Pharm/Tox

Review and Evaluation of Pharmacology and Toxicology Data
Division of Anti-Infective Drug Products, HFD-520

Le Sane

Date CDER Received: 12/22/95
Date Assigned: 12/27/95
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NDA # 20-634 (Original Submission dated 12/21/95)

Number of Volumes: 32 (1; 21-51)

Drug: **ELEQUIN™ (levofloxacin) Tablets (Oral)**
[levofloxacin is abbreviated as **LVFX**]

Other Drug Names/Codes: CRAVIT, levofloxacin, l-ofloxacin, L-OLFX, S-(-)-ofloxacin, RWJ-25213, RWJ-25213-000, RWJ-25213-097, DR-3355, and HR355

Sponsor: **The R.W. Johnson Pharmaceutical Research Institute, Raritan, NJ**

Contact Person: Heather L. Jordan 908/704-4607

Category: **Fluoroquinolone**

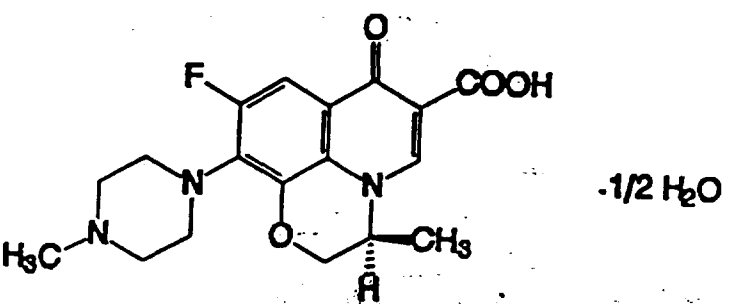
Dosage Form: **Tablets, 250 and 500 mg**

Indication: **Various acute bacterial infections, complicated UTI, uncomplicated skin and skin structure infections.**

Expected clinical dose: approximately 4 mg/kg.

Chemistry: Levofloxacin, a chiral fluorinated carboxyquinolone, is the pure (-)-(S)-enantiomer of the racemic drug substance ofloxacin. The chemical name is:

(S)-9-fluoro-2,3-dihydro-3-methyl-10-(4-methyl-1-piperazinyl)-7-oxo-7H-pyrido[1,2,3-de]-1,4-benzoxazine-6-carboxylic acid hemihydrate



Formulation:

Levofloxacin Tablet, 500 mg

Component	mg/Tablet
Levofloxacin (RWJ-25213-097)	mg[a]
HPMC	mg
Crospovidone	mg
Microcrystaline Cellulose	mg
Magnesium Stearate	mg[b]
	mg
	mg

[a] This quantity is equivalent to 500 mg of anhydrous levofloxacin.

[b] Received as a commercial blend from Colorcon, Inc.

[c] This excipient is essentially removed during processing.

Related Submissions:

Levofloxacin:	INDs'	NDA 20-635 (i.v.)
Ofloxacin:	NDAs 19-735 (tablets) and 20-087 (i.v.)	

Review Objectives: Review preclinical data with regard to safety for the proposed maketing of the drug product.

Index of Studies: Please see below. Note: Ref.# 1 to 20 pertain to pharmacology. For detailed bibliography see NDA 20-634, volume 1.021, pp 05-00298-05-00310.

LIST OF TOXICITY STUDIES (NDA 20-634 & 20-635)
(TOXICOLOGY REFERENCES # 21-127)

Ref#	Doc.ID#	Subject	Volume	Page
		OFLOXACIN:		
21	18836-1	Non-Clin. Pharm, Tox, ADME of **OFLOXACIN.**	1.024	05-01218
22	20351-1	- Addendum No. 1 to above	1.024	05-01417

LEVOFLOXACIN(DR-3355):

ACUTE TOXICITY:

23	22231-1	Oral tox in mouse and rat	1.025	05-1560
24	243755-1	Oral tox in mice comparison with DR-3354 and oflox(DL-8280	1.025	05-1579
25	339453	Not Applicable to the NDA		
26	Publication			
27	Publication			
28	22396-1	Single oral tox. of decomp osition producut(N-Oxide,etc) in mice	1.025	05-01646
29.	339458-1	Single oral tox of Main by-product in mice	1.025	05-01670
30	22231-1	Acute i.V. tox. in mice and rats.	1.025	05-01689
31.	22233-1	Acute i.v. tox in mice and 10-day i.v. tox with DR-3355	1.025	05-01706
32.	22410-1	Acute i.v. tox of metabolite	1.025	05-01727
33	22348-1	Acute Oral in male rats	1.025	05-01751
34	22232-1	Acute i.v. in dogs	1.025	05-01770
35	22229-1	Acute tox in cyno.monkeys	1.025	05-01786
36	22397-1	Acute i.v. witk levofloxacin in comparison with CPFX	1.025	05-01806

MULTIDOSE TOXICITY:

37	22253-1	4-week Oral(gavage) tox in CD Rats	1.026	05-01844
38.	22294-1	26-Week Oral(gavage) tox in CD Rats	1.025 to 1.027	05-02133 05-2506
39	339461-1	13-Week Dietary Dose-range-finding tox in Rats	1.028	05-02513

40	22393-1	Two-Week i.v. in juvenile rats: Comparison w/Cipro	1.028	05-02800
41.	22401-2	4-Week i.v. tox. in Rats	1.029	05-02867
42	339460-1	13-Week i.v. tox in Rats	1.029	05-03023
43	22394-2	2-Week i.v. in Dogs aged 4 to 5 months	1.030	05-03223
44.	22398-1	2-Week i.v. in dogs aged 18 months	1.030	05-03378
45	370763-1	4-Week (daily) i.v. in dogs (final report)	1.030	05-03378
46.	22252-1	4-week (daily) Oral tox in cynomologus monkeys	1:031	05-03585
47.	22372-2	26-week (daily) Oral tox in cynomologus monkeys (initial & revised report)	1:032	05-03815
48.	22390-1	4-week repeated i.v. comparative tox. of levofloxacin and ciprofloxacin in cynomologus monkeys.	1.033	05-04065
CARCINOGENICITY STUDY:				
49.	339457-1	2-year dietary oncogenicity study in rats with levofloxacin.	1.033	05-04260
50.	Publication		1.039	05-06500
ARTHROPATHY (JUVENILES):				
51.	22228-1	Joint tox of levofloxacin in juvenile rats: comparison with DR-3354 (d-isomer) & ofloxacin.	1.039	05-06506
52.	Publication		1.039	05-06527
53.	22225-1	Joint tox of levofloxacin in juvenile dogs.	1.039	05-06543
54.	22226-1	Joint tox of levofloxacin in juvenile dogs.	1.039	05-06576
55.	22227-1	Joint tox of levofloxacin in young adult dogs.	1.039	05-06605

56.	339454-1	Effect of levofloxacin on the activity of propyl-4-hydroxylase in vitro.	1.040	05-06638

PHOTOTOXICITY:

57.	22361-1	Quinolone-induced cutaneous phototoxicity: ear swelling reaction in Balb/c mice	1.040	05-06645
58.	243756-1	Phototoxicity of DR-3355	1.040	05-06681
59.	Publication		1.040	05-06697
60.	Publication		1.040	05-06706
61.	Publication		1.040	05-06716
62.	Publication		1.040	05-06722
63.	22386-1	Phototoxic potential of quinolone antibacterial agents phototoxicity test by i.v. administration.	1.040	05-06734
64.	Publication		1.040	05-06752

ANTIGENICITY:

65.	22375-1	Antigenicity study of DR-3355 in mice.	1.040	05-06759
66.	22237-1	Antigenicity study of DR-3355 in guinea pigs.	1.040	05-06793
67.	22237-1	Antigenicity study of DR-3355 in rabbits.	1.040	05-06832

SPECIAL STUDIES:

68.	22399-1	Study on neutropenia in rats induced by DR-3355.	1.040	05-06859
69	22395-1	Study of urinary crystals in DR-3355 injected rats.	1.040	05-06892
70.	339455-1	Effects of DR-3355 injection on dog serum biochem. data.	1.040	05-06920
71.	339459-1	Intestinal tox. study in rats: effect of combo of DR-3355 & aluminium gel or	1.040	05-06951

		magnesium oxide.		
72.	22230-1	10-day nephrotoxicity study of DR-3355 in rabbits.	1.041	05-06993
73.	339456-1	10-day i.v. administration of DR-3355 nephrotoxicity in rabbits.	1.041	05-06993
74.	244214-1	Ocular and ototoxicity study of DR-3355.	1.041	05-07086
75.	353455-1	DR-3355: hemolysis study	1.041	05-07220
76.	243754-1	Local irritation with DR-3355 injection.	1.041	05-07232
77.	339452-1	Effect of levofloxin and ciprofloxacin injection on permeability of the tail vein in mice and skin micro-vasculature in rats.	1.041	05-07260
78.	243974-1	Effects of DR-3355 injection on toxicities of various anticancer drugs in rats.	1.041	05-07289
79.	Publi		1.042	05-07337

REPRODUCTION STUDIES: [Levofloxacin]

80.	22221-1	Oral reproductive study of DR-3355 in SD rats prior to and early stage of pregnancy.	1.042	05-07356
81.	245109-1	I.V. reproductive study of DR-3355 in SD rats prior to and early stage of pregnancy.	1.042	05-07558
82.	22241-2	Terata study of DR-3355 in SD rats.	1.043	05-07760
83.	326117-1	I.V. reproduction tox. study of DR-3355 with rats during the period of fetal organogenesis.	1.044	06-07986
84.	326123-1	Oral reproductive study of DR-3355 in rabbits during the period of fetal organogenesis.	1.045	05-08324
85.	326119-1	I.V. development toxicity study of DR-3355 in rabbits.	1.045	05-08417

86.	245111-1	Oral reproduction study of DR-3355 in rats - Segment III	1.046	05-08712

MUTAGENICITY STUDIES: [Levofloxacin]

87.	22238-1	Reverse mutation assay	1.046	05-09063
88.	22411-1	Induced mutation frequency test.	1.047	05-09095
89.	22286-1	Chromosomal aberration test with mammalian cells in culture (in vitro cytogenetics)	1.047	05-09112
90.	22413-1	Chromosomal aberration test with mammalian cells in culture (additional test) (in vitro cytogenetics)	1.047	05-09147
91.	22412-1	Quinolone derivatives: Chromosomal aberration test with mammalian cells in culture (additional test) (in vitro cytogenetics)	1.047	05-09147
92.	22391-1	DR-3355: In Vitro sister chromatid exchange.	1.047	05-09214
93.	353456-1	DR-3355: In Vitro sister chromatid exchange. (supplementary study)	1.047	05-09199
94.	22382-1	CHO/HGPRT forward mutation assay.	1.047	05-09214
95.	22239-1	Micronucleus test in mice.	1.047	05-09238
96.	22414-1	Micronucleus test in mice, (i.v. administration)	1.047	05-09263
97.	22392-1	DR-3355 In Vivo sister chromatid exchange	1.047	05-09275
98.	22400-1	Dominant lethal test	1.047	05-09298
99.	243964-1	In Vivo UDS test	1.047	05-09335

Reviewer's Note: Reference # 100 to 127 are published reports.

TOXICOLOGY

ACUTE STUDIES: [Reference Nos. 23 to 36]

A - Levofloxacin (LVFX): LVFX exhibited a low potential for acute toxicity. Calculated LD_{50} values for LVFX are tabulated below:

Species	Route of administration	LD_{50} in Males (mg/kg)	LD_{50} in Females (mg/kg)	Reference No.
Mouse	Oral	1881	1803	23
Rat	Oral	1478	1507	23
Rat	Oral	1754	ND	33
Monkey	Oral	ND	>250	35
Mouse	i.v.	268	323	30
Mouse	i.v.	244	ND	31
Rat	i.v.	423	395	30
Dog	i.v.	ND	200	34
Monkey	i.v.	ND	>200	36

ND = Not Determined

Clinical Signs: Following a single administration of high doses of LVFX clinical signs were:

- decreased locomotor activity;
- ptosis;
- tachypnea (excessive rapidity of respiration);
- dyspnea;
- emesis, and
- salivation.
- Deaths occured from respiratory failure following convulsions.

B - Decomposition Products and/or Metabolites of LVFX:

The oral LD_{50} values in mice for the N-oxide, demethyated, and decarboxylated products of LVFX were >2000, >2000, and 192-250 mg/kg, respectively.

The i.v. LD_{50} values for the N-oxide and demethylated products in mice were >1000 and 44 mg/kg, respectively. The oral LD_{50} values in mice of two by-products of LVFX, "desfluoro-levofloxacin and levofloxacin-2-Me" were observed for both to be >2000 mg/kg.

C - Interaction of quinolones with NSAIDS:

In one study [Reference # 26] , mice were orally administered either LVFX, D-ofloxacin, ciprofloxacin, or enoxacin with fenbufen. Mortality and convulsions were observed after 800 mg/kg LVFX and 400 mg/kg fenbufen (2/6 mice). No effects were observed with 800 mg/kg LVFX and 200 mg/kg fenbufen. Concommitant use of fenbufen with other quinolones such as D-ofloxacin, ciprofloxacin, and enoxacin caused convulsions at lower doses. With 400 mg/kg fenbufen, the doses of quinolones associated with convulsions were as follows: 800 mg/kg LVFX, 400 mg/kg for D-ofloxacin, 200 mg/kg for ciprofloxacin, and 100 mg/kg for enoxacin. Ofloxacin produced convulsions at 800 mg/kg in combination with 200 or 400 mg/kg fenbufen. Coadministration of 100 mg/kg norfloxacin and 200 mg/kg fenbufen also produced convulsions.

