup>	X	X	X

## Safety Evaluations

Safety evaluations of studies 116 and 117 included vital signs, physical examinations, pregnancy testing as well as clinical laboratory testing (including hematology, serum chemistry and urinalysis). Any clinically significant abnormality that persisted at the end of the study was followed by the investigator until resolution or until a clinically stable endpoint was reached.

Because the study drug was not swallowed in studies 002 and 003 the risk to the subject was considered minimal and safety data capture was minimized to vital signs and urine pregnancy tests. Any clinically significant abnormalities that persisted at the end of the study were to be followed until resolution or until reaching a clinically stable endpoint.

## Subject Information

### *LOFBO-PHI-116*

The initial study design had planned for one group of 36 subjects to be enrolled. However, due to protocol violations with the first cohort of 36 subjects the study was terminated early after the first treatment period and a second cohort of 36 subjects were enrolled. Both groups were included in the safety evaluation. Thirty-four of the 36 subjects who enrolled in the reinitiated study completed the study. Two subjects withdrew early, 1 because of an adverse event (Subject 3034, who received the solution formulations) and 1 (Subject 3021, who received the tablet and formulations) due to a reason other than an adverse event.

The age range of participating subjects was 18 to 55 years (mean age of 31 years). 35% were white (N=25), 4% were black (N=3) and 61% (N=44) were of other races.

### *LOFBO-PHI-117*

The study design planned for 24 subjects that were enrolled. The age range of participating subjects ranged from 19 to 54 years (mean age of 35 years). 50% were women, 50% were men and all were of white race.

### *LOFBO-LSTT-002*

One hundred and twenty subjects were enrolled. The subjects ranged in age from 18-30 years (mean age of 25). 29 subjects were male (24%) and 91 were female (76%). 88% were white, 3% were black and 8% were of other race.

### *LOFBO-LSTT-003*

Seventy two subjects were initially planned for enrollment but the study site enrolled an additional four subjects without the sponsor consent or knowledge. The subjects ranged in age from 18-30 years (mean age of 24 years). 50% were male and 50% were female. 80% of the subjects were white, 4% were black, 4% were Asian and 12% were of other races.

### 3 DATA SOURCES, REVIEW STRATEGY, AND DATA INTEGRITY

#### Sources of Clinical Data

J&JPRD conducted two studies that were submitted in support of the bioequivalence claim. Specifically, LOFBO-PHI-116, an open label, randomized, single dose, 3 way crossover study that assess the bioequivalence of an oral solution (25 mg/ml) formulation of levofloxacin using the 500 mg marketed tablet as the reference drug. A second study, LOFBO-PHI-117 was an open label, randomized, single dose, 2 way cross over study used to evaluate the food effect on pharmacokinetics of the oral solution.

Two separate taste studies were also submitted. Study LOFBO-LSTT-002 was an open-label, randomized, 6 sequence, 6 period, crossover study to compare the overall taste and palatability of 6 varyingly flavored levofloxacin oral suspension formulations. Study LOFBO-LSTT-003 was a single-blind, randomized, 2 sequence, 2 period, crossover study to compare the overall taste and palatability of 2 flavored levofloxacin oral formulations (oral solution).

#### Review Strategy

The goal of NDA-21-721 is to establish bioequivalence (BE) with a marketed levofloxacin formulation and as such, no new efficacy data was submitted. Safety data was captured from all four studies submitted under NDA 21-721 and was used to evaluate the safety of the new oral solution. The two studies conducted for BE evaluations (LOFBO-PHI-116 and LOFBO-PHI-117) were combined for safety evaluation (referred to as COMBE in this review) and the two studies conducted for evaluation of taste (LOFBO-LSTT-002 and LOFBO-LSTT-003) were combined for safety evaluation (referred to as COMT in this review). After the initial review of the sponsor's study summaries, the SAS files from the combined studies were combined and imported into PPD Informatics Cross Graph Viewer for descriptive evaluations. For more granular assessments key variables were exported into an excel database for pivot table analyses.

### 4 INTEGRATED REVIEW OF SAFETY

#### *Deaths*

No deaths were reported in any of the 4 studies listed below that were submitted for review.

LOFBO-PHI-116  
LOFBO-PHI-117  
LOFBO-LSTT-002  
LOFBO-LSTT-003

**Other Serious Adverse Events**

There were no serious adverse events reported for any of the 4 studies submitted for review.

*Dropouts and Other Significant Adverse Events*Overall Profile of Dropouts

## LOFBO-PHI-116

2 subjects were withdrawn early from this study. Subject 3034 was withdrawn due to an adverse event described in 4.1.2.3 below. Subject 3021 was withdrawn secondary to having tested positive for cocaine and thereby met exclusionary criteria.

## LOFBO-PHI-117

1 subject (subject 7) withdrew from the study during the second treatment period (fed) at 25 hours after study drug administration. As detailed in the CRF the withdrawal was related to a withdrawal of consent and not related to an adverse event.

## LOFBO-LSTT-002

5 subjects were withdrawn early from this study. One subject (subject 71) withdrew from the study due to a viral infection 1 day after therapy initiation. The illness lasted 6 days. One subject (subject 9) withdrew from the study due to the development of aphthous stomatitis 2 days after therapy initiation. The stomatitis lasted 9 days. 3 of the 5 subjects withdrew from the study secondary to subject choice as denoted in the respective CRFs (subjects 1, 55, and 111).

## LOFBO-LSTT-003

No withdrawals occurred in study LOFBO-LSTT-003.

Other Significant Adverse Events

One subject (Subject 3034) was withdrawn from study LOFBO-PHI-116 due to an adverse event. This subject, a 28-year-old white woman, experienced mildly severe chest pain and moderately severe syncope after receiving the 500-mg levofloxacin → in Period II. These events were considered to be doubtfully and possibly related to study medication, respectively. The subject was withdrawn on Day 2 of Period II of the study. The physical examination performed at her early withdrawal visit showed no other abnormal changes from screening and that her symptoms had been resolved.

