

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

**020634Orig1s061, 020635Orig1s067,
021721Orig1s028**

**CLINICAL PHARMACOLOGY AND
BIOPHARMACEUTICS REVIEW(S)**

CLINICAL PHARMACOLOGY REVIEW

NDA: 20-634 S061(Tablets); 20-635 S067 (Injection); 21-721 S028 (Oral Solution)	Submission Date(s): October 27, 2011
Brand Name	Levaquin®
Generic Name	Levofloxacin
Reviewer	Seong H. Jang, Ph.D.
Team Leader	Kimberly Bergman, Pharm.D.
OCP Division	DCP4
OND Division	DAIP
Sponsor	Johnson & Johnson
Submission Type; Code	Efficacy Supplement; SE8
Formulation; Strength(s)	Tablets: 250 mg, 500 mg and 750 mg Oral Solution: 25 mg/mL Single dose Injection: 500 mg in 20 mL; and 750 mg in 30 mL Levaquin in 5% Dextrose Injection: 250 mg in 50 mL; 500 mg in 100 mL; and 750 mg in 150 mL
Proposed Indications	Pneumonic Plague-Post Exposure
Dosage and Administration	500 mg QD for adults and pediatric patients >50 kg and ≥6 months of age 8 mg/kg BID (not to exceed 250 mg/dose) for pediatric patients <50 kg and ≥6 months of age

1. EXECUTIVE SUMMARY 1

 1.1. Recommendation 2

 1.2. Phase 4 Commitments..... 2

 1.3. Summary of Important Clinical Pharmacology Findings 2

2. QUESTION BASED REVIEW 6

 2.1. General Attributes of the Drug..... 6

 2.2. General Clinical Pharmacology 6

 2.3. Pharmacokinetics of Levofloxacin in AGMs..... 9

 2.4. Analytical Section 15

3. LABELING RECOMMENDATIONS 19

4. APPENDICES..... 90

4.1. Individual Study Review 90

1. EXECUTIVE SUMMARY

The sponsor submitted these supplemental NDAs to provide for the use of Levaquin® in the treatment of pneumonic plague following the exposure to *Yersinia pestis* in adults and pediatric patients ≥6 months of age.

In the General Advice correspondence dated 7 February 2011, the FDA agreed that the Animal Rule (see 21 CFR 314.610 for drugs) is an appropriate regulatory pathway for the review of LEVAQUIN® for the treatment of pneumonic plague because the efficacy of levofloxacin in the treatment of pneumonic plague cannot be evaluated directly in humans due to ethical concerns. Thus, the FDA agreed that the data from the single GLP

animal efficacy study conducted in African Green Monkeys (AGMs) combined with information from the literature on rodents, along with levofloxacin PK data and natural history studies in AGMs are adequate to file an application for treatment of plague. As such, based on the FDA's *Draft Guidance for Industry: Animal Models — Essential Elements to Address Efficacy Under the Animal Rule (January 2009)*, the sponsor conducted one GLP efficacy study and three PK studies in AGMs.

A PK simulation study with the PK parameters of levofloxacin obtained in AGMs showed that a 30 min IV infusion of 8 mg/kg followed by an additional 30 min IV infusion of 2 mg/kg 12 hour later (8/2 mg/kg; humanized dose) would provide AGMs with a levofloxacin plasma concentration-time profile comparable to that in humans receiving the 500 mg QD IV dosing.

The results of the animal efficacy and PK studies demonstrated that (a) levofloxacin is efficacious for the treatment of plague in the AGM model with the humanized levofloxacin dose (a mortality rate of 2/17 vs. 7/7 for levofloxacin group and placebo group, respectively) and (b) the humanized levofloxacin dose used in the animal efficacy study provides AGMs with a PK profile similar to humans while keeping systemic exposure lower than that observed in humans receiving levofloxacin 500 mg QD (an approved levofloxacin dose for treatment of other indications).

1.1. Recommendation

Overall, the 8/2 mg/kg dose regimen protected AGMs from pneumonic plague (a mortality of 2/17). The regimen resulted in a humanized plasma concentration profile while keeping systemic exposure lower than that in humans receiving the 500 mg QD IV dosing. Thus, the PK results support the proposed dose of levofloxacin, i.e., 500 mg QD, for treatment of pneumonic plague (post-exposure) in adults and pediatric patients >50 kg and ≥6 months of age.

Previously, modeling and simulations conducted by the FDA Pharmacometrics reviewer (Dr. Fang Li, report dated May 02, 2008) showed that the approved levofloxacin dosing regimen for treatment of inhalation anthrax in pediatric patients <50 kg and ≥6 months of age (i.e., 8 mg/kg BID, not to exceed 250 mg/dose) provided systemic exposure comparable to adults receiving 500 mg QD. Thus, the proposed dose, i.e., 8 mg/kg BID (not to exceed 250 mg/dose), is acceptable for the treatment of pneumonic plague (post-exposure) in pediatric patients <50 kg and ≥6 months of age from the perspective of Clinical Pharmacology.

1.2. Phase 4 Commitments

No phase IV commitments are recommended.

1.3. Summary of Important Clinical Pharmacology Findings

Although *in vitro* microbiological data suggest that levofloxacin should be efficacious for the treatment of plague in humans at a dose of 500 mg once daily (QD), evaluation of the efficacy of levofloxacin in the treatment of pneumonic plague (post-exposure) cannot be conducted directly in humans due to ethical concerns and must rely on the results of animal models. Thus, the efficacy of levofloxacin in the treatment of pneumonic plague was evaluated with a humanized dose in AGMs, which exhibit similar pathogenesis and disease progression for pneumonic plague compared to humans. Accordingly, the purpose of the pharmacokinetic studies in the current development program was to demonstrate that the humanized levofloxacin dose used in the animal efficacy study provides the AGMs with concentration-time profiles and systemic exposure comparable to or lower than that in humans who received an approved levofloxacin dose for treatment of other infections.

Humanized Dose of Levofloxacin in AGMs

Levofloxacin plasma concentrations in humans exceed the MIC against *Y. pestis* (0.03 µg/mL) for the entire dosing interval following the administration of 500 mg QD via IV infusion. Since the $t_{1/2}$ of levofloxacin in AGMs is shorter than in humans (approximately 2 to 3 hours vs. 6 to 8 hours), a PK simulation was conducted to determine a humanized dosing regimen in order to mimic the human plasma profile of levofloxacin in AGMs. The simulation results showed that a 30 min IV infusion of 8 mg/kg followed by an additional 30 min IV infusion of 2 mg/kg 12 hours later (8/2 mg/kg) would provide AGMs with a levofloxacin plasma concentration-time profile comparable to that in humans receiving the 500 mg QD IV dosing. This humanized dose regimen was used in the pivotal efficacy study in AGMs (Study FY07-070).

Comparison of Levofloxacin PK in AGMs vs. humans

In healthy AGMs that received IV administration of the humanized dose, i.e., 8/2 mg/kg (Study B465-10), the plasma concentrations of levofloxacin did not exceed those observed in humans who received the 500 mg IV QD dose at any time during the 24-h period (Figure S1). The humanized dose (8/2 mg/kg) in healthy AGMs resulted in a C_{max} of 3.3 µg/mL and an AUC_{0-24} of 11.9 µg·hr/mL which were lower than those observed in humans who received the 500 mg IV dose by approximately 50% and 75%, respectively (Table S1).