Another study evaluated the interaction of several NSAIDS after oral administration of several quinolones in mice. The oral dose which induced convulsions by concomitant use with 4-biphenylacetic acid, α-methyl-4-biphenylacetic acid, ketoprofen, and naproxen could be ranked in the following order:

enoxacin < ciprofloxacin < ofloxacin <levofloxacin.

When quinolones (at 1000 mg/kg; except for enoxacin which was 400 mg/kg) were orally administered approximately 10 minutes after ibuprofen, ketoprofen, loxoprofen-Na, mefenamic acid, and oxaprozin, LVFX and OFLX produced convulsions with the concomitant use of ketoprofen only, whereas CPFLX and enoxacin caused convulsions with most of the NSAIDS tested.

Results from these two studies suggested that LVFX produced less CNS toxicity with or without NSAIDS interaction than other quinolones including OFLX.

MULTIDOSE STUDIES:

A - The Rat:

Ref #37. DR-3355: Toxicity Study by Oral (Gavage) For Four-Week in Rats: Doc.ID 22253-1.

This study was sponsored by and was conducted by The final report was dated 2/11/88

Study Dates: February 3, 1987 to March 9, 1987

Methodology: Three groups of 10/sex/group CD rats, 4-6 weeks old, received LVFX by oral gavage at dosages of 50, 200 or 800 mg/kg/day, for 4 weeks; controls received the vehicle (0.5% CMC).

Results:

General: Clinical Signs related to treatment were seen in the 800 mg/kg/day group and included salivation, associated with dosing, throughout the treatment period and orange/brown body staining and unkempt coat from Week 3. The staining was noted particularly in high dose females and was also seen, to a lesser extent in females receiving 200 mg/kg/day. Transient generalized pallor and hypothermia were seen in first 3 days of treatment in rats dosed at 800 mg/kg/day. The fecal size and number were also increased in high dose rats.

There was no mortality attributed to treatment.

Body Weight & Food Consumption: The body weight gain of high dose (800 mg/kg/day) males was slightly lower than that of control males during the first week of treatment; thereafter the weight gains of male rats were generally similar. The food consumption of treated males was lower than that of the control males during the first week of treatment; thereafter the food intakes of treated and control males were generally similar.

Ophthalmic Examination: Performed during Week 4, did not reveal any intergroup variations considered to be treatment related.

Hematology: It revealed an increase in the total white cell counts in high (800 mg/kg/day) rats, with an associated increase in lymphocyte numbers. The numbers of neutrophils were markedly lower than those in controls in treated females and low and mid-dose group males.

Bone marrow smears taken at necropsy from females receiving 800 mg/kg/day showed higher myeloid to erythroid ratios than in controls. Increases in the lymphoid and myeloid series

were also seen in some of these animals, one of which also had increased eosinophils.

Blood Chemistry: Biochemical analysis of the plasma revealed low plasma potassium concentrations in rats receiving 200- and 800 mg/kg/day, low chloride concentrations in treated females and in males receiving 800 mg/kg/day and high phosphorus concentrations in high dose rats. Plasma urea concentrations were reduced in drug-treated rats in dose-related manner. Males dosed at 800 mg/kg/day had slightly higher alanine amino-transferase activity than controls; females were similarly affected but to a lesser extent.

Urinalysis: There were no treatment-related effects during week 4.

Organ Weights: The data revealed a statistically significant dose-related increase ($P<0.05$ to 0.01) in the cecum weights of treated males and females receiving 200- or 800 mg/kg/day. The body weight-relative heart weights of rats receiving 800 mg/kg/day were lower than those of the controls.

Pathology (gross necropsy): It revealed a statistically significant increase ($P<0.05$) in the incidence of non-specific body staining in high dose rats.

Histopathology: Tissues from the high dose rats showed minimal or slight periacinar fine vacuolation of hepatocytes which was not attributable to fat accumulation. Minimal hypertrophy of hepatocytes was seen in seven rats. No similar changes were seen in controls. Four males and three females at 800 mg/kg/day had minor degenerative changes of the articular surfaces of the limbs.(rats were 4-6 weeks old)

Conclusions: Treatment with LVFX at 800 mg/kg/day was associated with minimal effects on the liver and on the articular surfaces of the femur and humerus. The NOEL dose was considered to be 200 mg/kg/day.

Ref.# 38. DR-3355: Toxicity Study by Oral (Gavage) For 26 Weeks in Rats: Doc.ID 22294-1. Report 90/0334

This study was sponsored by and was conducted by The final report was dated 4/25/90.

Study Dates: September 21, 1988 to March 30, 1989.

Methodology: Three groups of 20/sex/group CD rats, 4-5 weeks old, received LVFX by oral gavage at doses of 20, 80, and 320 mg/kg/day for 26 weeks. The controls received the vehicle, 0.5% CMC at the same volume-dosage as the treated animals.

Results:

General: From week 1 of treatment rats receiving 320 mg/kg/day produced an increased number of larger fecal pellets than the controls. Salivation associated with the dosing procedure was seen in high dose rats throughout the treatment period and on isolated occasions in some rats dosed at 80 mg/kg/day. There was also a greater incidence of stained coat in high dose group animals than in controls.

Mortality: One male receiving 20 mg/kg/day and one male and one female receiving 80 mg/kg/day died during the treatment period. These deaths were not considered to be related to the administration of DR-3355.

Body Weight: There were no variations in body weight gain that could be attributed to the drug treatment.

Food Consumption: The overall food consumption of animals treated at 80 or 320 mg/kg/day was slightly **higher** than that of the controls. The efficiency of food utilization in high-dose females was slightly inferior to that of the controls.

Hematology: Conducted after 25 weeks of treatment, it revealed significantly lower neutrophil counts in all treated groups (up to $P < 0.01$) than in controls. The cellularity and composition of the bone marrow were unaffected by treatment.

Blood Chemistry: In comparison with controls the following inter-group differences noted in the plasma of treated animals after 25 weeks of treatment:

- slightly higher glucose concentrations in males;
- lower triglyceride concentrations in females;
- lower ß-globulin concentrations in males and females, with lower gamma-globulins in females and
- slightly lower chloride concentrations in high dose animals and in females receiving 80 mg/kg/day.

Urinalysis: The urinary pH of rats receiving 80 or 320 mg/kg/day was slightly higher than that of the controls.

Organ Weights: There was a dose-related increase in the full cecum weights of treated rats, which was statistically significant at 80 and 320 mg/kg/day, when compared with controls; a similar effect was apparent in the empty cecum weights of rats treated with 80 or 320 mg/kg/day.

Gross Pathology: It revealed elongated ceca in 5 ♂♂ and 1 ♀ receiving 320 mg/kg/day; 1 ♂ and 1 ♀ receiving 80 mg/kg/day were similarly affected. Distension of the cecum was observed in one male from each treated group and in 2 high-dose

females. Thickening of the glandular mucosa of the stomach was also noted in few rats from each treated group.

Histopathology: Prominent goblet cells were seen in the cecal mucosa of high-dose rats.

Conclusion: 20 mg/kg/day was considered to be a non-toxic dose in rats treated with LVFX for 26 weeks. There was no evidence of arthropathy at dosages as high as 320 mg/kg/day (rats were 4-5 weeks old at the start of the study).

Ref.# 39.

13-Week Dietary Dose-Range Study in Rats with DR-3355. Doc.ID 339461. Study No. 2019-102

This study was sponsored by and was conducted by in accordance with US FDA and Japanese GLP requirements. The final report was dated 12/7/90.

Study Dates: 10/27/89 to 1/30/90.

Study Objective: To determine the doses for an oncogenicity study of LVFX.

Methodology: Fischer 344 (10/sex/group) received either 100, 200, 400 or 800 mg/kg/day LVFX (RWJ-25213-097) by dietary administration for approximately 13 weeks. The drug-treated groups corresponded to Groups 2, 3, 4 and 5) A control group (Group 1) was fed basal diet only (0 mg/kg/day).

The criteria evaluated for compound effect included survival, body weight, food consumption, clinical signs, organ weights and clinical, gross and microscopic pathology.

Results:

- There were no treatment-related effects on survival, food consumption, hematology findings, or clinical signs, with the exception of a slight increase in the incidence of urine stains in Group 4 and 5 females.

- Mean body weights in Group 4 and 5 animals of both sexes were consistently lower than in control animals. These were statistically significant [$p \leq 0.05$] lower in 400- and 800 mg/kg/day group males being 157.4g ± 14.96 and 153.5g ± vs 170.1 ± in controls, respectively.

- Clinical chemistry changes included decreased serum total protein levels at 200 mg/kg/day, serum globulin levels in all drug-treated rats, and serum triglycerides in 800

mg/kg/day males and increased alkaline phosphatase in females treated with 800 mg/kg/day LVFX.

These serum changes were considered to be suggestive of a hepatic involvement, however, there were no histologic changes in the liver. Absolute but not relative liver weight was decreased in 400- and 800-mg/kg/day males.

Conclusion: The dosage level of 100 mg/kg/day was selected as the high dose for the oncogenicity study since this the lowest dose at which clinical and gross pathology changes were observed.

Ref# 40.

A Two-Week Intravenous Toxicity Study of LVFX (DR-3355) in Juvenile Rats: Comparison with Ciprofloxacin(CPFX).
Document ID $ 22393.1.

This study was conducted by in compliance with the Japanese GLP requirements. The final report was dated 7/23/91.

Study Dates: 11/29/88 to 5/9/89.

Methodology: Forty-nine male Crj:CD rats, 4 weeks old, were assigned to one of the seven groups (7♂♂ rats/group) and dosed i.v. with either vehicle (saline) or 10, 40, or 160 mg/kg of either LVFX or CPFX daily for 14 days.

Results:

- There were no deaths attributed to administration of either LVFX or CPFX. Similarly there were no treatment-related effects on clinical signs or body weight.

- Crystalluria, increased cecal weights and mild decreases in SGOT and SGPT were found in the 160 mg/kg LVFX group.

- Articular cartilage did not reveal any abnormalities related to either LVFX or CPFX treatment in this 2 week study.

- Administration of 160 mg/kg CPFX primarily resulted in renal changes such as deposition of a crystalline substance in the kidney, increased kidney weights, increased urinary volume, decreased urinary pH, crystalluria and increased urea nitrogen. Crystalluria was also observed in the 40 mg/kg CPFX dose group. Other treatment-related effects of 160 mg/kg CPFX included slightly decreased Hb, HCT, alkalline phosphatase, and liver weight and increased platelets, fibrinogen, cholesterol and cecal weights.

- Crystalluria, increased cecal weights and mild decreases in SGOT and SGPT were also found in the 160 mg/kg LVFX group. Articular cartilage did not reveal any abnormalities related to eith LVFX or CPFX treatment.

Since crystalluria had not been associated with d,l-ofloxacin administration, these crystals were found not to be formed in the bladder but rather after micturition and not associated with nephrotoxicity.

Conclusions: The no effect level(NOEL) for LVFX was 40 mg/kg/day whereas the NOEL for CPFX was 10 mg/kg/day.

Ref# 41.

Four-Week Intravenous Toxicity Study With DR-3355 in Rats.
Doc. # 22401-2

This study was conducted by in compliance with the Japanese GLP requirements. The final report was dated 7/23/91.

Study Dates: 5/16/88 to 3/24/89

Methodology: Eighty male and female (40/sex/group) Slc:SD, 5-week old juvenile rats were assigned to one of four groups and dosed with either vehicle (saline) or 20-, 60- and 180 mg/kg of LVFX daily for 4 weeks. Some rats in the high dose group could not be dosed every day due to tail irritation (injection site) due to LVFX and therefore, on the average did not receive 3 doses. All rats were necropsied at the end of the treatment period.

Results:

- There were no deaths during the study. Decreased spontaneous activity and blepharoptosis were noted in the high dose males early in the dosing period as well as swelling at the injection site which began during week 2.

- The following parameters were **decreased** as a result of suppressed body weight gain: serum total protein, A/G ratio, cholinestrase activity, urinary proteins and weights of thymus, liver, heart, and ovaries.

- Decreased RBC count and increased WBC count, reticulocyte count and fibrinogen concentration were related to irritation at the injection site and were limited to the high (180 mg/kg) dose group.

- Cecal weights were increased in mid- and high dose groups.

- The precipitation of needle crystals in urine was observed in LVFX-treated rats, but more frequently in the high dose males. Since crystalluria had not been associated with d,l-ofloxacin administration, these crystals were further investigated and found not to be formed in the bladder but

rather after micturition and not associated with nephrotoxicity.

- Delayed thinning on the posterior surface of the medial condyle of the femur and in the articular cartilage was seen in most rats but with greater incidence in the 60 and 180 mg/kg dose groups.

Conclusion: The **NOEL was 20 mg/kg/day** of LVFX in 5 weeks old juvenile rats in this study.

Ref# 42.

Thirteen-Week Intravenous Toxicity Study With DR-3355 in Rats.
Doc. ID # 339460-1

This study was conducted at and sponsored by in compliance with the Japanese GLP requirements. The final japanese report was dated 7/23/91.

Study dates were neither given in the original japanese nor were they in the review summary prepared by the applicant, nor anywhere in the report looked for by this reviewer.

Methodology: Slc:SD rats (10/sex/group, 6 weeks old) were dosed i.v. with either 10, 30, or 90 mg/kg/day with LVFX or saline (vehicle) daily for 13 weeks. At the end of 13-week dosing period, rats were necropsied and selected tissues were examined histologically. Samples of liver and kidney (2/sex/group) were examined by electron microscopy.

Results:

There were no significant body weight changes, but a slight decrease in food consumption was noted at the end of the dosing period at 30 and 90 mg/kg/day (males only).