**MO Comment:** *In reviewing the CRF, 4 adverse events were reported for this subject during period 2: dizziness, syncope, chest tightness and hematuria. The hematuria is most likely related to the urinary tract infection documented in period 1. The patients dizziness (lasting 2 minutes), syncope (lasting 3 minutes), and chest tightness (lasting 12 minutes) were temporally separated. The study drug was stopped after the chest tightness AE. Without further information from the time of the event (e.g., vitals, ECG,*

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*narrative of complaints regarding loss of consciousness etc.) it is not possible to fully assess the event. This event is concerning but given the patient's age of 28 and no noted comorbid illness along with a doubtful attribution by the investigator this is unlikely to represent a coronary-related event.*

### Common Adverse Events

The sponsor's analysis of common adverse events as provided in section 2.1.1.1 in the Clinical Safety Review states that 31 (21%) of subjects experienced 1 or more adverse events with the most common being headache (11 subjects, 11%) and dizziness (5 subjects, 5%). The sponsor's summary of common adverse events is provided below in table 5.

**Table 5 Sponsor's summary of common adverse events (page 9, Clinical Safety Review)**

(Studies LOFBO-PHI-116 and LOFBO-PHI-117: Safety Analysis Set)				
	Solution (N=71) n (%)	— (N=48) n (%)	Tablet (N=47) N (%)	Total (N=96) n (%)
Body System				
Preferred Term				
<b>Total no. subjects with adverse events</b>	21 (30)	10 (21)	8 (17)	31 (32)
Central and peripheral nervous system disorders	11 (15)	3 (6)	2 (4)	15 (16)
Headache	8 (11)	2 (4)	1 (2)	11 (11)
Dizziness	4 (6)	1 (2)	1 (2)	5 (5)

Note: Incidence is based on the number of subjects, not the number of events.

Note: Subjects who received >1 formulation are counted once in the totals.

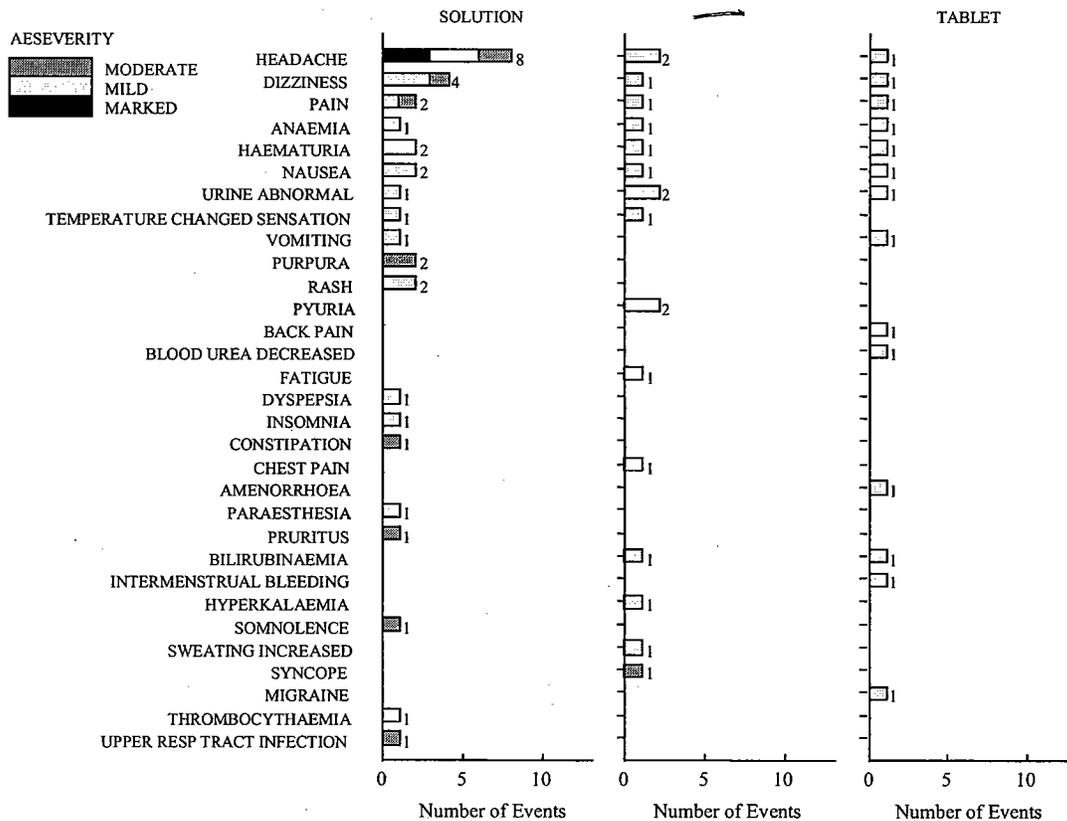
**MO Comment:** *The number of headache related adverse events as shown in the table is 8, not 11 as stated by the sponsor.*

The sponsor's evaluation of severity and relationship to treatment indicate a similar pattern of severity and relationship to treatment reported in all formulation groups with 79% of all events considered to be mild and either not related or doubtfully related to treatment (62%).

Below (Figure 1) is the adverse events listed by line item code and nested by severity as extracted from the submitted SAS file (LOFBO-PHI-116, KAE.xpt).