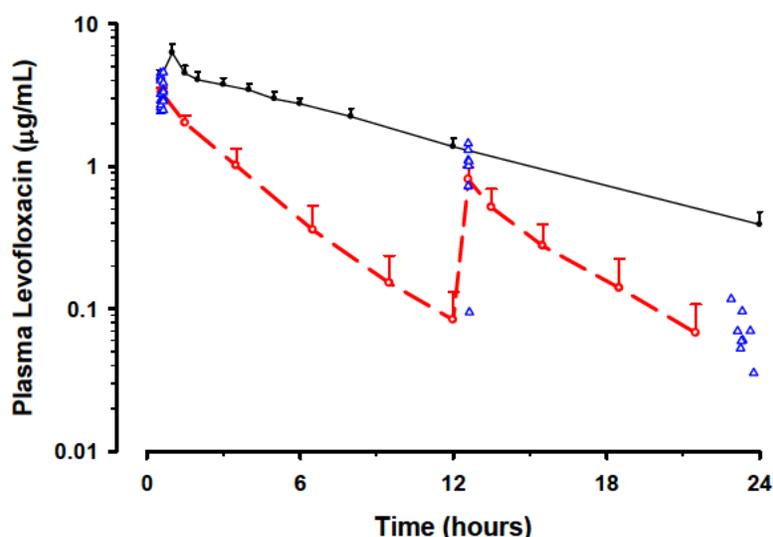


Figure S1. Comparison of plasma levofloxacin concentrations following intravenous (IV) dosing in AGMs and humans. The solid line and the closed circles represent concentrations in humans following a single IV administration of levofloxacin 500 mg (Study LOFBO-PHIO-097, n=23). The dashed line and the open circles represent concentrations in healthy AGMs following a single administration of levofloxacin 8/2 mg/kg (Study B465-10, n=6). The open triangles represent peak and trough concentrations in diseased AGMs following multiple IV administrations of levofloxacin 8/2 mg/kg (Cohort 3 of Study FY07-070).

Table S1. Pharmacokinetic parameters of levofloxacin in AGMs (Study B465-10) and humans (Study LOFBO-PHIO-097)

	Dose	C _{max} (µg/mL)	AUC ₀₋₂₄ (µg·hr/mL)	T _{1/2} (hour)
AGMs (n=6)	8/2 mg/kg ^a	3.3±0.27	11.9±3.13	2.69±0.42
Humans (n=24)	500 mg IV	6.2±1.0	48.3±5.4	6.4±0.7

^a: First dose 8 mg/kg, followed by a second dose of 2 mg/kg 12 hours later

The plasma levofloxacin concentrations observed in the diseased AGMs in the efficacy study (Cohort 3 in Study FY07-070) generally aligned with those observed in the PK study in healthy AGMs (Study B465-10) and were lower than those observed in humans who received the 500 mg IV QD dose throughout the 24-h period (Figure 1). The mean±SD of peak concentrations following the first and third doses (30-min infusion of 8 mg/kg levofloxacin) in Cohort 3 in Study FY07-070 was comparable to peak concentrations observed in healthy AGMs (Study B465-10), i.e., 3.3±0.82 vs. 3.3±0.27 µg/mL. Similarly, mean±SD of peak and trough concentrations following the 2 mg/kg dose in the efficacy study were also comparable to those in the PK study (1.08±0.22 vs. 0.81±0.18 µg/mL and 0.07±0.03 vs. <0.03 to 0.06 µg/mL, respectively).

There was no substantial difference in plasma protein binding of levofloxacin between AGMs (ranged from 15 to 32%) and humans (ranged from 24 to 38%). The extent of

urinary excretion of levofloxacin (i.e., as unchanged drug) was lower in AGMs treated with the humanized dose (8/2 mg/kg) compared with humans received a single oral levofloxacin 500 mg (28% vs. 80%). The reason for the difference in renal excretion of levofloxacin between AGMs and humans was not fully addressed.

Seong H. Jang, Ph.D.
Reviewer
Clinical Pharmacology
DCP4/OCP/OTS

Concurrence

Kimberly Bergman, Pharm.D.
Team Leader
Clinical Pharmacology
DCP4/OCP/OTS

2. QUESTION BASED REVIEW

2.1. General Attributes of the Drug

2.1.1. What are the highlights of the chemistry and physical-chemical properties of the drug substance and the formulation of the drug product?

Levofloxacin is currently approved and marketed as LEVAQUIN[®] in the United States [(New Drug Application [NDA] 20-634 (Oral tablet), NDA 20-635 (Injectable), and NDA 21-721 (Oral solution)] to treat specific infective conditions, such as acute maxillary sinusitis, acute exacerbation of chronic bronchitis, community-acquired pneumonia, complicated and uncomplicated urinary tract infections, and inhalational anthrax (post-exposure). In this supplemental NDA (sNDA) submission, drug substance and drug product remains unchanged from that of the approved NDAs.

2.1.2. What is the proposed mechanism of drug action and therapeutic indication?

Levofloxacin is a member of the fluoroquinolone class of antibacterial agents. The mechanism of action of levofloxacin and other fluoroquinolone antimicrobials involves inhibition of bacterial topoisomerase IV and DNA gyrase (both of which are type II topoisomerases), enzymes required for DNA replication, transcription, repair and recombination.

In this sNDA, levofloxacin is proposed for the treatment of pneumonic plague following the exposure to *Yersinia pestis* in adults and pediatric patients ≥ 6 months of age. The effectiveness of Levaquin[®] is based on plasma concentrations achieved in humans, a surrogate endpoint reasonably likely to predict clinical benefit. Levaquin[®] has not been tested in humans for the post-exposure treatment of pneumonic plague.

2.1.3. What is the proposed dosage and route of administration?

The proposed dose for the treatment of pneumonic plague following the exposure to *Yersinia pestis* in adults and pediatric patients > 50 kg and ≥ 6 months of age is 500 mg every 24 hours. In general, since the plasma concentration-time profile of levofloxacin after IV administration is similar and comparable in extent of exposure (AUC) to that observed for Levaquin[®] tablets when equal dose (mg:mg) are administered, the oral and IV routes of administration can be considered interchangeable. When Levaquin[®] Injection is used, 500 mg should be administered by slow infusion over 60 minutes.

For pediatric patients < 50 kg and ≥ 6 months of age, the proposed dose is 8 mg/kg BID (not to exceed 250 mg/dose).

2.2. General Clinical Pharmacology

2.2.1. What are the design features of the clinical pharmacology and clinical studies used to support dosing or claims?

In vitro microbiological data suggest that levofloxacin should be efficacious for the treatment of plague in humans at a dose of 500 mg once daily (QD). However, evaluation of the efficacy of levofloxacin in the treatment of pneumonic plague (post-exposure) cannot be conducted directly in humans due to ethical concerns and must rely on the results of animal models. Thus, the efficacy of levofloxacin in the treatment of pneumonic plague was evaluated with a humanized dose in AGMs, which exhibit similar pathogenesis and disease progression for pneumonic plague to humans. Accordingly, the purpose of the pharmacokinetic studies in the current development program was to demonstrate that the humanized levofloxacin dose used in the animal efficacy study provides the AGMs with concentration-time profiles and systemic exposure comparable to or lower than that in humans who received an approved levofloxacin dose for treatment of other infections. The development program consisted of three Natural History studies, one nonclinical efficacy study and three PK studies in AGMs.

Based on the results of the natural history studies in AGMs, this species were selected for the efficacy study of levofloxacin as a treatment of pneumonic plague. A single treatment efficacy study, FY07-070, with levofloxacin was conducted at Lovelace Biomedical and Environmental Research Institute (LBERI), Albuquerque, New Mexico.