Some significant changes in clinical pathology parameters such as decreased total protein, phospholipids, and cholesterol in males 90 mg/kg/day were mild and most likely related to decreased food consumption.

Urinary crystals were observed in males at 30 and 90 mg/kg/day and in one female in the 90 mg/kg/day group. Urinary crystals have been observed previously with LVFX as well as other quinolones. The crystals were believed to be formed after micturition and were not associated with nephrotoxicity.

A dose-dependent increase in cecal weight was also observed. There was also mild arthropathy at 90 mg/kg/day. Both these changes have been associated with quinolones in general.

Coclusions: The no adverse effect level (NOEL) was 30 mg/kg/day of LVFX in in this study.

B - The Dog:

Ref.# 43.

Two-Week Intravenous Toxicity Study in Beagle Dogs Aged 4 or 5 Months With DR-3355 (LVFX): Doc.ID# 22394-2

This study was conducted by the in compliance with the Japanese GLP requirements. The final report was dated 7/23/91.

Study Dates: 6/8/88 to 3/23/89; dosed from 6/13 to 6/26/88.

Methodology: Twelve male Beagle dogs (4 or 5 months of age) were assigned to 4 groups and administered daily i.v. doses of 0 (saline), 4, 15, or 60 mg/kg/day LVFX for 14 days.

Results:

- Clinical signs of toxicity such as mild convulsion, reddening of conjunctiva and auricles, lacrimation, mydriasis, and recumbency were observed on the first day of dosing in 1/3 high dose (60 mg/kg/day) dogs.

From the fourth administration onwards, all dogs at this high dose level exhibited clinical signs such as reduced spontaneous movement, prone position, and dysstasia (difficulty in standing) before and after drug administration. Dogs in mid-dose (15 mg/kg/day) group exhibited similar clinical signs but to a lesser extent.

- Body weight and food consumption were decreased in the 60 mg/kg/day group.

The high dose group also had increased urine specific gravity, plasma fibrinogen and alkaline phosphatase, and decreased serum iron concentration. These biochemical changes were seen sporadically in the low- and mid dose groups and were either present at pretest or remained within the normal range.

- The absolute and relative weights of the testes were significantly reduced in all 3 dose groups, and delayed maturation was histologically confirmed in these groups. Delayed testicular maturation has been reported with other quinolones.

- On gross examination, blisters and erosion of the articular cartilage were noted in the scapula, humerus, ulna, femur, and tibia. These were accompanied by increased

synovial fluid and were confirmed histologically as cavitation or erosion of the articular cartilage and were found in all three drug-treated groups (4-, 15- and 60 mg/kg/day). These articular changes were typical of quinolones and were considered to be the cause of dysstasia, ataxia and reduced activity observed clinically.

- A thrombus or partial occlusion of vascular lumens at the injection site by a fibroid substance was observed in the 60 mg/kg/day dose group.

Since a no observable adverse effect level (NOAEL) of LVFX was not observed in this study, a supplemental study was conducted.

Supplemental Study:

Three 4-month old Beagle dogs (from the same supplier) were administered LVFX at 2 mg/kg/day for 14 days (8/29-9/11/88).

No treatment-related effects on clinical signs, body weight, food consumption and clinical pathology parameters were observed at 2 mg/kg dose.

At necropsy, testicular atrophy was found in one 2 mg/kg animal, but since delayed maturation was found in 2/3 dogs in this group, a control group of another study (dogs were of the same age and shipment) were examined and it was concluded by the investigators that delayed maturation of the testes was not due to administration of 2 mg/kg LVFX.

Based upon the above, the investigators concluded that the **i.v. NOAEL of LVFX was 2 mg/kg.** There was no evidence of arthropathy in this supplemental study.

Ref.# 44.

Two-Week Intravenous Toxicity Study in Adult (18 Months Old) Male Beagle Dogs With DR-3355 (LVFX):
Doc.ID# 22398-1

This study was conducted by the in compliance with the Japanese GLP requirements. The final report was dated 7/23/91.

Study Dates: 6/19/89 to 1/17/90

Methodology: Nine male adult Beagle dogs were assigned to one of three groups (3/group) and dosed i.v. with vehicle, LVFX @ 10, 30 mg/kg/day daily for 14 days. All dogs were necropsied at the end of the treatment period.

Results:

- There was no mortality. Clinical signs included redness of cheek and auricles, lacrimation, salivation, respiratory depression, prostration, vomiting (at 30 mg/kg group only) and decreased locomotor activity after administration of 10 or 30 mg/kg/day LVFX. Except for the decreased locomotor activity at 30 mg/kg/day, these signs subsided by 30 minutes post administration.

At 10 mg/kg, most of these clinical signs lessened so that from day 6 onwards, only redenning was observed. A similar pattern occurred at 30 mg/kg; in addition to reddening, salivation and vomiting were also observed.

No changes related to the administration of LVFX were observed in clinical pathology or histopathology including the articular cartilage.

Similar clinical signs have also been observed after i.v. dosing with d,l-ofloxacin.

Conclusion: The no effect dose on the articular cartilage for this study was 30 mg/kg LVFX.

Ref.# 45:

DR-3355: Intravenous Toxicity Study in Beagle Dogs (Final Report - Repeated Daily Intravenous Infusion for 4 Weeks.
Doc.ID# 370763-1

This study was sponsored by and conducted by in compliance with the FDA GLP requirements. The final report was dated 2/20/89; reissued 4/24/90.

Study Dates: 5/11/88 to 6/14-17/88.

Animals: Beagle dogs, 29 to 33 weeks of age and weighing 12.2 kg (♂♂) and 11.0 kg (♀♀) at the beginning of the study. A total of 12 males and 12 females were divided into 4 groups (3 /sex/group).

Group	Dosage(mg/kg/day)	Test Solution(mg/ml)
1. Control	0	Vehicle
2. Low Dose	3	0.3
3. Mid Dose	10	1.0
4. High Dose	30	3.0

pH 6.5; infusion over a period of 1 hour period with a constant dose volume of 10 ml/kg (i.e. 0.167 ml/kg/minute)

Treatment: All dogs were dosed by i.v. infusion, once daily for 4 weeks.

Results:

Mortality: All dogs survived.

Clinical signs: thickening of ears and/or swelling of facial skin and vasodilation (pink ears, muzzle and/or abdomen) were observed at all dose levels with the greatest incidence receiving 30 mg/kg/day (high dose)

Slow, stiff or unsteady gait and/or pain on handling was observed for up to 4 dogs receiving 30 mg/kg/day from day 4 of dosing.

By day 28, pain and/or stiffness on manipulation of shoulder and/or hip joint for all animals receiving 30 mg/kg/day and for 2 dogs receiving 10 mg/kg/day.

Body Weight, Food Consumption: There were no adverse effects.

Ophthalmoscopy & EKG'S: There were no treatment related effects.

Laboratory investigations:

Hematology: There were no treatment related effects.

Blood Chemistry: During week 4 of dosing, group mean urea nitrogen (BUN) levels for males receiving 3, 10, 30 mg/kg/day and for females receiving 30 mg/kg/day; Creatinine levels for males receiving 30 mg/kg/day; triglyceride levels for females receiving 3, 10, 30 mg/kg/day, and cholesterol and phospholipid levels for males receiving 10 or 30 mg/kg/day, were all significantly lower than control values.

According to the investigators none of the above findings were of toxicological significance.

Urinalysis: There were no changes considered to be related to treatment. In particular, there was no increase in the production of urinary crystals for treated animals.

Terminal studies:

Bone myelograms & Organ Weights: There were no treatment related changes.

Macroscopic Post-Mortem Findings:

Injection Sites: Perivascular hemorrhage at most injection sites for all dogs from all groups, including controls. This finding was considered to be related to the method of i.v. injection.

Joints: Areas of erosion or detachment of the articular surface at both shoulder joints for all 30 mg/kg/day dogs, and at the left shoulder of one dogs at 10 mg/kg/day.

Areas of erosion and/or blistering of articular surface of one or both elbow, hip, stifle and/or tarsal joints for 4 dogs at 10 mg/kg/day and 5 dogs at 30 mg/kg/day.

No abnormalities of the joints were seen at 3 mg/kg/day.

Histopathology: The following were treatment-related.

Focal degeneration and erosion or focal disorganization and degeneration of the articular cartilage, often associated with hyperplasia of the synovium were seen for male and female dogs receiving 10 and 30 mg/kg/day.

Conclusion:

The non-toxic dose of LVFX in beagle dogs was close to 3 mg/kg/day.

The incidence of changes considered to be related to treatment were:

	Males				Females			
Dose Groups:	C	3	10	30	C	3	10	30
No. of Dogs:	3	3	3	3	3	3	3	3
Observation:								
Clinical Signs:								
*Thickening of skin and ear	0	1	2	2	0	0	0	2
Abnormal gait/pain of shoulders and hips	0	0	1	3	0	0	1	2
Gross Findings:								
Erosion or blistering of articular surfaces of shoulder and other joints	0	0	1	3	0	0	3	3
Histopathology:								
Focal degeneration and erosion or focal disorganization and degeneration of articular cartilage of joints	0	0	1	3	0	0	2	3
Hyperplasia of synonium of joints	0	0	1	3	0	0	1	3

Thickening of the skin and ears (*) was observed during infusion for male and female dogs receiving 30 mg/kg/day.
A low incidence of this sign was also noted in 2 males receiving 10 mg/kg/day and in 1 male receiving 3 mg/kg/day during weeks 1 and 2 only.
This sign was considered to be a reflection of the pharmacological activity of LVFX.

C. CYNOMOLGUS MONKEYS:

Ref.# 46:

Toxicity Study By Oral (Gavage) Administration to Cynomolgus Monkeys: Doc ID# 22252-1

This study was sponsored by and conducted by compliance with the FDA GLP requirements. The final report was dated 12/2/87.

Study Dates: 2/16/87 to 3/18/87.

Methodology: Male and female immature, wild-caught cynomolgus monkeys, estimated to be 2-4 years, (3/sex/group) were assigned to 4 groups and dosed orally (gavage) with LVFX suspended in 0.5% CMC. Doses of 0 (vehicle), 10, 30, or 100 mg/kg/day were administered by gavage daily for 4 weeks. At the end of dosing, all animals were necropsied.

Results:

- Animals treated at 100 mg/kg/day had salivation (associated with dosing) and diarrhea. A discoloration of the urine, resembling blood contamination was seen occasionally in high dose females and at a low incidence in low- and mid-dose animals. The investigators state that possibly the contaminant was a urinary metabolite.

- There were no deaths.

- There were no inter-group variations in food consumption which was related to treatment with LVFX.

- Small overall losses in bodyweight were noted in the 100 mg/kg/day (high dose) monkeys; a similar loss of weight was seen in one control male.

- Ophthalmoscopic and EKGs' did not show any treatment-related changes.

- Hematologic and clinical chemistry parameters were unaffected by treatment with LVFX.

- The pH of the urine of 2 high dose group monkeys was low.

- The adrenal weights of one monkey treated at 100 mg/kg/day were unusually high.

- Macroscopic and microscopic examination revealed no changes which could be attributed to treatment.

Conclusion: The dose of 30 mg/kg/day was considered to be a no-toxic-effect-level under the conditions of this study.

Ref.# 47.

DR-3355: Toxicity by Oral (Gavage) Administration to Cynomolgus Monkeys For 26 Weeks. Doc.ID# 22372-2

This study was sponsored by and conducted by in compliance with the FDA GLP requirements. The final report was dated 3/8/90.

Study Dates: Treatment started on 11/1/88 and necropsies were completed on 5/9/89.

Methodology: Thirty-two male and female wild-caught cynomolgus monkeys (2-4 years old) were assigned to 4 groups (4/sex/group) and dosed orally (by gavage) with LVFX at doses of 10, 25. or 62.5 mg/kg/day, 7 days/week, for 26 weeks. The controls received the vehicle (0.5% CMC). At the end of 26 weeks of drug-treatment, all monkeys were necropsied. Selected organs/tissues including the substantia nigra were prepared for histopathology. Electron microscopy of the liver and kidney were conducted in 2/sex/group of control and high dose animals.

Results:

General: There were no deaths. There were no signs which were considered to be related to drug treatment. During the treatment period isolated incidences of salivation and emesis, associated with the dosing procedure, were observed.

Food & Water Consumption: Low food consumption in 1 high-dose male was noted during the first half of the treatment period. Food consumption in all other treated animals was not affected. There was no evidence of any effect of treatment on water consumption.

Body Weights: Body weight gain was not affected by treatment.

Veterinary, Ophthalmoscopy: No abnormalities were reported.

Electrocardiography: There were no inter-group differences or abnormalities in EKGs' recorded 24 hours after dosing during week 25 which could be ascribed to treatment.

Hematology (blood): Slightly lower neutrophil counts were seen in the drug-treated males after 26 weeks of treatment when compared with controls. This inter-group difference was considered to be a result of high neutrophil count in one

control male and was not related to the treatment. There were no other differences from controls which might be ascribed to treatment.

Hematology (bone marrow): Taken before termination of treatment did not reveal any abnormalities in the composition or cellularity of the marrow or any changes in the myeloid : erythroid ratio which could be related to treatment.

Blood Chemistry, Urinalysis, Organ Weights: None of these revealed any drug treatment-related changes.

Macroscopic Pathology: No gross lesions related to treatment.

Microscopic Pathology: Microscopic changes seen in these monkeys were those which were commonly seen in monkeys of this age and strain. Some males had achieved puberty while others had not. In females various stages of a normal estrous cycle were apparent in the reproductive tract of all animals.

There were no changes which were considered to be related to drug treatment.