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**Figure 1 Adverse Events – Frequency and Severity in Studies LOFBO-PHI-116 and LOFBO-PHI-117**



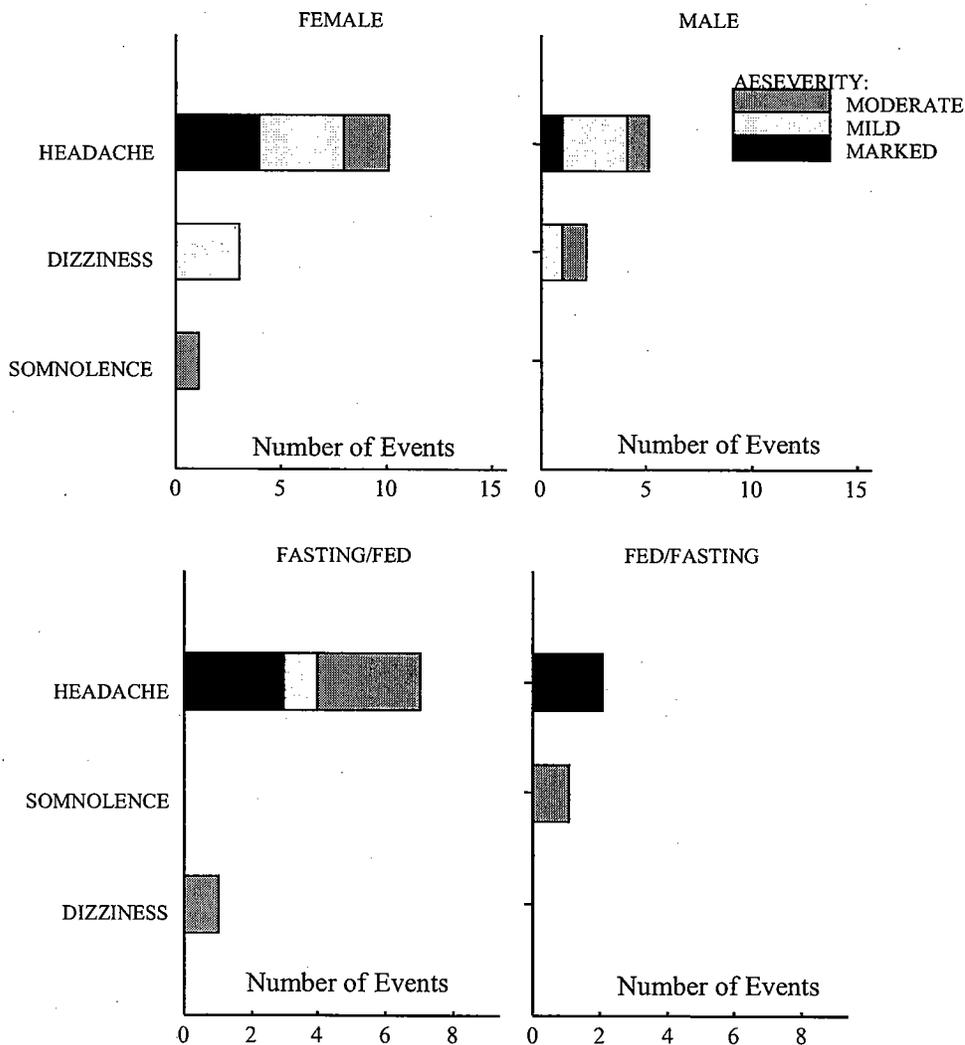
**MO Comment:** *These studies were not specifically designed to evaluate safety between formulations. They are in general equivalent in the character, severity and frequency of reporting. An obvious variation is the excess in headache and dizziness AEs reported in subjects that were exposed to the oral solution relative to the tablet or — On further evaluation based on sex distribution and treatment arm it appears that the majority of these events were in patients of female gender and specifically those that were enrolled in the Belgium-conducted food effect study. Confounders include fasting as well as foreign subject populations that may report adverse events either more or less frequently than a US population.*

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To better characterize the headache and dizziness events presented in Figure 1, the events were characterized by gender and treatment schedule. Headache was more frequently reported in the fasting/fed rather than the fed/fasting food effect arm (Figure2). There was also an increase of reporting by female subjects compared to male subjects.

**MO Comment:** 6/7 of the headache events occurred in the Belgian study (food effect study) and were more prevalent in the fasting/fed arm as well as in female subjects. This disparity may be related to the time of day in which each arm conducted the PK evaluation such that a prolonged morning fast induced a headache as well as either a gender or culture bias for more frequent reporting by female subjects.

**Figure 2 Gender and treatment arm effect on selected neurological adverse events**



Applicant’s Approach to Eliciting Adverse Events

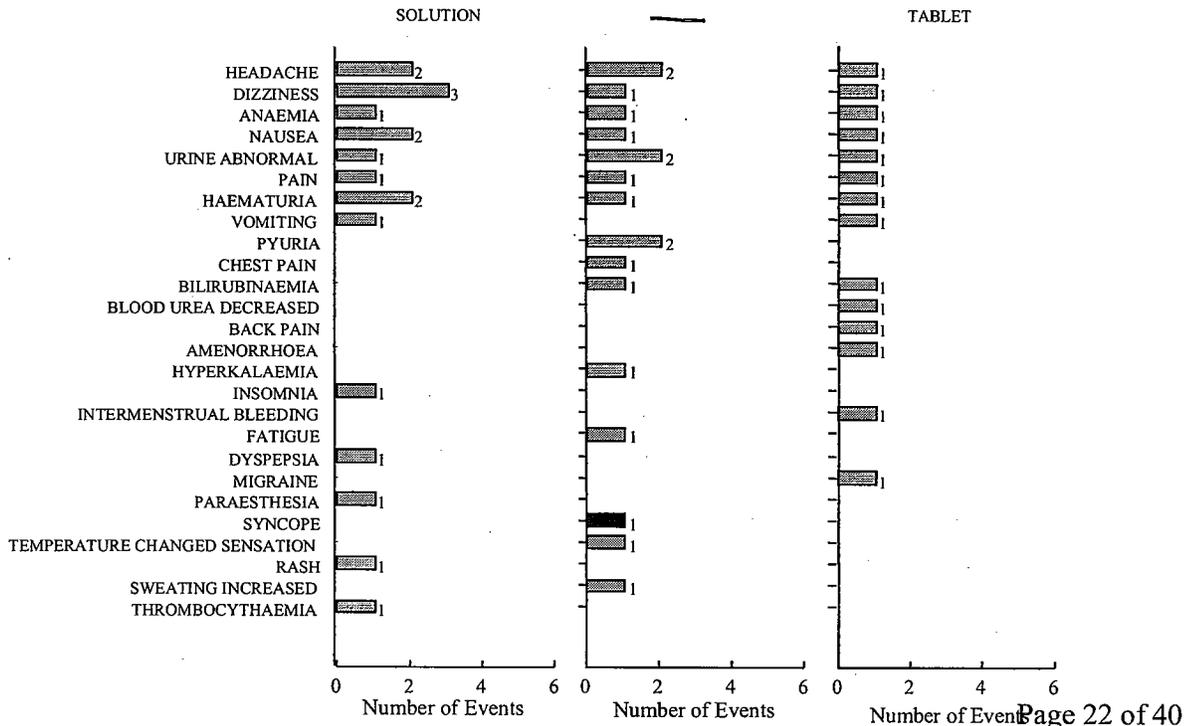
The sponsor stated in the safety evaluation section of the clinical study report that Safety was assessed throughout the study by “*recording and monitoring adverse events, standard clinical laboratory testing (hematology, serum chemistry, urinalysis), vital signs measurements, physical examinations, and pregnancy tests for women of childbearing potential. Any clinically significant abnormality that persisted at the end of the study was followed by the investigator until resolution or until a clinically stable endpoint was reached.*”