Study FY07-070: Levofloxacin vs. Placebo

The study was randomized, partially-blinded, and placebo-controlled. Three cohorts (Cohorts 1, 2, and 3) of AGMs (n=24) were studied. The objective of the study was to determine if intravenous infusion of levofloxacin would prevent death from established pneumonic plague in the AGM model.

Each cohort of African Green monkeys (*Chlorocebus aethiops*) was challenged via head-only aerosol inhalation to a multiple fifty percent lethal dose (LD₅₀) of *Yersinia pestis*, strain CO92. Based on the results of the natural history studies, established pneumonic plague was indicated by a body temperature of a mean fever >39°C for at least one hour, which was the signal to initiate levofloxacin or placebo infusions. Following challenge with aerosolized *Y. pestis*, the animals were monitored via telemetry to determine the onset of defined fever. The animals were treated within six hours (3.4 ± 1.8 hours) of onset of fever with either the test article, levofloxacin (5 mg levofloxacin/mL 5% dextrose), or control article, 5% dextrose, depending on predetermined treatment group. Seventeen AGMs (9 females and 8 males) were treated with test article and seven AGMs (3 females and 4 males) received control article.

For each animal, the infusion of levofloxacin was administered as a “humanized” dose regimen consisting of two infusions every 24 h period in order to target plasma concentrations achieved in humans with a single dose of levofloxacin every 24 h. Levofloxacin was administered for 10 days. In each 24 h period levofloxacin, 8 mg/kg (high dose) or control article was administered over 30 minutes followed by a second infusion of levofloxacin [2 mg/kg (low dose)], or control article administered over 30 ± 8 minutes within 12 (± 1.0) h. Infusions continued until the death of the animal or until 20 total infusions (10 high doses and 10 low doses) had been delivered. Animals were

monitored for up to 28 days post-challenge by twice daily observation and continuous monitoring of heart rate, respiration rate, and temperature via implanted telemeters.

None of the control animals survived; all were dead or euthanized by Day 5. Three of the control animals (U193, X702, X773) were euthanized moribund and four animals died spontaneously. A total of 16 (89%) levofloxacin-treated animals survived to the end of the study at Day 28. In the levofloxacin-treated group, one animal, X779, was removed from the study post-exposure to *Y. pestis* and was counted as a failure in the analysis of efficacy. Animal X779 received a challenge dose of *Y. pestis* (83 LD₅₀) and one dose of levofloxacin before it became febrile and it was removed from the study for a protocol violation. Animal Y160 was euthanized moribund for severe vomiting due to an ill-defined stomach problem on Day 9 and was considered a treatment failure for this analysis.

PK Studies in AGMs

An outline of the 3 PK studies is provided in Table 1. The initial PK study (Study B122-03) used saline as the vehicle whereas the subsequent studies (Studies FY08-150 and B465-10) and the efficacy study (Study FY07-070) used a 5% dextrose formulation.

Table 1. Summary of PK studies conducted in AGMs to support the plague indication.

Study type (Study No.)	N	Route of Administration	Duration of dosing	Dose (mg/kg)	Testing Facility	GLP status
Single and Repeat Dose-PK (B122-03)	3/sex	Phase I: po (nasogastric)	once	15-20-25	(b) (4)	GLP
		Phase II: IV (20-min inf.)	once	15		
		Phase III: IV (20-min inf.)	14 days	20		
Single Dose-PK (FY08-150)	3 F	IV	1 day (bid)	8,2	(b) (4)	Non-GLP
Single Dose-PK (B465-10)	3/sex	IV	1 day (bid)	8,2	(b) (4)	GLP

2.2.2. *What is the basis for selecting the response endpoints (i.e., clinical or surrogate endpoints) or biomarkers (collectively called pharmacodynamics [PD]) and how are they measured in clinical pharmacology and clinical studies?*

The primary endpoint of the animal efficacy study was survival on day 28 post-challenge.

2.2.3. *Are the active moieties in the biological fluid appropriately identified and measured to assess pharmacokinetic parameters?*

The active moiety levofloxacin was appropriately identified and measured in serum from AGMs by a validated high performance liquid chromatography assay with fluorescence detection (FLD) or mass spectrometry (HPLC/MS/MS) (see 2.6).

2.2.4. *Exposure-Response*

In the pivotal animal efficacy study (Study FY07-070), the mortality due to plague in AGMs that received a 10 day regimen of IV levofloxacin was significantly lower (2/17), compared to the placebo group (7/7) [$p < 0.001$]. Since the efficacy failure rate is substantially low (i.e., $< 10\%$), exposure-response analysis for efficacy was not conducted.

The approved levofloxacin dose for treatment of gram negative pneumonia is 500 mg every 24 hours. The levofloxacin plasma concentrations in healthy (Study B465-10) and diseased (Cohort 3 in Study FY07-070) AGMs were lower than those observed in humans who received levofloxacin 500 mg QD (see below). Thus, exposure-response analysis for safety was not conducted.

2.3. Pharmacokinetics of Levofloxacin in AGMs

2.3.1. *Was a humanized dose (i.e., the dose that would provide animal with plasma concentration-time profiles comparable to human receiving a therapeutic dose) for AGMs adequately determined?*

Levofloxacin plasma concentrations in humans exceed the MIC against *Y. pestis* (0.03 $\mu\text{g/mL}$) for the entire dosing interval following the administration of 500 mg QD. Since the $t_{1/2}$ of levofloxacin in AGMs was shorter than in humans (approximately 2 to 3 hours vs. 6 to 8 hours), a PK simulation with the PK parameters obtained from Study B122-03 (the first PK study in AGMs) was conducted to determine a humanized dosing regimen in order to mimic the human plasma profile of levofloxacin in AGMs. The simulation results showed that a 30 min IV infusion of 8 mg/kg followed by an additional 30 min IV infusion of 2 mg/kg 12 hours later (8/2 mg/kg) would provide AGMs with a levofloxacin plasma concentration-time profile comparable to that in humans receiving levofloxacin 500 mg QD IV dosing (Figure 1). This humanized dose regimen was used in the pivotal efficacy study in AGMs (Study FY07-070).

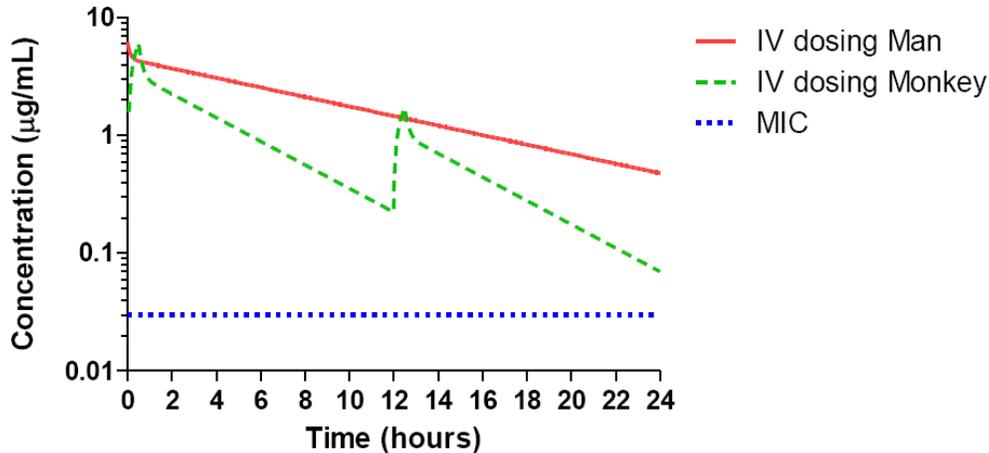


Figure 1. Predicted levofloxacin plasma concentration-time profile in AGMs following a 30 min IV infusion of 8 mg/kg followed by an additional 30 min IV infusion of 2 mg/kg 12 hours later (dashed line). These simulations approximate the concentration-time profile in humans following a single IV dose of 500 mg (solid line). The horizontal dotted line represents the MIC against *Y. pestis* (0.03 µg/mL).