Conclusion:

Oral administration of LVFX at dosages up to 62.5 mg/kg/day to cynomologus monkeys for 26 weeks did not give any evidence of systemic toxicity.

Reviewer's Note:

In the review summary the applicant states,

"The results of study with l-ofloxacin [LVFX] compare favorably with a one year oral study of dl-ofloxacin in cynomolgus monkeys in which the high dose, 40 mg/kg/day, was the no-effect dose. Furthermore, as in the previous cynomolgus monkey study with RWJ-18489-000 [dl-ofloxacin], there were no treatment-related histologic changes in the substantia nigra."

In the discussion portion of a published report (Kato et al, 1992) the authors state,

"... Lower neutrophil counts without changes in the total leucocyte count and bone marrow examination have been reported with other quinolones. In addition, these changes were a species difference (occuring in rats but not mice or monkeys) and not a dose-dependent. Furthermore, leucopenia related to quinolones in clinical use is relatively rare. The toxicological significance of these changes is therefore questioned."

"There are some differences in the pharmacokinetics of LVFX between rats and monkeys. Serum levels of the drug have been shown to attain a peak about 3 and 0.5 hours after oral administration of 20 mg/kg to monkeys and rats, respectively. In addition, maximum concentration and half-life in monkeys are about two times higher and longer than those in rats.

"Because the pharmacokinetics of this compound in monkeys resemble those in humans, toxicological data taken this species seem to be helpful in anticipating any potential adverse effects of the drug in humans.

" From above results, a no-effect dose under these conditions was considered to be 20 mg/kg in rats and 62.5 mg/kg in cynomolgus monkeys."

* Kato et al. 26-week oral toxicity of the new quinolone antibacterial agent LVFX in rats and cynomolgus monkeys. Arzneim-Forsch./Drug Res. 42(1). Nr. 3a , pp 367-373 (1992).

Ref.# 48.

DR 3355 And Ciprofloxacin: Toxicity to Cynomologus monkeys By Repeated Intravenous Administration For 4 Weeks.
Doc.ID# 22390-1.

This study was sponsored by and conducted by in compliance with the FDA GLP requirements. The final report was dated 9/4/90.

Study Dates: 12/12/89 to 1/11/90.

Methodology: Thirty cynomolgus monkeys (2-4 years old) were assigned to 5 groups (3/sex/group)

Group	Dose(mg/kg/day)
Controls	0 (vehicle)
DR 3355	10 mg/kg/day
DR 3355	25 mg/kg/day
DR 3355	63 mg/kg/day
CPFX	63 mg/kg/day

All animals were dosed i.v. (bolus) with either vehicle (saline) or 10, 25, 63 mg/kg/day of DR 3355 (LVFX), or 63 mg/kg/day CPFX once daily for 4 weeks. At the end of dosing period, all monkeys were necropsied.

Results:

General: No mortalities.

Clinical Signs: **For LVFX groups**
Heavy-lided eyes in 63 mg/kg/day animals; Occcasional quietness in 63 mg/kg/day group and loose/liquid feces at 25 or 63 mg/kg/day were related to LVFX treatment.

For CPFX group
Facial flushing in 63 mg/kg/day animals was considered to be related to CPFX

Body Weight: **For LVFX groups**
There was no effect of treatment

For CPFX group
Body weight in females was slightly reduced.

Food Consumption: **For LVFX groups**
Reduced in high dose animals compared to controls

For CPFX group
No effect of drug treatment

Water Consumption: **For LVFX groups**
A slight reduction in water consumption at mid and high dose animals

For CPFX group
No effect of drug treatment

Ophthalmoscopy & EKGs': **For LVFX & CPFX**
No effect of drug treatment

Hematology: No effect of drug treatment

Biochemistry: **For LVFX groups**
No effect of drug treatment

For CPFX group
During week 4, slightly increased serum urea concentration was seen at 63 mg/kg/day compared to controls.

Urinalysis: **For LVFX groups**
No effect of treatment.

For CPFX group
During week 4 decreased group mean urinary pH and specific gravity and increased urinary protein in 63 mg/kg/day compared to controls.

Bone marrow: **For LVFX & CPFX**
No treatment-related effects

Organ weight: **For LVFX groups**
No effect of treatment

For CPFX group

Group mean kidney weight of high dose animals was statistically significantly higher than in controls

Gross Pathology: **For LVFX groups**
No treatment-related findings
For CPFX group
Multiple pale foci were seen on the surface of one or both kidneys in 1 male and 1 female.

Histopathology: **For LVFX groups**
No treatment-related findings
For CPFX group
Cortical tubular basophilia, fibrosis and inflammatory cells, seen in the kidneys of 2 ♂♂ and 3 ♀♀ and cortical foci of multinucleate giant cells with crystalloid materials seen in the kidneys of all animals receiving CPFX were considered to be related to treatment.

In addition, an area of chronic myocarditis and a focus of myocardial interstitial edema was seen in the heart of one male. The toxicological significance of this finding was considered equivocal.

Conclusions: The no-effect level for LVFX was 10 mg/kg/day. However, the only changes observed in 25 mg/kg/day group was a slight decrease in water consumption and loose stools, which were both mild changes and not unexpected finding with an antibiotic.

REPRODUCTION: Ref.# 80 to 86

Ref.# 80. Oral Reproductive Study of DR-3355 In Sprague-Dawley Rats. [Segment 1 Reproduction Study] Doc. ID: 22221

This study was sponsored by and conducted by but does not contain Quality Assurance statement. The final report was dated 12/14/90.

Study Dates: 11/25/88 to 7/31/89

Methodology: Sprague-Dawley rats (24/sex/group) were administered orally (intubation) vehicle (0.5% CMC) or LVFX (DR-3355) in suspension at dosages of 10, 60 or 360 mg/kg/day.

Group	Dosage (mg/kg/day)	Concentration (mg/ml)		No. of Rats ♂♂	No. of Rats ♀♀
1. Control	0	0		24	24
2. Low Dose	10	2		24	24
3. Mid Dose	60	12		24	24
4. High Dose	360	72		24	24

Dose Volume: 5 ml/kg

Treatment Period:

Males: Beginning at 8 weeks of age, males were treated for 9 weeks premating, throughout the mating period, and until necropsy. Males were sacrificed at 20 weeks of age

Females: Beginning at 11 weeks of age, females were treated for 2 weeks premating, throughout the mating period, and for 7 days after copulation. Females were sacrificed at 20 days following copulation.

Results:

Maternal Toxicity:

- Mortality due to intubation error occurred in 2 high dose (360 mg/kg/day) males. Clinical signs related to treatment included salivation observed in most males in the mid-dose, and all rats in the high dose group.

- Drug treatment had no effect on body weight gain, food consumption, frequency of estrus or length of the sexual cycle, mating performance, and gross and histomorphologic examination of the F_0 (parents) generation.

- Mean water consumption by high dose males and mid- and high dose females was generally increased compared to control values during the treatment period.

Fetal Toxicity:

- Although the mean placental weight of the high dose group was decreased, the number of corpora lutea and implantation sites, implantation rate, intra-uterine mortality rate, number of live fetuses, the sex ratio and fetal weights were comparable between control and drug-treated groups. No significant effect of the drug treatment on the results of fetal examinations was apparent.

Conclusions:

LVFX had no effect on mating performance, intra-uterine survival or fetal development in rats when administered orally prior to mating through early pregnancy at dosage up to 360 mg/kg/day.

The no-effect dose of LVFX under the conditions of this study was 10 mg/kg/day for maternal toxicity (parental rats), and 360 mg/kg/day for fetal toxicity.

Ref.# 81.

Intravenous Reproduction Study of DR-3355 With Rats Prior To And In Early Stage of Pregnancy. [Segment 1 Reproduction Study] Doc. ID# 24509-1.

This study was conducted by and contains GLP Conformance Statement by R.W. Johnson PRI (the applicant). The final report was dated 7/11/91.

Study Dates: 5/30/89 to 9/25/90

Methodology: Sprague-Dawley rats [SLC Japan], 24/sex/group were injected i.v. the vehicle (0.5% CMC), or LVFX in solution at doses of 10, 30, or 100 mg/kg/day. A constant dose volume of 10 ml/kg was used for all groups.

Treatment Period:

Males: Beginning at 8 weeks of age, males were treated for 9 weeks premating, throughout the mating period (2 weeks), and until necropsy. Male rats were necropsied after the mating period. For male rats that did not impregnate females, testes were weighed and the epididymides were examined for the presence of sperm.

Females: Beginning at 12 weeks of age, females were treated for 2 weeks pre-mating, throughout the mating period (2 weeks), and for 7 days after copulation. Rats were paired 1:1 overnight, until mating was confirmed by the presence of a vaginal plug. Female rats that did not copulate were necropsied at the end of mating period. Mated females were sacrificed and C-sectioned on gestation day 21 (gestation day 0 = vaginal plug day).

Results:

Maternal Toxicity:

- High dose males (100 mg/kg/day) Swelling of tail and soft feces in 2 males and incontinence of urine in 1 male. High dose females: sweling of tail in 7 females and incontinence of urine in 3 females.

No adverse clinical signs in mid- and low dose rats.

- A dose-related slight decrease in body weights was noted in mid- and high dose in males. Females of the 100 mg/kg/day group experienced a significant suppression of body weight gain prior to and during gestation.

Body weight of females in the low- mid dose group was comparable to controls.

Reproductive Toxicity:

- No adverse effects of the drug administration were noted with regard to the number of estrous cycles in females, days required until mating, copulation rate, and pregnancy rate.

Reviewer's Note:
This note is with regard to effect on male fertility. Males, one from each group, which did not mate were necropsied at the end of mating period. One control group male showed tumor in left epididymis, and enlargement of cecum in the high dose male. However, no abnormalities were noted in reproductive organs in the LVFX-treated groups. Furthermore, presence of sperm in the epididymis was observed in all males.

- No adverse effects were noted in the corpora lutea, implants, live fetuses, and dead fetuses, implantation rate, fetal mortality, fetal body weight, and sex ratio.

- Combined malformation of single nostril and hypoplasia of the skin of the hindlimb was noted in one fetus in the 10 mg/kg/day group.

- With respect to visceral examination of fetuses, hypoplasia of testis was noted in 1 fetus of the control group and hypoplasia of lung lobe in 1 low dose fetus.

- With respect to fetal skeleton, no adverse effects were noted in the degree of ossification and incidences of skeletal variation and abnormalities.

Conclusion: The no-effect dose of LVFX was 10 mg/kg for males, 30 mg/kg for females, and 100 mg/kg in utero exposure for rat fetuses in this study, when adminstered intravenously.

Ref.# 82.

Teratology Study of Orally Administered DR-3355 In Sprague-Dawley Rats. Document ID# 22241-2

This study was conducted by in compliance with the FDA GLP requirements. The final report was dated 12/18/89.

Study Dates: 7/27/87 to 5/27/88.

Methodology:

One hundred and forty-four mated Sprague-Dawley rats (36/group) were orally administered vehicle (0.5% CMC) or LVFX in suspension at dose levels of 10, 90 or 810 mg/kg/day on days 7 to 17 of gestation. On day 21 of gestation, 20-23 rats/group were sacrificed and their uterine contents examined for terata.

The remaining 12 dams/group were allowed to deliver normally. The length of gestation and number of live and dead pups were determined; the sex and any gross morphological abnormalities apparent in F-1 offspring were recorded. The litter size was reduced to 8 pups (4♂♂+4♀♀)/group on day 4 post-partum. On day 21 post-partum, all pups, except 2 ♂♂ and 2♀♀/litter were sacrificed and subjected to terata evaluation. Surviving pups were evaluated for time of testes descent or opening of vaginal orifice, and 1 pup/sex/litter was subjected to behavioral testing. Between days 21 and 34 post-partum, each F-0 dam was sacrificed and the uterus examined for the number of implantation sites.

To determine the effect of test material on reproductive performance of the F-1 generation, males and females from the same test group were allowed to mate at 11-12 weeks post-partum. Mated females were sacrificed on day 21 of gestation and the fetuses were evaluated for the following parameters: mating and pregnancy rates, the number of corpora lutea, number of implantations and resorptions, litter size and survival in utero, fetal weight, sex, and gross external findings.

Results:

Maternal Toxicity:

- Mortality in F-0 dams was limted to 1 mid- and 1 high-dose rat; attributed to intubation error. Treatment related clinical signs included salivation, piloerection, alopecia and poor hair coat, soft stools, hyperuresis, and/or watery eyes shown by mid- and high dose rats.

- Although significant differences in mean body weight gain between control and drug-treated groups were restricted to a lower weight gain noted for high dose rats, mean food consumption values of both mid- and high dose animals were statistically significantly lower than the control values during most or all of the treatment period. In contrast, the mean water comsumption value of high dose animals were statistically significantly higher than that of the control group.

- Grossly, necropsy revealed enlargement of the cecum in all rats in the high dose group and several animals in the mid-dose level sacrificed on day 21 of gestation. No remarkable gross lesions were observed in dams sacrificed after the lactation period.

Fetal Toxicity:

- There were no significant differences in the test group when compared to the controls for: number of corpora lutea, number of implantation sites, implantation rate and sex ratio. Significant decreases of live fetuses and fetal body weight, and an increase of fetal mortality were observed in high group. Subcutaneous hemorrage was observed in 1 fetus of mid-dose group,. anal atresia and anury was seen in 1 high-dose fetus.

Visceral Examination: Dilatation of renal pelvis was observed in 2 fetuses in the control group, 3 fetuses in the low-dose group, 1 fetus in the mid-dose group, and 3 fetuses in the high dose group, respectively.