**MO Comment:** *The sponsor did not state if specific queries were utilized or if the safety database was composed of spontaneous reports. It would be useful to understand the sponsor’s methodology but given that the same method was applied throughout the studies a comparison of events between arms would still be valid.*

4.2.1.2 Incidence of Common Adverse Events

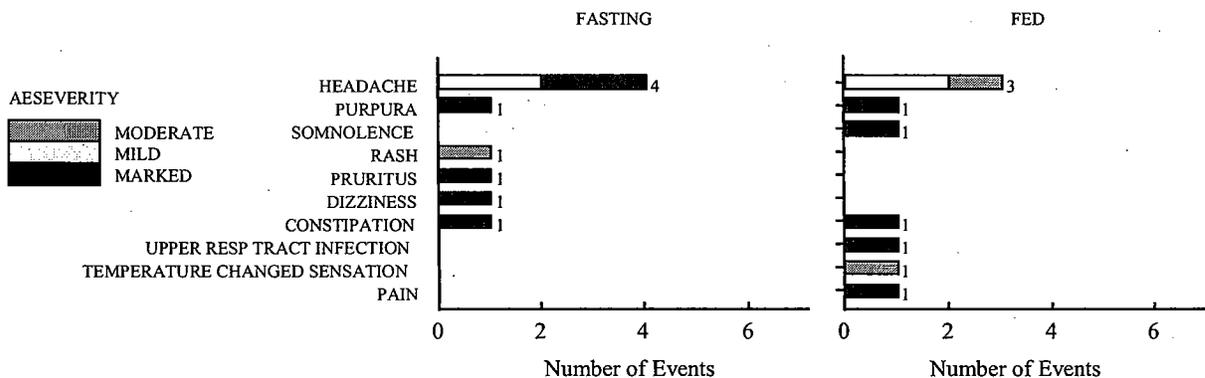
Given the small number of subjects enrolled in studies LOFBO-PHI-116 and LOFBO-PHI-117 (72 and 24, respectively) adverse event incidence rates do not represent an adequate safety population. To provide context to the calculated event rate, however, two variables require evaluation: (1) study specific AE rates as well as (2) formulation specific AE rates. In figure 3 and 4 below, total adverse events are displayed based on study-specific reporting. Formulation specific event rates were previously discussed in Figure 1 above.

**Figure 3 Study Based Adverse Events: LOFBO-PHI-116**



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**Figure 4: Study Based Adverse Events: LOFBO-PHI-117**



When comparing the specific rates (based on subjects, not events) between these two studies there is an elevated rate of adverse events in LOFBO-PHI-117 as well as the severity with all “marked” events (except 1 event of syncope) denoted by black graphic fill occurring in study LOFBO-PHI-117. The lighter bar graph fill represents those events coded as mild and the intermediate shade represents those events coded as moderate. The horizontal axis denotes the specific number of events captured. As stated earlier, the food effect study has more events of headache represented in the “fasting” arm that are of greater severity.

Table 6 below details the study specific AE rates (percentage of subjects with the event is provided in parentheses). Events are categorized by organ system.

**Table 6: Comparison of Study Specific AE Rates LOFB-PHI116 (N=72) and LOFB-PHI-117 (N=24)**

Description	LOFB-PHI-116 (N,%)	LOFB-PHI-117 (N, %)
<i>CNS and PNS Disorders</i>		
Headache	5 (7)	7 (25)
Dizziness	4 (6)	1(4)
Migraine	1 (1)	0
Syncope	1 (1)	0
Somnolence	0	1 (4)
Insomnia	1 (1)	0
Paresthasias	1 (1)	0
<i>Body as a whole</i>		
Pain	1 (1)	1 (4)
Back pain	1 (1)	0
Chest pain	1 (1)	0
Fatigue	1 (1)	0
Temperature changed sensation	1 (1)	1 (4)

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<i>Gastrointestinal</i>		
Nausea	4 (6)	0
Vomiting	2 (3)	0
Dyspepsia	1 (1)	0
Constipation	0	2 (8)
<i>Urinary System</i>	<b>LOFB-PHI-116 (N,%)</b>	<b>LOFB-PHI-117 (N, %)</b>
Hematuria	3 (4)	0
Urine abnormal	3 (4)	0
Pyuria	2 (3)	0
<i>Red blood cell disorders</i>		
Anemia	3 (4)	0
<i>Metabolic</i>		
BUN decreased	1 (1)	0
Hyperkalemia	1 (1)	0
<i>Reproductive disorder, female</i>		
Amenorrhea	1 (1)	0
Intermenstrual bleeding	1 (1)	0
<i>Skin and appendages</i>		
Rash	1 (1)	1 (4)
Sweating increased	1 (1)	0
Pruritis	0	1 (4)
<i>Liver and biliary system</i>		
Bilirubinemia	1 (1)	0
<i>Platelet, bleeding and clotting disorder</i>		
Thrombocythemia	1 (1)	0
Purpura	0	2 (8)
<i>Respiratory system disorder</i>		
Upper respiratory tract infection	0	1 (4)