Further PK studies were conducted to confirm that this humanized dosing regimen (8/2 mg/kg) would provide the AGMs with humanized concentration-time profiles while keeping systemic exposure lower in the animals than that in humans who received an approved levofloxacin dose for treatment of other infections.

2.3.2. *Were the levofloxacin PK profiles in AGMs that received the humanized dosing regimen comparable to in humans who received an approved levofloxacin dose (i.e., 500 mg QD)?*

In healthy AGMs received IV administration of the humanized dose, i.e., 8/2 mg/kg (Study B465-10), the plasma concentrations of levofloxacin did not exceed those observed in humans who received the 500 mg QD IV dosing throughout the 24-h period (Figure 2). The humanized dose (8/2 mg/kg) in healthy AGMs resulted in a C_{max} of 3.3 µg/mL and an AUC_{0-24} of 11.9 µg·hr/mL which were lower than those observed in humans who received the 500 mg IV dose by approximately 50% and 75%, respectively (Table 2).

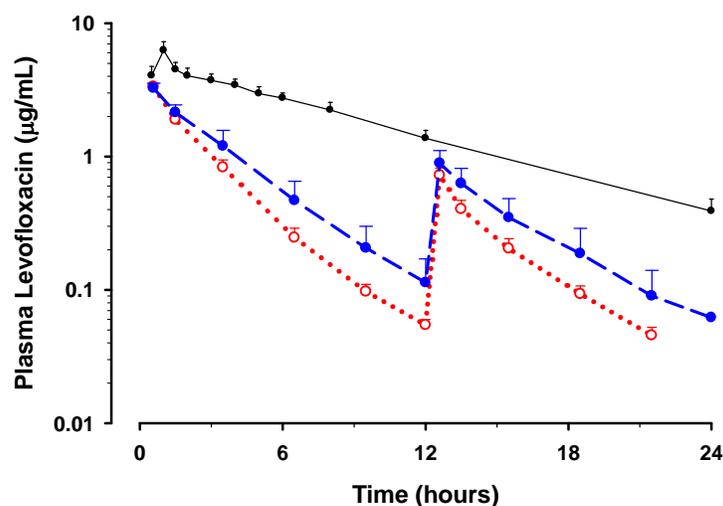


Figure 2. Comparison of plasma levofloxacin concentrations following intravenous dosing in healthy AGMs and humans. The solid line and the closed circles represent concentrations in humans following a single IV administration of levofloxacin 500 mg (Study LOFBO-PHIO-097, n=23). The dashed line (the closed circles) and the dotted line (the open circles) represent concentrations in healthy male (n=3) and female (n=3) AGMs, respectively, following a single administration of levofloxacin 8/2 mg/kg (Study B465-10).

Table 2. Pharmacokinetic parameters of levofloxacin in AGMs (Study B465-10) and humans (Study LOFBO-PHIO-097).

	Dose	C _{max} (µg/mL)	AUC ₀₋₂₄ (µg·hr/mL)	T _{1/2} (hour)
Male AGMs (n=3)	8/2 mg/kg ^a	3.25±0.36	13.83±3.61	2.81±0.61
Female AGMs (n=3)	8/2 mg/kg ^a	3.34±0.21	9.96±0.48	2.57±0.17
All AGMs (n=6)	8/2 mg/kg ^a	3.3±0.27	11.9±3.13	2.69±0.42
Humans (n=23)	500 mg IV	6.2±1.0	48.3±5.4	6.4±0.7

^a: First dose 8 mg/kg , followed by a second dose of 2 mg/kg 12 hour later

In Study B465-10, the levofloxacin plasma concentrations in male AGMs were higher compared to female AGMs (Figure 2). Accordingly, the mean AUC₀₋₂₄ in male AGMs was greater than in female AGMs (Table 2). Although the reason for this difference was not addressed, the levofloxacin plasma exposures in male AGMs (i.e., a higher-exposure subgroup) also did not exceed those observed in humans who received the 500 mg IV QD dose throughout the 24-h period.

2.3.3. *Was there any difference in the levofloxacin PK profiles after repeated dosing compared to that after single dosing in AGMs?*

Levofloxacin was administered for 10 days in the efficacy study (Study FY07-070) in AGMs. Thus, the comparability of PK profiles after repeat dosing versus PK profiles following single dose administration in AGMs should be addressed.

In Study B122-03 (an initial PK study), repeated IV dosing of 20 mg/kg levofloxacin to AGMs for 14 days increased the clearance of levofloxacin, and decreased levofloxacin AUC by approximately 30% (Table 3), indicating that the PK of levofloxacin in AGMs may be non-linear. Although the reasons for the increase in the clearance of levofloxacin by repeated dosing were not addressed, the results showed that the levofloxacin exposure in AGMs in the efficacy study (Study FY07-070) were lower than in humans who received a 500 mg QD dose during the entire dosing period (i.e., 10 days). It should be noted that in humans the mean AUC₀₋₂₄ increased by approximately 10% after repeated dosing compared to single dose administration (54.6 vs. 48.3 µg·hr/mL).

Table 3. PK parameters (Mean±SD) following repeat doses of levofloxacin IV 20 mg/kg (20-min infusion) in AGMs for 14 days (Study B122-03).

	C _{max} (µg/mL)	AUC ₀₋₂₄ (µg·hr/mL)	T _{1/2} (hour)	CL (mL/h/kg)
1 st dose	16.9±1.48	45.35±8.23	3.21±0.44	567±106
last dose	11.8±1.78	30.4±4.26	2.52±0.31	836±130

2.3.4. *Were levofloxacin plasma concentrations in the efficacy study (i.e., diseased AGMs) comparable to those observed in healthy AGMs?*

The plasma levofloxacin concentrations observed in the diseased AGMs in the efficacy study (Cohort 3 in Study FY07-070) generally aligned with those observed in the PK study in healthy AGMs (Study B465-10) and were lower than those observed in humans who received the 500 mg IV QD dose throughout the 24-h period (Figure 3). The mean±SD of peak concentrations following the first and third doses (30-min infusion of 8 mg/kg levofloxacin) in Cohort 3 in Study FY07-070 were comparable to peak concentrations observed in healthy AGMs (Study B465-10), i.e., 3.3±0.82 vs. 3.3±0.27 µg/mL. Similarly, mean±SD of peak and trough concentrations following the 2 mg/kg dose in the efficacy study were also comparable to those in the PK study (1.08±0.22 vs. 0.81±0.18 µg/mL and 0.07±0.03 vs. <0.03 to 0.06 µg/mL, respectively).