Skeletal Examination: The degree of ossification of the sternebre, the metatarsals, proximal phalanges of fore-limb and hind-limb, caudal vertibrae from the fetuses in the high dose group was significantly retarded when compared to the controls. The skeletal variations noted in the high dose fetuses were cervical ribs, dislocation of sternebre, and dumb-bell shape of the thoracic vertebral bodies. The incidence of skeletal anomaly was not affected by LVFX-treatment. Only 1 fetus in the high-dose group showed shortening and spliting of cervical vertebral arch and

hypoplasia of thoracic vertebral body. Since the dams given 810 mg/kg/day showed excretion of soft stool, a decrease of food intake and enlargement of cecum, the retardation of degree of ossification and skeletal variations were, in the opinion of investigators, were related to maternal toxicity.

F_2 Offsprings:

Viability of Pups: The survival rate and weaning rate of pups in all treated groups were comparable to that in the controls.

Body Weight: A significant decrease of body weight was observed in the males and the females of the 810 mg/kg (high dose) group at birth and from day 63 to day 77 post-partum.

Postnatal Differentiation (development) of Pups: No significant difference in the separation of ear auricles, appearance of dorsal hair, eruption of lower incisors and separation of eyelids were observed in treated groups, except for the delay of eruption of lower incisors in the 810 mg/kg/day (high dose) group.

Stillborn and Visceral Observation: No stillbirths were observed in any groups. The number of dead pups were 2 in the mid-dose group; no visceral anomalies were observed in any dead pups.

Auditory Sensation and Visual Placing Reflex: No change was observed in these.

Skeletal Observation: Shortening and absence of 13th ribs were found in one pup each in the mid- and high-dose group. Abnormal arrangement of caudal vertebre was observed in 1 pup in the low dose group. An increase in the number of caudal vertebre was observed in the high dose group.

Sexual Maturation: No significant change was noted in descent of testes. The opening of the vaginal orifice in all treated groups was earlier than that in the control group on day 35 postpartum.

Behavioral Responses: The spontaneous motor activity of male pups in the low and high dose group was significantly lower than in the control group at first trial at 5 weeks post-partum but comparable to that in the control group at 24 and 25 week post-partum. The spontaneous motor activity of female pups in all groups tested was comparable to that in the control group. No change was noted in the open-field performance and the shuttle box performance except for a decrease in rearing in the high dose males.

Reproductive Performance of F_1 Pups: No significant change was noted in days required for mating, copulation rate, pregnancy rate and body weight in the treated group.

Litter Examination of F_2 Pups: No change was noted in the number of corpora lutea, the implantatiobn sites, implantation rate, the number of live fetuses, fetal mortality, and body weights of live fetuses. No external anomaly was found in any F_2 fetuses.

Conclusion:

- No drug-related effect was observed in the 10 mg/kg/day (low dose) group.

- Some dams of the 90 mg/kg/day (mid-dose) group showed salivation and dirty hair coat - signs of maternal toxicity.

- Dams of the 810 mg/kg/day (high dose) group showed signs of maternal toxicity.

The fetuses from high dose group showed an increase of mortality, a decrease of body weight gain, the retardation of degree of ossification, and the skeletal variance.

Reviewer's Note: The investigators state, "DR-3355 elicited no evidence of teratogenicity when administered during the fetal organogenesis period to pregnant rats at doses of up to 810 mg/kg ..."

Ref.# 83.

An Intravenous Reproduction Toxicity Study of DR-3355 (LVFX) With Rats During the Period of Fetal Organogenesis. Document ID# 326117-1

This study was conducted by , in compliance with the FDA GLP requirements. The final report was dated 8/1/91.

Study Dates: 6/6/89 to 6/22/90

Methodology: Mated females Slc:SD rats (36♀♀/group were dosed i.v. at doses of 10, 40, 160 mg/kg/day LVFX. The pregnant rats were treated once daily from days 7 to 17 of gestation.

- 12 females were allowed to litter and the remaining 24♀♀/group were necropsied for fetal examination.

- To determine the effect of test material on reproductive performance of the F-1 generation, males and females from the same test group were allowed to mate at 11-12 weeks post-partum. Mated females were sacrificed on day 21 of gestation

and the fetuses were evaluated for the following parameters: mating and pregnancy rates, the number of corpora lutea, number of implantations and resorptions, litter size and survival in utero, fetal weight, sex, and gross external findings.

Results: Maternal:

- Food consumption was reduced in the mid-dose (40 mg/kg/day) at early stage of the treatment period. In the high dose (160 mg/kg/day), swelling of tail, a decrease in food consumption and an increase in water intake was noted.

FETAL:

- In the 160 mg/kg dose group, a delayed ossification of sternebrae and caudal vertebrae were noted . However, no treatment related effects were noted in external, skeletal, and visceral findings.

- With respect to the effects on post-natal growth of pups, in auditory tests with 15 KHz, the threshold of preyer (auditory) reflex was decreased in the 40- and 160 mg/kg groups. In addition, in emotionality test a decrease in the number of rearings was noted in the 160 mg/kg group. However, these changes were considered not to be treatment related.

- No adverse effects were noted in the number of newborn, sex ratio, birth index, weaning rate, body weight, sensory functions, skeleton, sexual maturation, spontaneous motor activity, shuttle avoidance, reproductive performance, and F_2 fetuses.

Conclusions:

Based on these findings, the no-effect dose was 10 mg/kg for dams, 40 mg/kg for fetuses, and 160 mg/kg for pups.

Ref.# 84.

Oral Reproductive Toxicity Study of DR-3355 (LVFX) in Rabbits During the Period of Organogenesis. (Segment II terata study) Doc.ID# 326123-1

Study Dates: 6/1/89 to 6/12/90.

This study was conducted by , in compliance with the Japanese GLP requirements. The final report was dated 8/5/91.

Methodolgy:

Pregnant female Nosan/NZW rabbits (16/group) were dosed orally with either 5, 16, or 50 mg/kg LVFX or 0.5% CMC (vehicle) for

controls. The treatment was given once daily from days 6 to 18 of gestation. Surviving females were killed on day 28 of gestation, necropsied and evaluated for terata.

Results: **Maternal:**

One dam each in the 5- and 50 mg/kg groups showed local alopecia (forelimb) at the end of treatment period. Vaginal hemorrhage was noted in 1/16 dams of the 50 mg/kg group on days 23 and 24 of gestation, and another on day 25 of pregnancy. Four dams of the 50 mg/kg group aborted their litters on days 21, 22, 24, and 26 of gestation. In the 50 mg/kg group, a significant suppression of body weight gain was noted on days 16, 17, and 21 of gestation. A significant decrease of food consumption was noted days 8 and 9 of gestation in the 16 mg/kg group and on days 8-21 of gestation in the 50 mg/kg group.

Dams & Fetal Growth: In the 50 mg/kg group, an increase in number of deaths at mid-stage of pregnancy was noted, but no significant increase was noted in total number of embryonic/fetal deaths. No adverse effects were noted in number of implants, implantation sites, number of embryonic/fetal deaths, fetal growth, and sex ratio in the 5 mg/kg and 16 mg/kg groups.

Fetal Examination: Several abnormalities were noted in external, visceral, and skeletal findings, but no treatment-related changes were noted. Thus,

- Dosages of 50 mg/kg of LVFX induced abnormalities in clinical signs of dams, a suppression of body weight gain, and a decrease of food consumption.

- In the 16 mg/kg group, only transient decrease of food consumption were noted

- At 5 mg/kg dose group no adverse effects were noted in the dams and fetuses.

Conclusions: The no-effect dose was 5 mg/kg/day for dams and 50 mg/kg/day for fetuses.

Ref.# 85.

An Intravenous Development Toxicity Study of DR-3355 in Rabbits. **Doc.ID# 326119-1**

Study Dates: 12/27/91 to 3/18/92.

This study was sponsored by and conducted by in compliance with the Japanese GLP requirements. The final report was dated June 2, 1992.

Methodology: Artificially inseminated New Zealand white rabbits (20/group) were dosed i.v. with 6.25-, 12.5-, or 25 mg/kg/day LVFX or saline (control) once daily from days 6 to 18 of gestation. All surviving females were killed on day 29 of gestation, necropsied and evaluated for terata.

Results: **Maternal:**

- Treatment had no adverse effects on survival of dams.

- Possible local effects at injection site (left ear swollen and reddened with scabbing) in one 25 mg/kg/day group animal.

- A treatment-related group mean body weight loss (7 g) was observed in 25 mg/kg/day group during the initial 3 days of treatment (gestation days 6-9); a group mean body weight gain in the control group (27 g) was observed during this period. Reduced group mean food consumption values (16% and 17% when expressed as g/animal/day and g/kg/day, respectively) were observed in the 25 mg/kg/day group during this same interval.

Fetal:

No adverse effects were observed in intrauterine growth and survival of the fetuses.

No treatment-related fetal malformations or developmental variations were observed in this study.

Conclusions: Based on the results of this study, a dose-level of 12.5 mg/kg/day was considered to be the no-toxic-effect dose for maternal toxicity and a dose level of 25.0 mg/kg/day was considered to be the no-toxic-effect dose for fetal toxicity. LVFX was not teratogenic under the conditions of this study.

Ref.# 86.

An Oral Reproduction Study of DR-3355 (LVFX) With Rats During the Perinatal And Lactation Period. [Segment III study]. **Doc. ID# 245111-1**

This study was sponsored and conducted by in compliance with the Japanese GLP requirements. The final report was dated 7/11/91.

Study Dates: 8/21/89 to 7/25/90

Methodology:

The vehicle (0.5% CMC) or dose levels of 10, 60, or 360 mg/kg/day LVFX were administered to groups (24/group) of presumed pregnant rats (Slc:SD) orally by intubation (gavage) once daily starting on day 17 of gestation and continuing to

lactation day 21. All groups received a constant volume of 5 mL/kg. Subsequent generations were not treated.
All F-0 females (dams) were observed daily from gestation day 17 to lactation day 21. The dams were allowed to deliver and pups permitted to suckle their treated mothers. At lactation day 4, litters were culled to 8 pups (4♂♂+4♀♀) when possible. At lactation day 21, 1♂ +1♀ in each litter were selected for reproductive performance tests, and an **additional** male and female from each litter were selected for behavioral and learning ability tests.

All F-1 animals were weighed once a week from birth to day 77 post-partum, and examined for morphological developments (separation of ear auricles, appearance of dorsal hair, eruption of lower incisors, and separation of eyelids), with functional tests (visual replacement reaction and Preyer reflex), and for sexual maturation (testes descent or vaginal opening).

Dead pups were examined for visceral abnormalities

Five males and 5 females from F-1 pups were retained for reproductive performance tests were examined using the auditory startle test. Reproductive test animals (F-1 animals) were mated at 11-15 weeks of age and body weights of F-1 females were determined for gestation days 0, 7, 14, and 21 of gestation. Days required for mating, copulation rates, and pregnancy rates were determined

Copulated F-1 females were killed on day 21 of gestation and evaluated for various reproductive parameters.

Results:

Maternal:

Salivation was noted in the 360 mg/kg/day group and food and water consumptions were decreased at the end of gestation, but they increased during lactation. A decrease of food consumption was also noted in the 60 mg/kg/day group. However, no adverse effects were noted in parturition and nursing.

Fetal:

No adverse effects were noted in number of newborns, sex ratio, birth rate, survival rate, weaning rate, body weight, skeletal findings, visceral findings, sexual maturation (F-1), spontaneous activity, shuttle avoidance, reproductive performance, and findings of F-2 fetuses in any group.

Conclusion:

No drug related effects were reported for F-0 females of the 10 mg/kg group, or for F-1 and F-2 generation animals of any group. Thus, the no effect dose was considered to be 10 mg/kg for dams and 360 mg/kg for pups.

MUTAGENICITY: Ref.# 87 to 99]

The potential genotoxic effects of LVFX are tabulated verbatim (see next page). In summary, LVFX was:

- not mutagenic in the bacterial mutation, CHO/HGPRT forward mutation, micronucleus, dominant lethal, unscheduled DNA synthesis (in vivo), and in vivo sister chromatid exchange (SCE) assays.

- The probable mechanism of action in the positive assays was the inhibition of topoisomerase II, resulting in the induction of chromosomal effects. [Ciprofloxacin has also tested positive in both in vitro and in vivo chromosomal aberration assays.]