**MO Comment:** Overall the rate and character of events were similar save for headache which occurred more frequently in study LOFB-PHI-117 and nausea/vomiting which occurred more frequently in study LOFB-PHI-116. It is not unexpected to have more headache related adverse events in the Belgian food effect study (LOFB-PHI-117) since there was a fasting arm to the trial which may independently cause headache. The increased rate of nausea/vomiting in study LOFB-PHI-116 compared to study LOFB-PHI-117 may be related to the difference in sample size (72 vs 24, respectively) which would enhance reporting or to the methodology of adverse event reporting capture between the two studies. In either case, the events were considered mild and did not persist. As a frame of reference, data present in the current Levaquin® label derived from clinical trials data describe an incidence of headache of 6.2%, nausea 7.1% and vomiting 2.5%, all consistent with data from the larger study, LOFB-PHI-117.

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There were 12 adverse events noted by 10 subjects. The details of these 12 events are provided below, categorized by gender (Table 7).

**Table 7: Adverse Events in LOFBO-PHI-002**

Adverse Event	Female	Male	Total
Upper Abdominal Pain	1		1
Earache		1	1
Head Discomfort	1		1
Headache	4		4
Viral Infection		1	1
Oral Numbness	1		1
Apthous Stomatitis	2		2
Blurred Vision	1		1
Grand Total	10	2	12

5 subjects experienced a headache and 1 each had hypoesthesia, abdominal pain, stomatitis (listed twice), earache, viral infection and abnormal vision. 10/12 events were self limited and resolved. Two events (both related to stomatitis) persisted. There was female preponderance of reporting.

There were 4 adverse events noted in LOFBO-PHI-003 by two subjects. The first subject reported sinus congestion and headache of moderate severity that resolved. Headache was reported as of moderate severity. The second subject reported allergies of mild severity that resolved.

#### 4.2.1.3 Additional Analyses and Explorations

There was a panoply of persistent adverse events that were considered of either mild or moderate severity. Presented below are these eight events:

1. Headache: Subject 3035, Hispanic female, solution arm (PHI-116)
2. Hematuria: Subject 3024, Hispanic female, tablet arm (PHI-116)
3. Urine abnormal: Subject 3024, Hispanic female, — (PHI-116)
4. Pyuria: Subject 3024, Hispanic female, — (PHI-116)
5. Constipation: Subject 24, White female, fed (PHI-117)
6. Pruritis: Subject 20, White female, fasting (PHI-117)
7. Thrombocytopenia: Subject 3027, Hispanic female, solution (PHI-116)
8. Upper respiratory tract infection: Subject 21, White female, fed (PHI-117)

**MO Comment:** *Subject 3024 accounted for 3/8 events, likely related to a urinary tract infection. Given the mild nature of these events and lack of biologic plausibility that a causal explanation would account for this finding it seems likely that the adverse events are merely reflective of reported adverse events and are not associated with a particular*

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formulation. All of the remaining events are however, currently listed in the product label and were not considered unexpected.

### Laboratory Findings

As outlined previously, hematology, chemistry and urinalyses were conducted in studies LOFB-PHI-116 and LOFB-PHI-117. Hematological evaluations included white blood cell count with differential, platelet count and hemoglobin. Serum chemistries included ALT, AST, LDH, alkaline phosphatase, total protein, uric acid, albumin, cholesterol, glucose, sodium, potassium, BUN, and creatinine. Urinalysis included pH, protein, glucose, and microscopy evaluation for RBC, WBC, casts, mucus and crystals. There were no clinically significant laboratory abnormalities detected when comparing the post treatment values with pretreatment values for either study. An evaluation of laboratory changes from baseline based on formulation arm showed no variation between tablet, solution or  $\rightarrow$  rms.

### Additional Analyses and Explorations

#### Vital Signs

Measures of blood pressure, heart rate, respiration rate and temperature were evaluated pretreatment as well as during each treatment period of studies LOFB-PHI-116 and LOFB-PHI-117. Specifically, variations between baseline and post treatment vital sign assessment is denoted in Table 8 below:

**Table 8: Vital Sign Variations, LOFB-PHI-116 and LOFB-PHI-117**

<b>LOFB-PHI-116</b>				
Vital Sign (Baseline)	Value Range	Mean	Mean Percent Change	Percent Change Range
<b>Solution</b>				
Temperature	35.6 to 37.8	36.9	-.53	-3.9 to 1.6
Heart Rate	59 to 94	68.2	5.2	-8.0 to 23.1
Systolic BP	98 to 154	109	2.7	-14.7 to 20.1
Respiratory Rate	10 to 18	13.5	10.0	-3.6 to 20
<b>Tablet</b>				
Temperature	36.0 to 37.7	36.8	-.32	-1.6 to 1.6
Heart Rate	56 to 88	64.7	11.0	-15.7 to 51.7
Systolic BP	98 to 150	109	1.3	-11.2 to 10.8
Respiratory Rate	9 to 20	14.1	-1.06	-77.8 to 33.3