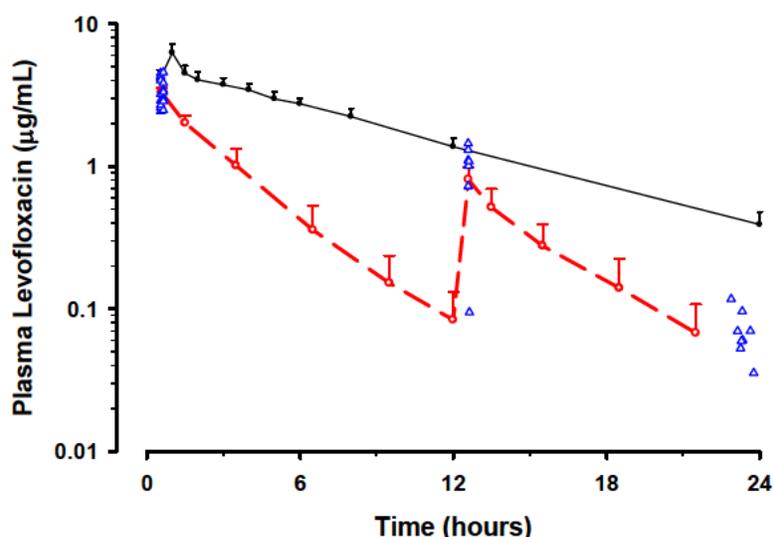


Figure 3. Comparison of plasma levofloxacin concentrations following intravenous (IV) dosing in AGMs and humans. The solid line and the closed circles represent concentrations in humans following a single IV administration of levofloxacin 500 mg (Study LOFBO-PHIO-097, n=23). The dashed line and the open circles represent concentrations in healthy AGMs following a single administration of levofloxacin 8/2 mg/kg (Study B465-10, n=6). The open triangles represent peak and trough concentrations in diseased AGMs following multiple IV administrations of levofloxacin 8/2 mg/kg (Cohort 3 of Study FY07-070).

2.3.5. *Were there any other differences in the levofloxacin PK between AGMs and humans?*

In Study B465-10, urine samples were collected and analyzed for levofloxacin concentration to evaluate the percentage of dose recovered in the urine in AGMs. In addition, plasma protein binding of levofloxacin in AGM plasma was also evaluated.

Urinary Excretion

The mean±SD percent of total administered dose recovered in the urine up to 48 hr was 29.3±15% and 26.5±1.4% for male (n=3) and female (n=3) AGMs, respectively. The corresponding value for all AGMs (n=6) was 27.9±9.7%. Levofloxacin is excreted largely (~80%) as unchanged drug in the urine in humans. The reason for the difference in renal excretion of levofloxacin between AGMs and humans was not fully addressed.

Protein Binding

Table 4 shows the plasma protein binding data of levofloxacin in AGMs. The fraction of levofloxacin bound to plasma proteins was 0.24-0.32 for males, and 0.15-0.28 for females at concentrations of 0.34 to 2.48 µg/mL. *In vitro*, over a clinically relevant range (1 to 10 µg/mL) of serum/plasma levofloxacin concentrations, levofloxacin is approximately 24 to 38% bound to serum proteins in rats, dogs, monkeys, and humans, as

determined by the equilibrium dialysis method. There was no substantial difference in plasma protein binding of levofloxacin between AGMs and humans.

Table 4. Unbound plasma concentrations of levofloxacin in AGMs (Study B465-10)

Nominal time (hour)	Sex	Animal	Total conc. (µg/mL)	Unbound conc. (µg/mL)	Fraction unbound
1.5	Males	001	1.92	1.33	0.69
		002	2.01	1.42	0.71
		003	2.48	1.73	0.70
	Females	004	2.03	1.66	0.82
		005	1.71	1.45	0.85
		006	1.92	1.44	0.75
Mean±SD					0.75±0.06
13.5	Males	001	0.416	0.305	0.73
		002	0.686	0.519	0.76
		003	0.78	0.527	0.68
	Females	004	0.339	0.244	0.72
		005	0.401	0.331	0.83
		006	0.470	0.375	0.80
Mean±SD					0.75±0.06

2.3.6. *Do the results of the animal studies adequately support the proposed dosing regimen for the treatment of the treatment of pneumonic plague following the exposure to Yersinia pestis in humans?*

Overall, the 8/2 mg/kg dose regimen provided AGMs protection from pneumonic plague (a mortality of 2/17) with a humanized plasma concentration profile while keeping systemic exposure lower than that in humans receiving the 500 mg QD IV dosing. Thus, the PK results support the proposed dose of levofloxacin, i.e., 500 mg QD, for treatment of pneumonic plague (post-exposure) in adults and pediatric patients >50 kg and ≥6 months of age.

Previously, a modeling and simulation study conducted by the FDA Pharmacometrics reviewer (Dr. Fang Li, reported dated May 02, 2008) showed that the approved levofloxacin dosing regimen for treatment of inhalation anthrax in pediatric patients < 50 kg and ≥6 months of age (i.e., 8 mg/kg BID, not exceed 250 mg/dose) provides systemic exposure comparable to in adults receiving 500 mg QD. Figures 4 and 5 show the predicted steady state AUC and C_{max} as a function of body weight and age in pediatric patients following 7.5 mg/kg BID levofloxacin IV. For practical reasons, it was accepted to round the pediatric dose up from 7.5 mg/kg to 8.0 mg/kg since the maximal additional total daily dose is 15 mg (i.e., 8-7.5 mg/kg*250 mg/8 mg/kg =15 mg) which is less than a 10% increase in the total daily dose. Thus, the proposed dose for the treatment of pneumonic plague, i.e., 8 mg/kg BID (not to exceed 250 mg/dose), is acceptable for the treatment of pneumonic plague (post-exposure) in pediatric patients <50 kg and ≥6 months of age from the perspective of Clinical Pharmacology.

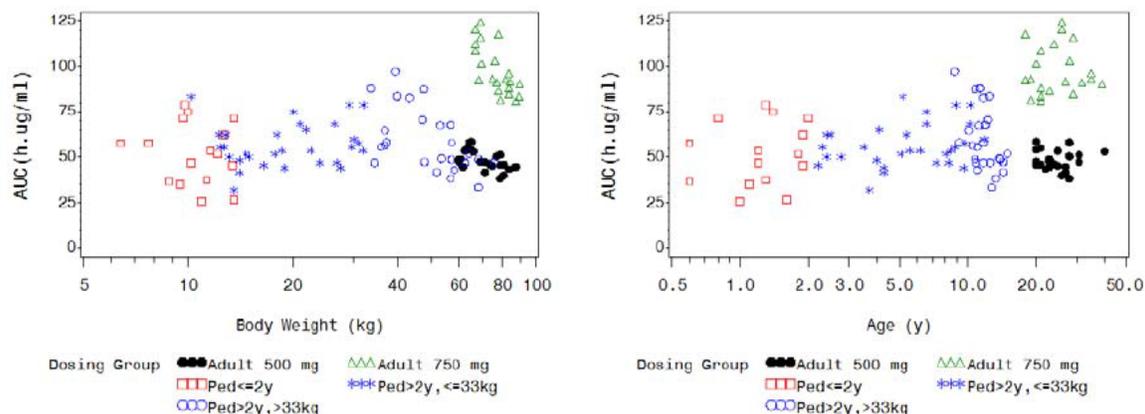


Figure 4. Predicted steady state AUC following 15 mg/kg levofloxacin (not exceeding 500 mg) vs. Body Weight and Age (from the FDA Pharmacometrics review by Dr. Fang Li, reported dated May 02, 2008).