Table III-16: Mutagenicity Studies - Protocol Summary/Results

Doc ID (Ref No.)	Test Type	Study	Dose Levels/ Concentrations	Results
22238:1 (87)	Bacterial Mutation	Salmonella typhimurium Escherichia coli	0.0016-0.5 µg/plate dep on strain of bacteria (w/ & w/o S-9)	Negative
22411:1 (88)	Bacterial Mutation	Salmonella typhimurium TA98 and TA100	0.31-10 µg/mL w/ & w/o S-9	Negative
22286:1 (89)	Chromosome Aberration	CHL cell line	50-4000 µg/mL w/ & w/o S-9	Positive
22413:1 (90)	Chromosome Aberration	CHL cell line	50-500 µg/mL w/o S-9	Positive
22412:1 (91)	Chromosome Aberration	CHL cell line	100-750 µg/mL w/o S-9 500-4000 µg/mL w/ S-9	Positive w/o S-9 only
22391:1 (92)	Sister Chromatid Exchange	CHL/IU cell line	50-300 µg/mL w/o S-9 125-1000 µg/mL w/ S-9	Positive
353456:1 (93)	Sister Chromatid Exchange	CHL/IU cell line	10-100 µg/mL w/o S-9	Positive
22382:1 (94)	Forward Mutation	(CHO/HGPRT) CHO-K1 cell line	375-1500 µg/mL w/ & w/o S-9	Negative
22239:1 (95)	Micronucleus	Mouse	0, 150, 300, 600 mg/kg single dose (i.p.), 0, 100, 200, 400 mg/kg, 5 daily doses (i.p.)	Negative
22414:1 (96)	Micronucleus	Mouse	0, 100, 150, 200, 250 mg/kg single dose (i.v.)	Negative

CHL = Chinese hamster cells; CHL/IU = Chinese hamster lung cells; CHO-K1 = Chinese hamster cell line; dep = depending

Table III-16: Mutagenicity Studies - Protocol Summary/Results (Continued)

Doc ID (Ref No.)	Test Type	Study	Dose Levels/ Concentrations	Results
22392:1 (97)	Sister Chromatid Exchange	Mouse	0, 150, 300, 600 mg/kg single dose (i.p.)	Negative
22400:1 (98)	Dominant Lethal	Mouse	0, 30, 90, 270 mg/kg daily for 5 days (i.p.)	Negative
243964:1 (99)	Unscheduled DNA Synthesis	Rat	0, 300, 600 mg/kg single dose (p.o.)	Negative

ARTHROPATHY (JUVENILE)

Ref.# 51

Joint Toxicity Study of DR-3355 In Juvenile Rats: Comparison With DR-3354 And Ofloxacin: **Doc.ID# 22228-1**

This study was conducted by in compliance with the FDA GLP requirements. The final report was dated 1/24/90.

Study Dates: 12/6/88 to 3/24/89

Methodology:

Seventy 4-week old male Crj:CD rats (7/treatment group) were dosed daily with 0 (0.5% CMC), 100, 300 or 900 mg/kg/day DR-3355(LVFX), DR-3354 (d-ofloxacin) or ofloxacin for 7 days. On the 8th day all rats were necropsied and the distal femur and humerus removed. The articular surface were examined grossly and histologically.

Results:

- Body weight gain was slightly suppressed in the DR-3354 900 mg/kg/day group. Blister and cavity formation of the articular cartilage was induced in a dose-related manner by each of the three test articles at 300 and 900 mg/kg/day. No adverse effects were observed in rats receiving 100 mg/kg/day of the three test articles.

Conclusion:

The arthropathic toxicity of DR-3355, DR-3354 and dl-ofloxacin in juvenile rats was comparable, with their no-effect dose being 100 mg/kg/day for 7 days.

Ref.# 53:

Joint Toxicity of DR-3355 in Juvenile Dogs. **Doc.ID# 22225-1**

This study was conducted by in compliance with the FDA GLP requirements. The final report was dated 1/22/90.

Study Dates: 7/8/87 to 3/7/88

Methodology:

Twelve 4 month old male beagle dogs (3♂♂/group) were dosed orally with 0, 10, 20, or 40 mg/kg/day DR-3355 in gelatin capsules for 7 days. At the end of treatment period all dogs

were neropsied and the articular surfaces examined grossly and later histologically.

Results:

One 40 mg/kg/day dog lost weight by the end of the study.

There were no effects on hematology or clinical chemistry parameters.

Blister formation, cavitation and increased synovial fluid of the diarthric joints occurred in a dose-related manner in dogs of all 3 drug-treatment groups. The findings of this study correspond with those for dl-ofloxacin.

Ref.# 54

Joint Toxicity of DR-3355 in Juvenile Dogs (2). Doc.ID# 22226-1

This study was conducted by in compliance with the FDA GLP requirements. The final report was dated 1/20/90.

Study Dates: 8/18/87 to 3/15/88

Methodology:

Nine 4-month old male dogs (3♂♂/group) were dosed orally with 0, 2.5, or 5 mg/kg/day DR-3355 in gelatin capsules for 7 days. On the 8th day all dogs were necropsied, and their diarthric joints examined.

Results:

There were no abnormalities in the diarthric joints of either treatment group.

The highest no-effect dose for DR-3355 (LVFX) was 5 mg/kg/day for 7 days. This finding corresponds with those of dl-ofloxacin.

Ref.# 55:

Joint Toxicity of DR-3355 in Young Adult Dogs. Doc.ID# 22227-1

This study was conducted by in compliance with the FDA GLP requirements. The final report was dated 1/24/90.

Study Dates: 7/28/88 to March 24, 89.

Methodology:

Nine 13-month old male dogs (3♂♂/group) were dosed orally with 0, 10, or 40 mg/kg/day DR-3355 in gelatin capsules for 7 days. On the 8th day all dogs were necropsied, and their diarthric joints examined.

Results:

There were no treatment-related effects on body weight, hematology or clinical chemistry parameters.

Blister formation and cavitation of the arthric joint was observed in 1/3 dogs receiving 40 mg/kg/day. No drug-related abnormalities were observed in any joint of 10 mg/kg/day group dogs. One dog which received the 10 mg/kg/day was found to have spontaneous osteochondrosis.

Conclusion:

Under the conditions of this study, 10 mg/kg/day DR-3355 (LVFX) administered orally to 13-month old male dogs was the no-effect dose.

Ref.# 56:

Effect of LVFX On the Activity of Propyl 4-Hydroxylase In Vitro. Report No. 013969

This in vitro study was conducted by and does not contain a GLP statement. The report was dated 1/13/94.

Study Objective:

To investigate possible mechanisms of tendon rupture associated with the administration of Ofloxacin and LVFX. The influence of LVFX and OFXN on the activity of purified propyl 4-hydroxylase and on the synthesis of procollagen type I in chicken calvaria cells was studied.

Methodolgy:

Propyl 4-hydroxylase was purified from embryonic chicken tissue. Various concentrations of ofloxacin and LVFX were incubated with the purified enzyme to evaluate its activity. A 1 mM concentration of LVFX or ofloxacin was incubated with embryonic chicken calvaria to measure procollagen type I.

Results:

LVFX inhibited purified propyl 4-hydroxylase at an IC50 of 0.65 mM. Ofloxacin was not sufficiently soluble to allow determination of IC50 values. Neither LVFX nor OFLX had an effect on procollagen type I.

Even though LVFX was a weak inhibitor of purified propyl 4-hydroxylase, it had no effect on cellular propyl 4-hydroxylase activity or synthesis of procollagen type I. These results indicate that inhibition of cellular propyl 4-hydroxylase activity or synthesis of procollagen type I was not the mechanism leading to tendon rupture.

ANTIGENICITY:

Allergic reactions to antibacterial agents have occurred clinically. LVFX was not antigenic in guinea pigs or rabbits and exhibited a low potential in mice. Ofloxacin was not antigenic in guinea pigs in one study, although in another study, ofloxacin at concentrations of ≥ 2 mg/ml was positive for cutaneous anaphylactoid activity in guinea pigs. In the same study, both norfloxacin, ciprofloxacin, and enoxacin were also positive but at lower concentrations (0.13 mg/ml) Ref.# 65 to 67 are tabulated below:

Doc ID (Ref No.)	Test Type	Study	Dosage Levels	Results
22375:1 (65)	Antigenicity	antigenicity, mouse	1, 10, 100 mg/kg (ip)	Negative when levofloxacin is used as challeng antigen on serum sensitized with levofloxacin when challenged with conjugate of Guinea albumin. Positive response in two to three o animals using serum of levofloxacin-ovalbu sensitized group. Conclusion: low potential antigenicity.
22237:1 (66)	Antigenicity	antigenicity, guinea pig	10 or 100 mg/kg (p.o.) 4 or 40 mg/kg (i.p.) 2 or 20 mg/kg (s.c.)	Negative
22380:1 (67)	Antigenicity	antigenicity, rabbit	2 or 20 mg/kg (s.c.)	Negative

PHOTOTOXICITY:

Background: Wagai et al have reported a simple method for detecting phototoxicity caused by naladixic acid (a quinolone) and chlorpromazine in Balb/c mice. The incidence of marked erythema of the ear is regarded as a major phototoxic parameters. Naladixic acid is known to be a photosensitizer and recently some case reports of photosensitivity due to other newer quinolones such as enoxacin (ENX) and ciprofloxacin (CPFX) have been reported. These quinolone-induced erythema on the ears of mice after oral administration plus ultraviolet-A (UVA: 320 - 400 nm) irradiation; and these reactions were dose-dependent. Phototoxic effects were measured by recording erythema/edema and necrosis of the ears and the tail. **Ref# 57 to 64 are tabulated (Please see next 3 pages)**

Table III-14: Special Studies Protocol Summary/Results

Doc ID (Ref No.)	Test Type	Study	Dosage Levels	Results
22361:1 (57)	Phototoxicity	ear swelling, mouse	0-800 mg/kg, single dose (p.o.)	For levofloxacin, the 50% ear thickness increment-inducing dose was 526.6 mg/kg. Generation of free radicals may play a role in the phototoxicity induced by quinolones.
243756:1 (58)	Phototoxicity	ear swelling, mouse	Levo: 0, 200 or 800 mg/kg ENX: 50 or 200 mg/kg single dose (p.o.)	Erythema and edema at 800 mg/kg levofloxacin and 200 mg/kg ENX. Erythema at 50 mg/kg ENX also.
Publ (59)	Phototoxicity	ear swelling and histopathology of ear and retina (mouse)	Spar: 50, 100 mg/kg ENX: 400, 800 mg/kg Levo: 400, 800 mg/kg single p.o. dose	Histologic effects in the auricle after 50 and 100 mg/kg sparfloxacin included degeneration of basal epidermal cells and fibroblasts, edema, followed by neutrophil infiltration in the dermis which became severe 96 h posttreatment. In the retina, sparfloxacin caused vacuolation of photoreceptor segments which became disorganized with time and reduced cellularity of the outer nuclear layer. The segments and layer thinned and were lost 96 h later. ENX at 400 and 800 mg/kg and levofloxacin at 800 mg/kg showed similar lesions in the auricle to sparfloxacin but levofloxacin at 400 mg/kg produced only very mild edema and cell infiltration in the dermis. Levofloxacin had no effect on the retina. Levofloxacin was found to be less phototoxic than both ENX and sparfloxacin.

Publ = publication; Spar = sparfloxacin; ENX = enoxacin; Levo = levofloxacin

Table III-14: Special Studies Protocol Summary/Results (Continued)

Doc ID (Ref No.)	Test Type	Study	Dosage Levels	Results
Publ (60)	Phototoxicity	ear swelling - mouse	Levo: 200-800 mg/kg OFLX: 200-800 mg/kg CPFX: 200-800 mg/kg ENX: up to 200 mg/kg NA: up to 200 mg/kg LMFX:up to 200 mg/kg single p.o. dose Levo: 100 mg/kg OFLX: 100 mg/kg CPFX: 100 mg/kg single i.v. injection	After exposure to UV, phototoxic changes were characterized grossly by erythema, and histopathologically by edema and cell infiltration (mainly neutrophils) into the connective tissue. Lomefloxacin, nalidixic acid, and enoxacin caused marked phototoxic changes at 200 mg/kg, whereas, levofloxacin, ciprofloxacin, and ofloxacin did not cause phototoxicity until 800 mg/kg. The 50% erythema inducing doses of lomefloxacin, enoxacin, nalidixic acid, ofloxacin, levofloxacin, and ciprofloxacin were 19, 102, 143, 553, 619, and 741 mg/kg, respectively. In the i.v. study, neither levofloxacin or ofloxacin induced erythema, whereas ciprofloxacin caused phototoxicity. The results of this study indicate that lomefloxacin, enoxacin, and nalidixic acid are more phototoxic than levofloxacin, ofloxacin, and ciprofloxacin.
Publ (61)	Phototoxicity	role of O_2 Metabolites - Ear swelling (mouse) and in vitro data	Levo - 800 mg/kg OFLX - 800 mg/kg CPFX - 800 mg/kg ENX - 200 mg/kg LMFX- 50 mg/kg Single p.o. dose 0.03 mL irradiated quinolone solution single intra-auricular injection	Cutaneous phototoxicity did not depend on generation of toxic photoproducts and the results suggested that oxygen metabolites generated in the xanthine oxidase pathway were involved.

Publ = publication; Levo = levofloxacin; OFLX = ofloxacin; CPFX = ciprofloxacin; ENX = enoxacin; NA = nalidixic acid; LMFX= lomefloxacin

Table III-14: Special Studies Protocol Summary/Results (Continued)

Doc ID (Ref No.)	Test Type	Study	Dosage Levels	Results
Publ (62)	Phototoxicity	superoxide anion, H_2O_2, B-NDMA determination	Levo: 0.1 mM OFLX: 0.1mM CPFX: 0.1mM LMFX: 0.1mM ENX: 0.1mM	Apparent levels of H_2O_2 and B-NDMA/mole of quinolones paralleled phototoxic potentials in mice. The B-NDMA induced by quinolones and UVA was partially inhibited by treatment with DMSO, DTPA, and D-mannitol. The ear swelling induced by the five quinolones and UVA was completely inhibited by pretreatment with DMSO. O_2 consumption was detectable with photodegradation and ↑ with time. Results indicate that phototoxicity potentials of the five quinolones were probably related to amount of toxic oxygen generated in target cells during irradiation. Levofloxacin, ofloxacin, and ciprofloxacin were less toxic than lomefloxacin and enoxacin.
		ear swelling, mouse	Either treatment with DMSO, H_2O_2 (1-100 μM) into auricle alone or followed by oral gavage of one below: Levo: 800 mg/kg OFLX: 800 mg/kg CPFX: 800 mg/kg LMFX: 50 mg/kg ENX: 200 mg/kg	
		O_2 consumption in irradiated quinolone solution	0.3 mM quinolone solution	
22386:1 (63)	Phototoxicity	erythema auricles, mouse	Levo: 100 mg/kg CPFX: 100 mg/kg NFLX: 100 mg/kg NA: 100 mg/kg AM-1091: 100 mg/kg NY-198: 100 mg/kg T-3262: 100 mg/kg ENX: 10, 30, 100 mg/kg CI-934: 10, 30, 100 mg/kg single dose (i.v.)	Levofloxacin was the only nonphototoxic agent in this study.
Publ (64)	Phototoxicity	cytotoxicity, 3T3 fibroblasts	Levo - up to 300 μM OFLX - up to 300 μM CPFX - up to 300 μM ENX - up to 300 μM LMFX - up to 300 μM	Cytotoxicity after irradiation was assayed by neutral red and MTT assay. Notable concentration-dependent increased cytotoxicity was obeserved with all quinolones. Ciprofloxacin caused slight but significant changes at 10 μm. Lomefloxacin induced marked ↓ in survival at 30 μM whereas the other three quinolones (enoxacin, levofloxacin, and ofloxacin) caused significant ↓ at 100 and 300 μM. DMTU exhibited a protective effect against phototoxicity except for enoxacin.