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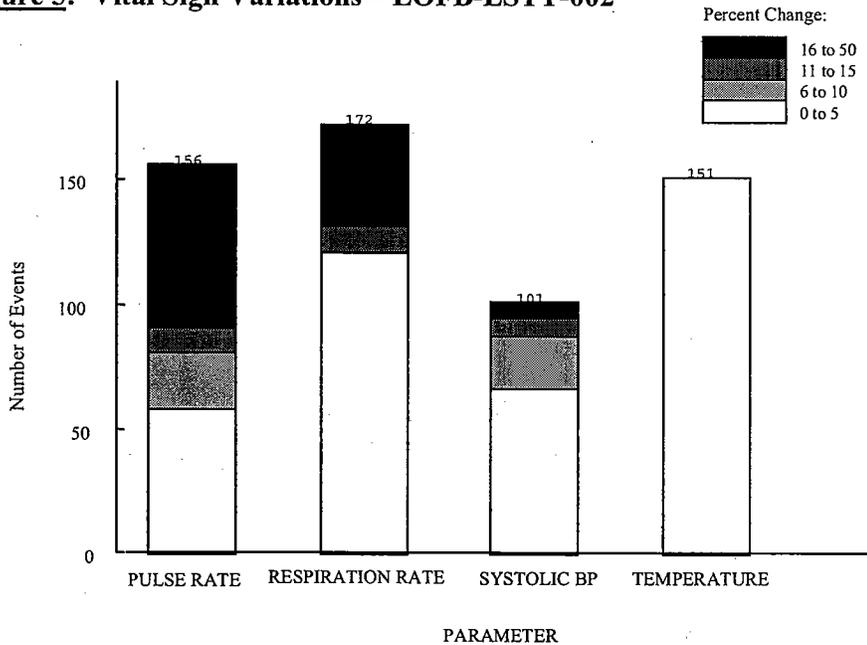
Temperature	36.4 to 37.6	37	-.16	-1.1 to .53
Heart Rate	54 to 90	65.9	8.0	-16.4 to 33.6
Systolic BP	90 to 146	107	2.8	-12.2 to 18.2
Respiratory Rate	12 to 20	14.7	5.6	-5.5 to 16.7
<b>LOFB-PHI-117</b>				
<b>Fasting</b>				
Temperature	35.5 to 36.8	36.2	-.17	-3.8 to 3.6
Heart Rate	48 to 91	58.1	4.9	-16.7 to 23.2
Systolic BP	91 to 142	106	11.6	-21.9 to 31.9
Respiratory Rate	8 to 20	14.3	-68.3	-206 to 89
<b>Fed</b>				
Temperature	35.4 to 36.7	35.9	1.0	-3.8 to 3.6
Heart Rate	50 to 91	57.2	7.0	-12.1 to 6
Systolic BP	93 to 138	103.7	14.1	-18.3 to 26.5
Respiratory Rate	8 to 24	14	-45.2	-137 to 33.3

**MO Comment:** *There were no clinically significant variations in temperature, heart rate, systolic blood pressure or respiratory rate between treatment arms in LOFB-PHI-116. The greater variation evident with heart rate and respiratory rate is a reflection of a lower baseline count that is more sensitive to small variations (e.g., a respiratory rate that changed from 10 to 15, although clinically meaningless reflects a 50% change, whereas a change in temperature of 37.1 to 37.5, also clinically meaningless carries only a 1% change). This variation is likewise reflected in LOFB-PHI-117 where there were no clinically meaningful outliers and the increased variability in respiratory rate is reflective of the lower baseline count.*

The two studies in which exposure was sole oral and not systemic, LOFB-LSTT-002 and LOFB-LSTT-003 likewise had no clinically significant variations in vital sign when comparing the post exposure parameters with the pre exposure parameters. In figure 6 below (LOFB-LSTT-002), pulse rate (beats/minute), respiration rate (breaths/minute), systolic blood pressure (mmHg), and temperature (°C) had minimal baseline changes with the majority of changes less than 5%. Where changes exceeded 15% (mostly pulse rate and respiratory rate) the variations were not considered clinically significant since as stated earlier, there is greater variation in parameters in which the baseline is subject to large fluctuations in values.

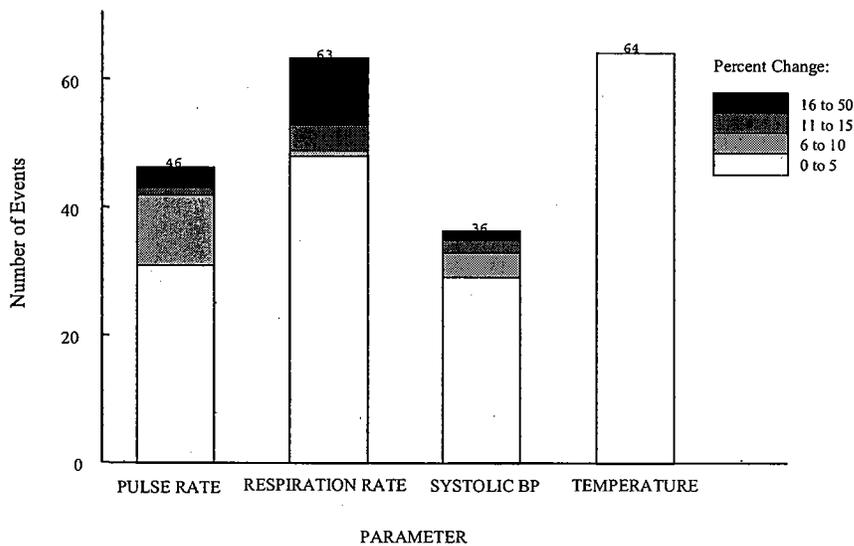
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**Figure 5: Vital Sign Variations – LOFB-LSTT-002**



The dark shading present mostly in pulse rate and respiratory rate is reflective of these variations. Similar variations from baseline values were present in study LOFB-LSTT-003, as shown below in Figure 7.

**Figure 6: Vital Sign Variations – LOFB-LSTT-003**



Overall, vital sign variations were not clinically significant and reflected similar means as well as percent changes from baseline as studies LOFB-LSTT-002 and LOFB-LSTT-003. Table 9 below describes the range, average and percent change of

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temperature, heart rate, systolic BP from baseline to after oral drug exposure. Variations of these values were all within clinically acceptable ranges.