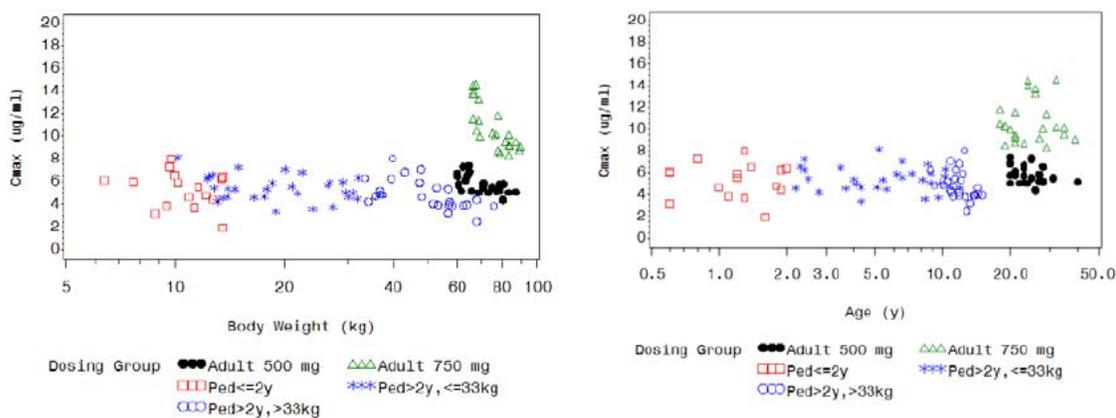


Figure 5. Predicted steady state C_{max} following 7.5 mg/kg BID levofloxacin (not exceeding 250 mg) vs. body weight and age (from the FDA Pharmacometrics review by Dr. Fang Li, reported dated May 02, 2008).

2.4. Analytical Section

2.4.1. Bioanalytical Methodology for Study B122-03

Initially, a high performance liquid chromatography assay with fluorescence detection (HPLC/FLD) was developed and validated by (b) (4) for the detection and quantitation of levofloxacin in AGM plasma samples obtained from an exploratory PK study. An internal standard (b) (4) was added to plasma samples, followed by

(b) (4)

Calibration ranges for levofloxacin were 0.05 to 10.0 µg/mL. Tests to assess specificity, linearity, accuracy and precision of the assay were within acceptable levels of specification (<15%). Freeze/thaw stability analysis of quality control (QC) samples frozen at ≤ -70 °C revealed no apparent significant decrease in analyte concentration after three cycles. Samples thawed and stored at room temperature for 1 h and then analyzed in triplicate exhibited no apparent loss of levofloxacin upon analysis. Additional analyses demonstrated the stability of levofloxacin for up to 3 days while in the autosampler.

2.4.2. *Bioanalytical Methods Supporting Study FY07-070 and Study FY08-150*

A high performance liquid chromatography/triple quadrupole mass spectrometry (HPLC/MS/MS) assay was developed at (b) (4) for the determination of levofloxacin in AGM plasma. The method, however, which was utilized in support of Cohorts I and II of the definitive efficacy study FY07-070, was determined to be unsuitable as the assay performed poorly; results were uninterpretable, and not consistently within the validated range of the assay. Although the efficacy study yielded expected results, in that control animals succumbed to disease while the levofloxacin treated animals survived, the pharmacokinetic data from Cohorts I and II of efficacy study FY07-070 were thus considered invalid and are not reported.

Therefore, a decision was made to abandon the HPLC/MS/MS method and subsequently a HPLC/FLD assay was developed and qualified by (b) (4) for the quantification of levofloxacin in AGM plasma. The assay was used in support of Cohort III from study FY07-070, and study FY08-150, a study in AGMs that used the same humanized dosing regimen as the pivotal efficacy study (i.e., 8/2 mg/kg IV).

Calibration ranges for levofloxacin were 0.03 to 0.50 µg/mL. Stability was not conducted as part of the assay; rather, information on stability was obtained from the previously conducted methodology used in QP08-045. The results of that bioanalytical method indicated that levofloxacin was stable in plasma stored at -80 °C for 9 days, and that

freeze/thaw stability was proven for 3 cycles. Additionally, post-preparative stability of extracted plasma samples was proven for 24 h at room temperature storage.

Based on various qualification issues with the assay (i.e., assay runs were accepted despite three QC standards not meeting acceptance criteria, one of the internal QC standards was eliminated from the curve, there was no incurred sample re-analysis, additional procedures did not follow current bioanalytical sample analysis guidelines), and due to the fact that PK samples volumes were small, thus obviating re-analyses and limiting levofloxacin concentration determinations (C_{max} and C_{trough} only), an additional PK study (Study B465-10) using the same humanized dosing regimen (i.e., 8/2 mg/kg IV) was conducted.

The PK results (i.e., concentration-time profiles and PK parameters) of Study FY 08-150 (Figure 6 and Table 5) were comparable to the results of Study B465-10, indicating that the exposure data obtained from the efficacy study (Study FY07-070) were not substantially flawed by the different assay method.

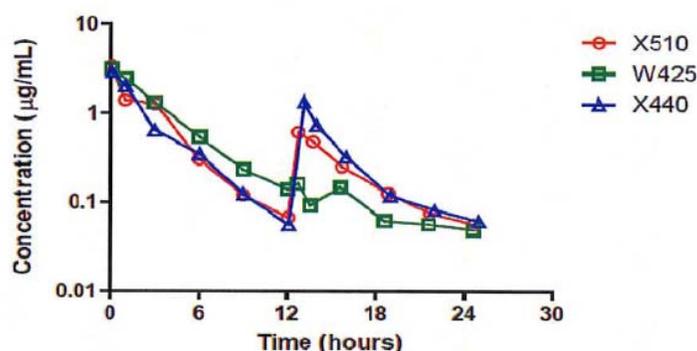


Figure 6. Plasma concentration-time profiles of levofloxacin in 3 female AGMs given 8 mg/kg followed by 2 mg/kg (Study FY08-150).

Table 5. Comparison of pharmacokinetic parameters of levofloxacin in AGMs between Study FY08-150 and Study B465-10.

	Dose	C_{max} (µg/mL)	AUC_{0-24} (µg·hr/mL)	$T_{1/2}$ (hour)
Study FY08-150 (Female AGMs, n=3)	8/2 mg/kg ^a	3.17±0.71	8.86±3.58	2.65±0.61
Study B465-10 (Male and Female AGMs, n=6)	8/2 mg/kg ^a	3.3±0.27	11.9±3.13	2.69±0.42

^a. First dose 8 mg/kg, followed by a second dose of 2 mg/kg 12 hour later

2.4.3. Bioanalytical methodology for Study B465-10

More recently, and in support of an additional monkey PK study utilizing the humanized dosing regimen, a HPLC/FLD assay was developed and validated by (b) (4) for the quantification of levofloxacin in AGM plasma.

The current HPLC/FLD assay was validated under GLP conditions and was consistent with FDA's Guidance for Industry - Bioanalytical Method Validation (2001) (b) (4)

The final extract was then analyzed via HPLC/FLD.

Non-GLP HPLC/FLD assays for the quantification of levofloxacin in AGM urine and in plasma ultrafiltrate (for plasma protein binding determination) were subsequently developed, qualified and validated by (b) (4) for use in study B465-10. The assays used 50.0 µL aliquots of AGM urine or plasma ultrafiltrate, and were conducted according to the same methodology described above.

Calibration ranges for levofloxacin were 0.03 to 15.0 µg/mL (plasma, urine and plasma ultrafiltrate). Inter-assay precision and accuracy was below 12%, 19% and 4% for plasma, urine, and plasma ultrafiltrate, respectively. Freeze/thaw stability analysis of QC samples at -20 °C (urine and plasma ultrafiltrate) and at -20 °C and -70 °C (plasma) revealed no apparent abnormalities after 4 cycles for plasma ultrafiltrate or after five cycles for plasma and urine. Stability in plasma, plasma ultrafiltrate, and urine samples in thawed matrix for 24 h also exhibited no apparent abnormalities upon analysis. No abnormalities were associated with reinjection of sample extracts, or with post-preparative storage for up to 130 h at room temperature (plasma samples). Analyte stability in frozen matrix was also confirmed for plasma samples stored for 7 days at -20 °C and -70 °C, respectively, and for plasma ultrafiltrate and urine samples stored for 4 and 12 days at -20 °C, respectively. Data from additional tests assessing specificity, effects of hemolysis on levofloxacin quantitation, cross-analyte interference, or run length evaluation for plasma samples, and the potential for carryover from a plasma, urine, and plasma ultrafiltrate sample containing a high concentration of analyte to the following sample in an injection sequence were considered acceptable.