H_2O_2 = hydrogen peroxide; B-NDMA = bleaching of p-nitrosodimethylaniline; O_2 = oxygen; DMSO = dimethylsulfoxide; Levo = levofloxacin; OFLX = ofloxacin; LMFX = lomefloxacin; ENX = enoxacin; CPFX = ciprofloxacin; DTPA = Fe ion chelator

NEUTROPHILS:

Decreased circulating neutrophils were observed in some of the rat multi-dose toxicity studies. In a special toxicity study in rats, but not mice, the numbers of circulating neutrophils were **decreased** after repeated oral administration of LVFX for more than 1 week at dosages greater than 2 mg/kg/day, although the decrease at this dose was minimal. The reduction in neutrophil counts appeared to correlated with the decrease in marrow myelocytes. Decreased neutrophil counts were observed in some but not all studies in rats but has not been observed for dogs or monkeys. Furthermore, this decrease has not usually been dose-related (i.e., all treated groups exhibit similar decreases) and while the neutrophil counts have been decreased they were usually within normal range for the rat. Other quinolones such as tosufloxacin and ciprofloxacin have also been shown to decrease number of circulating neutrophils.

CRYSTALLURIA:

Crystalluria, a common finding with some quinolones, was observed in the intravenous rat studies. (Ref.# 107) Three kinds of crystals were observed in the urine. These included board-like (the most common), followed by needle-like with an irregular edge crystals. The ball-like crystals were found only in urine kept at 4° C. Crystals were never found in bladder urine, only in excreted urine. In excreted urine, there did appear to be an increase in crystal formation with increasing dosages of LVFX. Crystals were not found in urine from rats that were fasted and in general, were not found in urine kept at either room temperature or 37° C. Furthermore, these crystals, unlike found with ciprofloxacin, have not been associated with histologic changes in the kidney and therefore do not appear to represent a toxicologic concerns. (Ref.# 40)

OTHER:

In other special toxicity studies, LVFX produced only minor biochemical changes in dogs following a single i.v. injection of 30 mg/kg, exhibited no **intestinal** toxicity when dosed (up to 50 mg/kg) for 7 days with aluminum gel (200 mg/kg) or magnesium (100 mg/kg), was not **nephrotoxic** in rabbits when administered orally (120 mg/kg) or i.v. (50 mg/kg) for 10 days, did not produce **ocular or ototoxicity** in rats at oral dosages of 100 mg/kg for 2 weeks, and was less **cytotoxic** to mammalian and dendritic cells than norfloxacin, pefloxacin, and ciprofloxacin.

A 0.2% solution of LVFX did not produce significant **hemolysis** in human blood and produced mild irritation when injected intramuscularly. The effect of LVFX and ciprofloxacin (up to 1%) solutions injected intra-cutaneously and i.v. on skin and tail permeability was investigated in rats and mice, respectively. LVFX increased **permeability**, although to a lesser extent than ciprofloxacin (mouse only) in both the skin and tail. Concomitant administration of an antihistamine and

either quinolone abrogated (abolished) the increased permeability suggesting that injection of LVFX was associated with histamine release.

INTERACTION:

Potential interaction of LVFX with anticancer agents such as adriamycin, cyclophosphamide, and cisplatin was evaluated in rats. Intravenous administration of LVFX at 20 and 100 mg/kg for 6 days slightly exacerbated the decreased marrow granulocyte:erythrocyte ratio with adriamycin. LVFX had no significant effect on cyclophosphamide toxicity but recovery of renal toxicity (increased urea nitrogen and creatinine) induced by cisplatin was delayed by LVFX. Ciprofloxacin by itself caused renal toxicity (unlike LVFX, but the toxicity was not exacerbated by the addition of cisplatin.

CARCINOGENICITY STUDIES:

Two-Year Dietary Oncogenecity Study in Rats with LVFX:
Doc.ID # 339457:1

This study was conducted by for in compliance with the Japanese GLP requirements (as well as U.S. FDA GLP requirements). The final report was dated 4/13/94.

Study Dates:
Study Initiation: 3/23/90
Initiation of Dosing: 5/9/90
Completion of Necropsy: 5/13/92

Animals: A total of 462 (231/sex) approximately 4 week old CDF^{R} (Fischer-344)/CrlBR were received from Charles River Labs. A total of 400 (200/sex) were assigned to four groups (50/sex/group).

Groups:

Group	Dose (mg/kg/day)	No. of Animals Males	Females	Animal Numbers Male	Female
1. Control	0	50	50	B11200-B11249	B11250-B11299
2. Low Dose	10	50	50	B11300-B11349	B11350-B11399
3. Mid Dose	30	50	50	B11400-B11449	B11450-B11499
4. High Dose	100	50	50	B11500-B11549	B11550-B11599

Dose Selection: These were based upon results of a 13-week Dietary Dose-Range Finding study with LVFX. [Ref.# 39; see my review, vide supra] In that study 100 mg/kg/day was the lowest dose tested at which clinical and gross pathology changes were observed.

Dose levels were selected with the intent that the low dose should produce no toxicity; the high dose should result in toxicity, but should not be highly lethal precluding a meaningful evaluation; the mid dose should produce intermediate toxic effects.

- A slight non-dose-related decrease in neutrophil counts was observed in treated males and in 30- and 100 mg/kg/day females. [The investigators state, "A similar pattern has been reported has been observed with quinolone administration and has **not** been considered to be toxicologically significant (DS-91230).

- During week 104 of treatment, mean serum **drug concentrations** of LVFX were found to be 0, 205.5, 654.1, and 2358 ng/mL for males; and 183.0, 658.4, and 2952 ng/mL for females in the vehicle, 10-, 30-, and 100 mg/kg/day groups, respectively. This would suggest that there was a fairly dose-proportional increase in the exposure of the rats to LVFX when it was administered in their diet.

Pathology Report: The following is quoted verbatim.

"No test-compound-related changes were observed in F-344 rats which received up to 100 mg/kg/day DR-3355 (LVFX) by dietary administration for 105 weeks. DR-3355 was not considered oncogenic under the conditions of this study.

119 animals (75 males; 44 females) died before scheduled terminal sacrifice. The most commonly identified underlying cause of death in each sex was LGL-lymphoma (leukemia) (Fischer Rat leukemia, mononuclear cell leukemia), a common neoplasm in this rat strain.

481 primary neoplastic changes were observed. The [second] most common was LGL-lymphoma while the next[deleted] most common was benign interstitial cell tumor of the testis. These are both common age-related neoplasms in the F-344 rat.

Miscellaneous microscopic changes observed in F-344 rats which received up to 100 mg/kg/day DR-3355 [LVFX] by dietary administration for up to 105 weeks were considered consistent with commonly occurring spontaneous, agonal, and parasitic processes in the rat and unrelated to the test compound."

Conclusion: Under the conditions of this study, LVFX at dietary doses up to 100 mg/kg/day was not oncogenic in the rat.

PHARMACOLOGY:

The following is abstracted from the applicants' summary of nonclinical pharmacology. The major effects of LVFX observed in nonclinical pharmacology studies are summarized in **Table II-1 (see attached next page)**. For effects of LVFX on various organ systems **(see Appendix 3)**

The nonclinical pharmacology of LVFX was **similar qualitatively** to that of ofloxacin, the parent D,L-racemic compound. While there were effects of LVFX on CNS, cardiopulmonary system, gastrointestinal system, and urinary tract functions in a variety of animal species, all observations need to be evaluated with perspectives both of comparing effects in animals with those that would be expected in humans and comparing the doses required to elicit the responses in animals to those used in the clinical setting.

- At orally administered doses of 200 mg/kg or greater, LVFX caused CNS depressing effects indicated by decreased spontaneous locomotor activity, lowered body posture, diminished muscle tone, and reduced body temperature.

- When administered parenterally at 200 mg/kg, LVFX also affected CNS parameters, including inhibition of the conditioned-avoidance response.

- At lower i.v. doses, spinal reflexes were blunted. Effects on the autonomic nervous system, indicated by reduced contractile responses of the cat nictating membrane to ganglionic stimulation and inhibited dog blood pressure responses to acetylcholine were observed with LVFX 20 mg/kg i.v.

- LVFX effected a decrease in blood pressure mainly when administered as an i.v. bolus injection at doses of 6 mg/kg or greater. Higher doses were required when the compound was administered by a prolonged infusion. The effect was possibly mediated by a rise in serum histamine concentrations.

- Effects on gastrointestinal and urinary tracts, in the form of decreased gastric emptying, decreased pepsin and acid output, and gastric fluid volume in the former(gastrointestinal) case, and decreased urinary volume and electrolyte excretion in the latter (urinary tract) case, were seen at doses equal to or greater than 200 mg/kg either orally or i.v. administered. An inhibition of an experimentally induced inflammatory response was observed at 600 mg/kg, oral LVFX.

- In the context of clinical setting, a dose of 500 mg LVFX would equate to 10 mg/kg in a 50 kg human. **The observations made in these nonclinical pharmacology studies at relatively high doses and/or with rapid parenteral administration suggest that the findings were not, per se, indicative of reactions to LVFX in the clinical setting.**

Table II-1: Summary of Major Nonclinical Pharmacological Effects of Levofloxacin

System	Species	Major Findings
Central Nervous System	mouse	≥600 mg/kg, p.o., decreased spontaneous locomotor activity, CNS depression, decreased pinna reflex, decrease writhing response to acetic acid; increased incidences of strychnine, pentylenetetrazol, and caffeine induced convulsions; ≥200 mg/kg, i.v., convulsions after rapid injection, decreased spontaneous motor activity, muscle tone, posture, body temperature; increased respiratory rate; prolonged hexobarbital sleep time
	rat	At 200 mg/kg, i.v., inhibition of conditioned-avoidance response; At 200 mg/kg, i.p., increased spontaneous motor activity, lowered body posture, increased restlessness
	rabbit	At 200 mg/kg, p.o., decrease in body temperature
	cat	≥6 mg/kg, i.v., decreased spinal reflex; ≥30 mg/kg, i.v., increased EEG awake stage, seizure discharges
Autonomic Nervous System	cat	At 20 mg/kg, i.v., reduced contractile response of nictitating membrane to pre- and postganglionic stimulation; suppression of acetylcholine depressor response
Cardiopulmonary System	dog	≥6 mg/kg, i.v. bolus, decreases in blood pressure, left ventricular pressure, respiration depth; ≤10 mg/kg, i.v. infusion, no effect on blood pressure; ≥20 mg/kg, i.v. infusion, decrease in blood pressure, decrease in cardiac output and stroke volume; increase in serum histamine concentrations
Gastrointestinal System	mouse	At 200 mg/kg, i.v., inhibition of gastric propulsion
	rat	≥200 mg/kg, p.o., decrease in gastric fluid volume, total acidity, pepsin output; increase in gastric fluid pH; at 600 mg/kg, decrease in gastric emptying; at 200 mg/kg, i.v., decrease in gastric fluid volume, acid and pepsin output and gastric emptying; increase in gastric pH
Urinary Tract	rat	≥200 mg/kg, p.o., decrease in urinary volume and electrolyte excretion; at 200 mg/kg, i.v., decrease in urinary volume
Inflammation	rat	At 600 mg/kg, p.o., inhibition of carrageenan-induced foot edema
Isolated Smooth Muscles		On dog mesenteric, renal, femoral, and basilar arteries, inhibition of norepinephrine-induced contractions ≥10×10^{-6} M; competitive inhibition of phenylephrine-induced contractions of rabbit thoracic artery

Metabolites of LVFX:

The observations made on the two studied metabolites of LVFX, the N-oxide and desmethyl metabolites were not necessarily reflective of what contributions these metabolites might make to the effects of LVFX in the clinical setting. The maximum plasma concentrations of each of these metabolites and their cumulative urinary excretion 24 hours after dosing with LVFX represented approximately only 2% of the parent compound and only 2% of the dose, respectively.

ABSORPTION, DISTRIBUTION, METABOLISM & EXCRETION (ADME)

The following is abstracted from the applicants' summary of nonclinical ADME. Summary of in vivo non-clinical studies are tabulated in Table IV-1 and the results of these studies are tabulated in Table IV-2. Both these tables are appended [**see Appendices 2 and 3**]

1. **Absorption and Pharmacokinetics(PK):**

The absorption and PK of LVFX were investigated after oral administration to mice, rats, dogs, and monkeys, and after a single i.v. administration to rats, dogs, and monkeys. LVFX was rapidly and completely absorbed after oral administration.

- In all species studied, the absorption of LVFX was rapid following administration of a single oral dose or after repeated daily oral doses.