**Table 9: Vital Sign Variations, LOFB-LSTT-002 and LOFB-LSTT-003**

Vital Sign (Baseline)	Value Range	Mean	Mean Percent Change	Percent Change Range
<b>LOFB-LSTT-002</b>				
Temperature	35.0 to 38.0	36.7	-.01	-4.8 to 5.1
Heart Rate	52 to 96	67.6	7.4	-25.0 to 69.2
Systolic BP	84 to 138	111.8	-2.4	-26.7 to 24.4
Respiratory Rate	14 to 24	19.1	-.1	-33.3 to 50.0
<b>LOFB-LSTT-003</b>				
Temperature	35 to 38	36.7	.34	-15.1 to 3.93
Heart Rate	56 to 92	69.5	.23	-13.9 to 17.6
Systolic BP	90 to 140	117.4	-.29	-18.3 to 18.0
Respiratory Rate	12 to 20	15.5	2.2	-22.2 to 66.7

### Special Assessments - Hepatotoxicity

As stated earlier, there were no clinically relevant laboratory abnormalities. As presented in attachments 7.2 in study report LOFBO-PHI-116, ALT, AST, alkaline phosphatase, and bilirubin in the 47 subjects evaluated had no significant change from baseline. As stated in the adverse reactions section of the current label, however, “abnormal hepatic function” as well as “elevated bilirubin” and “hepatic enzymes increased” are described.

### Electrocardiograms (ECGs)

No ECGs were obtained during any of the 4 submitted studies.

### Post-marketing Experience

As stated in the current label, currently reported adverse events in addition to the events from clinical trials that are described in the label include: “allergic pneumonitis, anaphylactic shock, anaphylactoid reaction, dysphonia, abnormal EEG, encephalopathy, eosinophilia, erythema multiforme, hemolytic anemia, multi-system organ failure, increased International Normalized Ratio (INR)/prothrombin time, Stevens-Johnson Syndrome, tendon rupture, torsades de pointes, and vasodilation.”

### Adequacy of Patient Exposure and Safety Assessments

The goal of the current submission is to establish bioequivalence between the approval tablet formulation of levofloxacin with the new oral solution formulation. As such, it is a small trial with minimal safety data relative to a typical large phase 3 trial. Nonetheless, the adverse events depicted in Figure 1 are all described in the current label and are not unexpected. They are also not more severe than expected. The frequency of

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events is difficult to compare with the labeled frequency table due to the marked difference in the subject population. Overall, the exposure of subject is commensurate with the study goals of bioequivalence.

**Summary of Selected Drug-Related Adverse Events**

Adverse events as denoted in Table 6 are all labeled events. See section 4.1.3.2 for further detail.

**Safety Conclusions**

Based on the submitted studies that included safety data (LOFBO-PHI-116 and LOFBO-PHI-117), there is no significant variation between the solution, or tablet formulation with regard to adverse events profile. The events captured during these studies reflects currently labeled events and do not occur in a more severe fashion. Assessment of frequency in the submitted data is limited by the small dataset that includes 72 subjects in study 116 and 24 subjects in study 117 (see section 4.1.3.2 for more detail).

Given the relative lack of Levaquin pediatric exposure and the clear potential for the new formulation's use in the pediatric population, it will be of paramount importance to maintain post-marketing surveillance of adverse events in this population should utilization increase. There may be unexpected, more severe or more frequent events not currently described in the levofloxacin label that will become manifest should pediatric utilization become more prominent.

**5 PHARMACOKINETIC FINDINGS**

The 6 pharmacokinetic parameters presented in Table 10 below (sponsor's table 7, page 37 of LOFBO-PHI-116 Study Report) demonstrate the bioequivalence between the solution formulation and tablet formulation.

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**Table 10: Mean (+/- SD) Pharmacokinetic Parameters After Administration of a Single 500-mg Oral Dose of Levofloxacin as a Suspension, — and Tablet (LOFBO-PHI-116)**

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Parameter	Formulation N=34	Solution Formulation N=34	Levaquin Tablet N=34
$C_{max}$ , $\mu\text{g/mL}$		5.76 $\pm$ 1.77	5.18 $\pm$ 1.52
$t_{max}$ , hr		0.76 $\pm$ 0.67	1.5 $\pm$ 0.81
$t_{1/2}$ , hr		7.0 $\pm$ 1.4	6.9 $\pm$ 1.3
$AUC_{\infty}$ , $\mu\text{g}\cdot\text{h/mL}$		47.8 $\pm$ 10.8	48.5 $\pm$ 12.6
CL/F, L/hr		11.0 $\pm$ 2.42	11.0 $\pm$ 2.72
Vd/F, L		112 $\pm$ 37.2	110 $\pm$ 39.5

In comparing the ratios of means for the pharmacokinetic parameters of  $C_{max}$  and  $AUC_{\infty}$  between the solution and tablet formulations, the confidence intervals were 98%-108% and 99%-103%, respectively. These ranges fall within the 80% to 125% limits of bioequivalence. For further detail please see Dr. Seong Jang's Biopharmaceutical Review.

In study LOFB-PHI-117 the effect of food on the pharmacokinetics of the oral levofloxacin solution was evaluated. Other than a decrease in the  $C_{max}$ , there was no significant difference in the pharmacokinetics between the fed and fasting states (see Table 11 below).

**Table 11: Mean (+/-SD) Pharmacokinetic Estimates Following a Single 500 mg Oral Dose of Levofloxacin Solution Under Fed and Fasted Conditions (from the Sponsor's Clinical Study Report, LOFB-PHI-117, page 37)**

Parameter	Solution Fed N=24	Solution Fasted N=24
$C_{max}$ , $\mu\text{g/mL}$	3.78 $\pm$ 0.884	5.24 $\pm$ 2.01
$t_{max}$ , h	1.5 $\pm$ 1.1	0.81 $\pm$ 0.52
$t_{1/2}$ , h	6.2 $\pm$ 1.1	6.2 $\pm$ 1.0
$AUC_{\infty}$ , $\mu\text{g}\cdot\text{h/mL}$	34.1 $\pm$ 8.23	39.4 $\pm$ 10.9
CL/F, L/h	15.4 $\pm$ 3.51	13.6 $\pm$ 3.76
Vd/F, L	137 $\pm$ 35.4	121 $\pm$ 35.2

Regarding pharmacokinetic equivalence, the 90% confidence intervals (CI) for the ratio of mean  $AUC_{\infty}$  between fed and fasted conditions fell within the 80% to 125% bioequivalence criteria. The 90% CI for the ratio of mean  $C_{max}$  between fed and fasted conditions fell outside the 80% to 125% limits, however. For further detail please see Dr. Seong Jang's Biopharmaceutical Review.