3. LABELING RECOMMENDATIONS

70 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

4. APPENDICES

4.1. Individual Study Review

A1. A Pharmacokinetic Study of Intravenous Infusion of Levofloxacin in African Green Monkeys ^{(b) (4)} Study No. B465-10)

Objective of Study: The objective of this study was to determine the pharmacokinetics of levofloxacin in African Green Monkey (AGM) when administered as a single intravenous dose of 8 mg/kg followed by a 2 mg/kg dose 12 hours later. This study was to confirm the exposure in AGM in support of an efficacy study in AGM and thereby demonstrate that the exposure in AGM does not exceed that in humans at a 500 mg dose. In addition, selected urine samples were collected and analyzed for levofloxacin concentration in urine. The percentage of dose recovered in the urine was calculated. Plasma protein binding potential of levofloxacin in AGM plasma was also evaluated.

Experimental Design: AGMs with venous access ports (VAPs) in the left saphenous vein for blood withdrawal and trained to poles and collars, chairs, and limb restraints were used for the study. In each individual animal, an infusion of test article (levofloxacin, 8 mg/kg [high dose]) was administered over 30±5 minutes beginning at T=0. To mimic the human pharmacokinetics of levofloxacin, a second infusion of levofloxacin (2 mg/kg [low dose]) was administered over 30 ±5 minutes beginning at Y=12 hours after the high dose infusion. A single infusion of each dose was administered. This in-life portion of the study was terminated 36 hours after administration of the 2 mg/kg dose (48 hours after the initiation of dosing). Blood samples (1.5 ml per sample) for levofloxacin plasma concentration analyses were collected prior to dosing and at 5 minutes, 1, 3, 6, and 9 hours after completion of the 8 mg/kg infusion. Blood samples were also collected prior to the start of the 2 mg/kg infusion, 5 minutes after completion of the infusion, 1, 3, 6, 9, and 12 hours after the 2 mg/kg dose. Blood was never collected from the vein in which drug was administered.

A noncompartmental analysis based on IV infusion administration was performed using WinNonlin (ver. 5.2). The curve fitting of the terminal phase slope used uniform weighting, area under the concentration-time curve was calculated using the linear up/log down trapezoidal method. Time points from the terminal elimination phase were selected manually and minimum of three non-zero plasma concentration values after the T_{max} were required. If the resulting goodness of fit parameter (r^2) after curve fitting was <0.8, the data set was not considered evaluable for terminal phase parameters.

The following PK parameters were reported for levofloxacin after each infusion: maximum plasma concentration (C_{max}), time at C_{max} (T_{max}), elimination half-life ($t_{1/2}$), apparent volume of distribution (V), total clearance (CL), and mean residence time up to the last sampling time point (MRT_{last}). Systemic exposure for various time intervals was determined by area under the concentration-time curve (AUC) for 0 to 12 hr (start of the first infusion up to predose of second infusion, AUC_{0-12}), AUC from 0- 24 hr (start from first infusion up to the last actual time point, AUC_{12-24}), and AUC from 0 hr extrapolated

to infinity (start of first to infinity, $AUC_{0-\infty}$). Mean residence time up to the last sampling time point (MRT_{last}) was also calculated.

PK Results

Mean levofloxacin plasma concentrations are summarized in Figure 1. Male and female animals administered 8 mg/kg of levofloxacin by IV infusion showed peak plasma concentrations at the first time point following the 0.5 hr infusion. Levofloxacin concentrations decreased quickly over time up to ~12 hr after the start of the first infusion and plasma levels increased significantly. Levofloxacin concentrations declined rapidly after the second infusion and the decline continued up to ~9 hr after the second infusion (~21.5 hr elapsed) for females and up to 112 hr after the second infusion (~24.5 hr elapsed) for males. Females had noticeably lower plasma concentrations than males after each infusion.

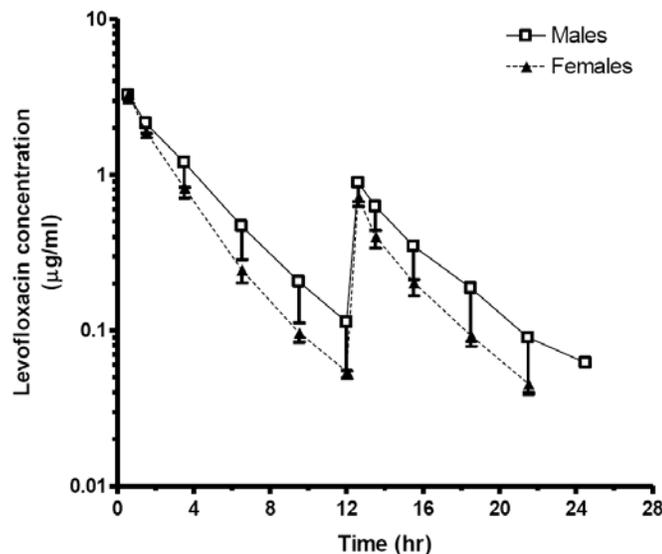


Figure 1. Levofloxacin plasma concentration-time profiles in AGMs (Study B465-10)

Individual and mean PK parameter values are presented in Table 1. Mean levofloxacin C_{max} values after the first infusion were similar for males and females (3.25 ± 0.36 and 3.34 ± 0.21 $\mu\text{g/mL}$, respectively), and the T_{max} was 0.6 ± 0.1 hr for both genders. The majority of systemic exposure occurred between 0-12 hr after the first infusion; AUC_{0-12} was 10.3 ± 2.33 and 7.95 ± 0.69 $\text{hr} \cdot \mu\text{g/mL}$ for males and females, respectively. After the second infusion, C_{max} and AUC_{12-24} values were 0.9 ± 0.22 $\mu\text{g/mL}$ and

Table 1. Pharmacokinetic parameters of levofloxacin in AGMs (Study B465-10)

Sex		1st infusion (8 mg/kg)						2nd infusion (2 mg/kg)						AUC ₀₋₂₄	AUC _{0-inf}	MRT _{12st}
		C _{max} (µg/ml)	T _{max} ^a (hr)	AUC ₀₋₁₂ (hr·µg/ml)	t _{1/2} (hr)	V (L/kg)	CL (ml/hr/kg)	C _{max} (µg/ml)	T _{max} ^a (hr)	AUC ₁₂₋₂₄ (hr·µg/ml)	t _{1/2} (hr)	V (L/kg)	CL (ml/hr/kg)			
M	Mean	3.25	0.60	10.30	2.36	1.98	602.15	0.90	12.8	3.53	2.81	2.50	661.62	13.83	14.05	6.00
	SD	0.36	0.01	2.33	0.44	0.30	179.28	0.22	0.1	1.33	0.61	0.71	340.76	3.61	3.70	0.95
F	Mean	3.34	0.60	7.95	2.01	2.30	793.83	0.72	12.6	2.04	2.57	3.60	964.32	9.96	10.13	4.90
	SD	0.21	0.01	0.69	0.01	0.11	37.93	0.10	0.1	0.32	0.17	0.69	130.89	0.48	0.50	0.40
All animal mean		3.30	0.60	9.13	2.19	2.14	697.99	0.81	12.7	2.79	2.69	3.05	812.97	11.90	12.09	5.45
All animal SD		0.27	0.01	2.01	0.34	0.27	156.38	0.18	0.1	1.19	0.42	0.86	284.23	3.13	3.19	0.88

^a Actual times are based on the start of the first infusion, which lasted 0.5 hr.

Conclusions

The levofloxacin exposure in male and female African Green monkeys after two iv infusion was lower in this study than that reported in humans following iv administration of 500 mg, based on C_{max} and AUC values. Males had higher plasma levels for the majority of the 24 hr study period even though plasma levels peaked at similar values 0.08 hr after the first infusion for both genders. Males consistently showed a trend for higher AUC values for 0-12 hr, 12-24 hr, 0-24 hr and 0-inf (14.05±3.7 versus 10.13±0.5 hr·µg/mL for females). Levofloxacin had appreciable tissue distribution based on V (~2-2.4 L/kg), and a substantial rate of elimination based in CL (~600-800 mL/hr/kg) and t_{1/2} (~2-2.4 hr). There was a trend for gender differences in V and CL, which possibly influenced the higher systemic exposure for males. The slower CL for pharmacokinetic parameters was not statistically significant.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

SEONG H JANG
04/13/2012

KIMBERLY L BERGMAN
04/13/2012

CLINICAL PHARMACOLOGY FILING CHECKLIST For Supplement Review

Office of Clinical Pharmacology

New Drug Application Filing and Review Form

General Information About the Submission

	Information		Information
NDA Number	20-634/S-061 20-635/S-067 21-721/S-028	Brand Name	Levaquin
OCP Division (I, II, III, IV, V)	IV	Generic Name	Levofloxacin
Medical Division	ODE4, DAIP	Drug Class	
OCP Reviewer	Seong Jang, Ph.D.	Indication(s)	
OCP Team Leader	Kimberly, Bergman, Pharm.D.	Dosage Form	
Pharmacometrics Reviewer		Dosing Regimen	
Date of Submission	10/27/2011	Route of Administration	
Estimated Due Date of OCP Review	02/28/2012	Sponsor	J&J
Medical Division Due Date	03/28/2012	Priority Classification	Yes
PDUFA Due Date	04/28/2012		

Clin. Pharm. and Biopharm. Information

	"X" if included at filing	Number of studies submitted	Number of studies reviewed	Critical Comments If any
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data, etc.	X			
Tabular Listing of All Human Studies	x			
HPK Summary	x			
Labeling	x			
Reference Bioanalytical and Analytical Methods	x	2		
I. Clinical Pharmacology				
Mass balance:				
Isozyme characterization:				
Blood/plasma ratio:				
Plasma protein binding:				
Pharmacokinetics (e.g., Phase I) -				
Healthy Volunteers-				No human studies were conducted/submitted.
single dose:				
multiple dose:				
Patients-				No human studies were conducted/submitted.
single dose:				
multiple dose:				
Dose proportionality -				
fasting / non-fasting single dose:				
fasting / non-fasting multiple dose:				
Drug-drug interaction studies -				
In-vivo effects on primary drug:				
In-vivo effects of primary drug:				
In-vitro:				
Subpopulation studies -				
ethnicity:				
gender:				

CLINICAL PHARMACOLOGY FILING CHECKLIST For Supplement Review

	pediatrics:				
	geriatrics:				
	renal impairment:				
	hepatic impairment:				
PD -					
	Phase 2:				
	Phase 3:				
PK/PD -					
	Phase 1 and/or 2, proof of concept:				
	Phase 3 clinical trial:				
Population Analyses -					
	Data rich:				
	Data sparse:				
II. Biopharmaceutics					
Absolute bioavailability					
Relative bioavailability -					
	solution as reference:				
	alternate formulation as reference:				
Bioequivalence studies -					
	traditional design; single / multi dose:				
	replicate design; single / multi dose:				
Food-drug interaction studies					
Bio-waiver request based on BCS					
BCS class					
Dissolution study to evaluate alcohol induced dose-dumping					
III. Other CPB Studies					
Genotype/phenotype studies					
Chronopharmacokinetics					
Pediatric development plan					
Literature References					
Animal PK			3		
Total Number of Studies			5		

Reviewer Comments: This efficacy supplement was submitted under the Animal Rule (21 CFR 314.600), thus no human studies were conducted. Historical PK data in humans will be used for dose extrapolation.

On **initial** review of the NDA application for filing:

	Content Parameter	Yes	No	N/A	Comment
Criteria for Refusal to File (RTF)					
1	Has the applicant submitted bioequivalence data comparing to-be-marketed product(s) and those used in the pivotal clinical trials?			x	
2	Has the applicant provided metabolism and drug-drug interaction information?			x	
3	Has the sponsor submitted bioavailability data satisfying the CFR requirements?			x	
4	Did the sponsor submit data to allow the evaluation of the validity of the analytical assay?	x			
5	Has a rationale for dose selection been submitted?	x			
6	Is the clinical pharmacology and biopharmaceutics section of the NDA organized, indexed and paginated in a manner to allow substantive review to begin?			x	

CLINICAL PHARMACOLOGY FILING CHECKLIST For Supplement Review

7	Is the clinical pharmacology and biopharmaceutics section of the NDA legible so that a substantive review can begin?			x	
8	Is the electronic submission searchable, does it have appropriate hyperlinks and do the hyperlinks work?	x			
Criteria for Assessing Quality of an NDA (Preliminary Assessment of Quality)					
Data					
9	Are the data sets, as requested during pre-submission discussions, submitted in the appropriate format (e.g., CDISC)?	x			
10	If applicable, are the pharmacogenomic data sets submitted in the appropriate format?			x	
Studies and Analyses					
11	Is the appropriate pharmacokinetic information submitted?	x			Appropriate animal PK data for purposes of extrapolation to humans was submitted.
12	Has the applicant made an appropriate attempt to determine reasonable dose individualization strategies for this product (i.e., appropriately designed and analyzed dose-ranging or pivotal studies)?			x	
13	Are the appropriate exposure-response (for desired and undesired effects) analyses conducted and submitted as described in the Exposure-Response guidance?			x	
14	Is there an adequate attempt by the applicant to use exposure-response relationships in order to assess the need for dose adjustments for intrinsic/extrinsic factors that might affect the pharmacokinetic or pharmacodynamics?			x	
15	Are the pediatric exclusivity studies adequately designed to demonstrate effectiveness, if the drug is indeed effective?			x	
16	Did the applicant submit all the pediatric exclusivity data, as described in the WR?			x	
17	Is there adequate information on the pharmacokinetics and exposure-response in the clinical pharmacology section of the label?			x	
General					
18	Are the clinical pharmacology and biopharmaceutics studies of appropriate design and breadth of investigation to meet basic requirements for approvability of this product?			x	
19	Was the translation (of study reports or other study information) from another language needed and provided in this submission?			x	

IS THE CLINICAL PHARMACOLOGY SECTION OF THE APPLICATION FILEABLE?

___yes___

CLINICAL PHARMACOLOGY FILING CHECKLIST For Supplement Review

If the NDA/BLA is not fileable from the clinical pharmacology perspective, state the reasons and provide comments to be sent to the Applicant.

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

Seong Jang, Ph.D.	11/28/11
Reviewing Clinical Pharmacologist	Date
Kimberly Bergman, Pharm.D.	11/28/11
Team Leader/Supervisor	Date

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

SEONG H JANG
01/04/2012

KIMBERLY L BERGMAN
01/04/2012