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**6 2003 PEDIATRIC RESEARCH EQUITY ACT (PREA)**

On December 3, 2003 the Pediatric Research Equity Act (PREA) was signed into law and mandates pediatric studies for new indications, active ingredients, or changes to dosing forms/regimens/routes. The act also allows for the deferral or waiver of pediatric studies until a specified date after approval if the adult approval is ready and the treatment does not provide a benefit over existing treatments in children and is not likely to be used in a substantial number of children as detailed below (21 CFR 505B (a)(3)).

*(3) DEFERRAL- On the initiative of the Secretary or at the request of the applicant, the Secretary may defer submission of some or all assessments required under paragraph (1) until a specified date after approval of the drug or issuance of the license for a biological product if--*

*(A) the Secretary finds that--*

*(i) the drug or biological product is ready for approval for use in adults before pediatric studies are complete;*

*(ii) pediatric studies should be delayed until additional safety or effectiveness data have been collected; or*

*(iii) there is another appropriate reason for deferral; and*

*(B) the applicant submits to the Secretary--*

*(i) certification of the grounds for deferring the assessments;*

*(ii) a description of the planned or ongoing studies; and*

*(iii) evidence that the studies are being conducted or will be conducted with due diligence and at the earliest possible time.*

*(4) WAIVERS-*

*(A) FULL WAIVER- On the initiative of the Secretary or at the request of an applicant, the Secretary shall grant a full waiver, as appropriate, of the requirement to submit assessments for a drug or biological product under this subsection if the applicant certifies and the Secretary finds that--*

*(i) necessary studies are impossible or highly impracticable (because, for example, the number of patients is so small or the patients are geographically dispersed);*

*(ii) there is evidence strongly suggesting that the drug or biological product would be ineffective or unsafe in all pediatric age groups; or*

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*(iii) the drug or biological product--*

*(I) does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients; and*

*(II) is not likely to be used in a substantial number of pediatric patients.*

As such the following indications currently labeled for Levaquin™ will be evaluated under the Pediatric Research Equity Act in the following manner:

1. Acute Maxillary Sinusitis

Pediatric studies (age between 0 and 16 years) will be waived.

2. Acute Bacterial Exacerbation of Chronic Bronchitis

Pediatric studies will be waived since the condition does not exist in children.

3. Community Acquired Pneumonia

Pediatric studies (age between 0 and 16 years) will be deferred until February 2, 2009 since the formulations is ready for use in adult before pediatric studies have been completed and there may be safety concerns related to use in children.

4. Complicated Urinary Tract Infections

Pediatric studies (age between 0 and 16 years) will be deferred until February 2, 2009 since the formulations is ready for use in adult before pediatric studies have been completed and there may be safety concerns related to use in children.

5. Acute Pyelonephritis

Pediatric studies (age between 0 and 16 years) will be deferred until February 2, 2009 since the formulations is ready for use in adult before pediatric studies have been completed and there may be safety concerns related to use in children.

6. Uncomplicated Skin and Skin Structure Infections

Pediatric studies (age between 0 and 16 years) will be waived.

7. Uncomplicated Urinary Tract Infections

Pediatric studies (age between 0 and 16 years) will be waived.

CLINICAL REVIEW

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## 8. Complicated Skin and Skin Structure Infections

Pediatric studies (age between 0 and 16 years) will be deferred until February 2, 2009 since the formulations is ready for use in adult before pediatric studies have been completed and there may be safety concerns related to use in children.

## 9. Nosocomial pneumonia

Pediatric studies (age between 0 and 16 years) will be deferred.

## 10. Prostatitis

Pediatric studies (age between 0 and 16 years) will be waived.

## 7 OVERALL ASSESSMENT

### Conclusions on Available Data

Based on the similarities of the pharmacokinetic profiles of the levofloxacin oral solution (25 mg/ml) to the currently marketed 500 mg tablet formulation (see section 5) and that the ratio of means for  $C_{max}$  and  $AUC_{\infty}$  fell within the regulatory requirement of 80% to 125% the oral solution formulation is considered bioequivalent to the marketed tablet formulation (see Dr. Seong Jang's Biopharmaceutical review for further detail). Given the lower  $C_{max}$  and  $AUC_{\infty}$  exhibited during the food effect study LOFB-PHI-117 however, specific recommendations regarding timing of drug administration with regard to food should be provided in the combined Levaquin™ label.

Systemic levofloxacin exposure occurred in studies LOFB-PHI-116 and LOFB-PHI-117. Adverse events were of similar quality and severity to those described in the current Levaquin™ label and were of relatively similar frequency between the solution, — and tablet formulations. Two events that occurred more frequently in subjects receiving the oral solution formulation that did have a higher frequency were headache as well as dizziness. These reports were mostly related to the food effect study completed in Belgium and may be related to either a fasting state or reporting variations among the Belgian population. Since LOFB-PHI-116 which contained two comparator arms showed no effect and the food effect study had no comparator arms, the headache/dizziness events were not considered to be of clinical concern. Clinically significant laboratory changes were related primarily to one subject (Subject 3024) in LOFB-PHI-116 with a urinary tract infection. Vital sign variations captures between the pre-exposure and post-exposure time points revealed no clinically concerning changes.

Studies LOFB-LSTT-002 and LOFB-LSTT-003 were taste related studies in which the goal was to determine the most palatable formulation of the levofloxacin oral solution. There was no systemic exposure to levofloxacin and no clinical laboratory samples were evaluated. Five adverse events reported by three subjects and four adverse events reported by 2 subjects in LOFB-LSTT-002 and LOFB-LSTT-003 were self-limited and not clinically concerning.

**Recommendation on Regulatory Action**

The levofloxacin oral solution (25 mg/ml) is approvable as bioequivalent to the currently marketed 500 mg tablet formulation.

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