- Distribution and elimination was also rapid, with most of the dose eliminated within 24 and 48 hours after single and multiple doses, respectively.

- C_{max} and AUC values increased in dose-related manner in all species.

- No differences were noted in PK parameters between single and multiple daily doses.

- The PK of LVFX after oral administration to animals was similar to that observed in man (Table IV-2). In humans administered a single oral 500 mg dose (approximately 10 mg/kg), LVFX was rapidly absorbed. Maximal plasma concentrations were 5.19 μg/mL at approximately 1.0 hour postdose. In humans as well as animals the PK profile of LVFX was linear. In clinical trials it had been established that the AUC values of LVFX following oral administration were approximately 99% relative to an i.v. dose; these results were consistent with the findings in rats and monkeys, and to a lesser extent, in dogs. LVFX was also rapidly eliminated in man. Plasma concentrations 24 hours after an oral dose were approximately 0.5 μg/mL; the elimination half-life of LVFX was approximately 7 hours.

2. **Toxicokinetics:**

- In the 2-year rat carcinogenicity study, mean LVFX concentrations in the 10, 30 and 100 mg/kg in diet were 0.20, 0.66, and 2.66 μg/mL, respectively. The plasma concentration at the high dose was 34% of the human steady-state concentration of 7.9 μg/mL after 500 mg b.i.d. dosing.

- In male monkeys receiving 10, 25, and 62.5 mg/kg/day of LVFX orally for 25 weeks, mean maximal plasma concentrations of LVFX were 2.1, 8.6, and 22.9 μg/mL, respectively. At the high dose, the C_{max} values obtained in monkeys were approximately three-fold higher than those obtained in humans at steady state.

- In monkeys administered 10, 25, and 63 mg/kg/day by bolus intravenous administration for 4 weeks, mean maximal plasma concentrations in males were 8.21, 21.9, and 58.7 µg/mL, respectively. The high dose in the monkey i.v. study resulted in plasma concentrations that were 7.4-fold higher than the highest anticipated human therapeutic concentration.

3. **Protein and Red Blood Cell Binding:**

- The ultracentrifugation method was used to determine the in vivo protein binding of LVFX in male mice, rats, pregnant female rats, dogs and monkeys at doses which covered the full range of therapeutic concentrations.

- LVFX was moderately bound (16-73%) to the serum proteins of male rats administered ^{14}C-LVFX, 5-320 mg/kg, orally and after i.v. administration of 20 mg/kg.

- In pregnant rats binding to serum proteins was somewhat less; binding ranged from)%.

- Protein binding in the dog and monkey after oral and i.v. administration of 20 mg/kg generally ranged from % of the dose.

4. **Distribution:**

- The tissue distribution of ^{14}C-LVFX was assessed in the mouse after a single oral administration, and in rats after single and multiple oral administration.

- After a single oral administration (20 mg/kg) to mice, radioactivity (RA) was extensively distributed to tissues in the following rank order: kidney >> liver > spleen > lung, whole blood, heart, muscle, bone > skin > testes, eyeball > fat > brain.

- In rats peak concentrations of RA were recorded at 0.5 hour postdose. The concentration ratios of tissue to whole blood were greater than one in most tissues, except the C.N.S., testis, epididymis, and fat tissues, indicating the tissue distribution of LVFX was extensive but penetration of the blood:brain barrier was limited. The decline of tissue concentrations was similar to the decline of RA in whole blood; by 24 hours postdose tissue RA concentrations had declined to undetectable amounts.

- The distribution of RA following daily oral administration of 20 mg/kg for 21 days was similar to that observed after a single dose. RA concentrations in the heart, spleen, pancreas, prostate, thymus, and salivary gland on day 21 were higher than observed after a single dose, suggesting some potential for accumulation after multiple doses; although by 72 hours postdose RA in these tissues had declined to undetectable levels. After multiple dosing at 72-168 hours postdose, small amounts of drug-related material was still present in the liver, kidney, bone, skin, and trachea, indicating a slower elimination rate in these tissues.

- Whole body autoradiography (WBA) was studied at C_{max} and 24 hours after i.v. bolus infusion of 20 mg/kg ^{14}C-LVFX into male rats and squirrel monkeys. The amount of RA was determined by imaging analysis. LVFX-derived RA in the monkey was distributed in the following rank order:

uveal tract, hair follicle > thyroid gland > trachea, cartilage > liver, kidney.

The estimated concentrations of RA by WBA were in good agreement with those obtained by direct measurements using liquid scintillation spectrometry. Remaining RA at 24 hours postdose was highest in the gall bladder, uveal tract, and hair follicles.

Placental transfer after oral administration to pregnant rats was studied by tissue distribution and WBA. In these studies the concentration of drug-related RA in the fetus 30 minutes after dosing on gestation day 12 was 1.3 µg equiv/g (0.01% of the administered dose), which was 45% of the concentration in maternal blood. By 24 hours postdose the concentration of RA in the tissues was at or near background. On gestation day 19 the mean concentration of RA in the fetuses at 30 minutes postdose was 1.86 µg equiv/g (0.07% of the administered dose), which was 54% of the maternal blood concentration. This data indicated limited transfer of drug to the fetus and no potential for drug accumulation.

WBA studies of ^{14}C-LVFX to **pregnant rats** confirmed that LVFX-derived RA was widely distributed into maternal tissues and the placenta, with small amounts associated with fetuses. RA concentrations in the fetus declined rapidly and indicated no potential for accumulation.

5. <u>Enzyme Induction/Inhibition:</u>

The effects of LVFX on hepatic drug metabolizing enzymes were investigated after repeated dosing to rats.

Liver weight (per 100 g of body weight) was significantly decreased after 14 days of daily oral administration of 20 or 800 mg/kg LVFX. The effect was ameliorated following 1-week recovery period. There was no decrease in the content of cytochrome P_{450} or cytochrome P_{b5}, nor in the activity of NADPH-cytochrome P_{450} reductase, when compared to vehicle control groups on a per mg protein basis. A slight, but statistically significant induction of 7-ethyoxycoumarin O-deethylase activity was noted, but the activities of aminopyrine N-demethylase and aniline p-hydroxylase remained unchanged. When added in vitro to an incubation medium containing an NADPH-generating system, at a concentration of 1 mM (361 µg/mL) or below, LVFX showed no inhibitory effects on the activities of the aforementioned drug metabolizing enzymes. These data indicated that **LVFX was neither an enzyme inducer or inhibitor** in the therapeutic plasma concentration range and no drug metabolizing enzyme-related interactions with other drugs or agents were anticipated.

6. <u>Metabolism:</u> **[see appendix-4 Figure IV-2; NDA page 05-00334]**

The metabolism of LVFX was investigated after oral dosing to rats, dogs, and monkeys. A total three metabolites of LVFX [MO] have been identified: These were **M1**, **M2** (desmethyl-levofloxacin), and **M3** (levofloxacin N-oxide). The three metabolites may be formed by the following proposed pathways

(A) O-glucuronidation at the carboxylic acid group to form the corresponding ester glucuronide (**M1**);

(B) oxidative demethylation of the 4-methyl piperazinyl group to form the desmethyl piperazinyl metabolite (**M2**);

(C) N-oxidation at the 4-N-methyl position of piperazinyl group to form the corresponding N-oxide metabolite (**M3**).

These metabolites were reported to have little relevant pharmacological activity.

7. **Excretion:**

The excretion rate of ^{14}C-LVFX was investigated in mice, rat, dog and monkey at doses ranging from 50-600 mg/kg.

- After oral administration of 20 mg/kg to mice, 42% of the dose was excreted in the urine and 50% in the feces by 24 hours postdose. At the 600 mg/kg dose in mice, urine and fecal excretion accounted for 48% and 35% of the dose, respectively.

- After a single dose of 5, 80, or 320 mg/kg to rats, approximately 1/3rd of the dose was excreted in the urine and remainder (2/3rd) in the feces by 48 hours postdose.

- In rats receiving multiple oral dosing of 20 mg/kg for 21 days, results were identical to those after a single dose: on day 21, 32% of the dose was excreted in the urine and 63% in the feces by 24 hours postdose.

- In bile duct cannulated rats administered 20 mg/kg orally, 37% of the dose was excreted in the urine and 57% of the dose was recovered in the bile at 24 hours postdose, indicating biliary excretion to be a major route of excretion in rats.

- After a 30-minute i.v. drip administration of 20 mg/kg to rats the amount of drug recovered in the urine (50%) was equal to that excreted in the feces (51%) at 48 hours postdose suggesting a larger degree of biliary excretion after oral administration than after i.v. administration.

- For all these studies, most of the dose (80-100%) was recovered in the excreta within 24 hours.

-The **excretion pattern** in **dogs** after oral and i.v. administration showed that the majority of the drug was excreted in the urine. In dogs administered 20 mg/kg orally approximately 52% of the dose was excreted in the urine and 39% in the feces at 96-120 hours postdose. Recovery at 72 hours postdose was approximately 90%, a reflection of the longer elimination of LVFX in this species. After i.v. dosing of an

equivalent dose, 67% and 24% of the dose was excreted in the urine and feces at 72 hours post dose.

- In contrast to the rat and dog, in **monkeys** administered ^{14}C-LVFX, urinary excretion accounted for almost all the RA. In monkeys administered 20 mg/kg orally, approximately 82% of the drug was excreted in the urine by 72 hours postdose. After an i.v. infusion of an equivalent dose, 86% was excreted in the urine and 4% in the feces by 72 hours. Approximately 84% of the administered dose was recovered in the excreta after 4 hours.

Excretion in Milk: The administration of 20 mg/kg of LVFX orally to **lactating rats** showed that the drug could be transferred to the pup during lactation. Milk/maternal whole blood ratios ranged from 2.1 - 2.7 up to 8 hours after dosing of the dams.

8. Comparison of ADME of LVFX and Ofloxacin. [page 05-00427]

The in vivo disposition of LVFX, the active isomer of ofloxacin appeared to be consistent with that documented for racemic ofloxacin. For both compounds, absorption was rapid and complete after oral and i.v. administration. The amount of drug in whole blood was proportional to dose for both compounds. Elimination was also rapid, with most of the administered drug eliminated within 24-48 hours postdose. No differences in the pharmokinetic parameters of LVFX or ofloxacin were observed after multiple doses.

Distribution of both LVFX and racemate ofloxacin was extensive, but the rate of elimination of RA from the tissues was similar to that in the blood, with most of the RA in tissues undetectable by 24-48 hours postdose, suggesting little potential for accumulation except in the skin, bone, and cartilage.

Protein binding was moderate in all species for both LVFX and ofloxacin. Both compounds undergo minimal metabolism; parent drug accounted for approximately 80% of urinary RA in all species. Glucuronidation was a major metabolic pathway only in the rat for both drugs.

The only notable difference between these compounds was observed in the rats where a larger degree of fecal elimination of LVFX was observed in comparison to ofloxacin.

SUMMARY:

A - The RAT:

Cecal Weight and/or Cecal Distension:

This was the most common finding in the rat, administered orally or i.v.

- In oral studies, cecal changes were observed at ≥ 200 mg/kg for 4 weeks, ≥ 100 mg/kg for 13 weeks (dietary), and ≥ 20 mg/kg for 26 weeks.

- In the i.v. studies, cecal changes were observed at 160 mg/kg for 2 weeks, ≥ 60 mg/kg for 4 weeks, and ≥ 10 mg/kg for 13 weeks.

- Cecal enlargement is a characterstic finding in rodents treated with antibiotics including quinolones.

Body Weight & Food Consumption:

These changes have been bserved in some rat studies. In the 13-week dietary study and 4-week i.v. study, body weight gain was decreased at ≥400 and ≥180 mg/kg, respectively.

Food consumption was decreased after i.v. administration of LVFX at 30 and 90 mg/kg (♂♂ only) for 13 weeks but was increased after oral administration of 80 and 320 mg/kg for 26 weeks. Slightly higher food conversion ratios, indicating decreased efficiency of food utilization, were noted in ♀♀ given 320 mg/kg orally for 26 weeks.

The body weight and food consumption changes may be due to changes in the balance of gut microflora which resulted in a decreased capacity for rodents to digest complex carbohydrates including cellulose.

Serum Biochemical Changes (Rats):

These appeared to be related to either decreased body weight, inflammation at the injection site (i.v. studies), or nutritional changes associated with either body weight, food consumption, or cecal changes.

26-week oral rat study, the following changes were noted:

slightly higher glucose (≥20 mg/kg, ♂♂),
lower triglycerides (320 mg/kg, ♀♀),
lower ß-globulin (≥20 mg/kg),

lower α-globulin (≥20 mg/kg, ♀♀),
lower chloride (320 mg/kg rats and 80 mg/kg ♀♀), and
slightly lower total protein (≥80 mg/kg, ♂♂),
increased urinary pH (≥80 mg/kg), and
increased ketones in urine (≥80 mg/kg).

13-week dietary rat study:

globulin decreased at ≥100 mg/kg/day,
total protein decreased at 200 mg/kg/day,
triglycerides decreased at 800 mg/kg/day .
These changes were attributed to nutritional changes.

4-week i.v. rat study:

decreased total protein, albumin, A/G ratio, cholinestrase activity, and urinary protein resulted from suppressed body weight gain, and decreased RBC count and increased WBC count, reticulocyte count, and fibrinogen concentration were believed related to irritation at the injection site. These serum biochemical and hematology were limited to the highest dose of 180 mg/kg/day.

13-week i.v. rat study:

mild decreases in total protein, phosolipids, and cholesterol at 90 mg/kg/day (♂♂ only) and mild increases in A/G ratio and albumin at 30 and 90 mg/kg/day in males were observed.

Neutrophil counts:

Decreased neutrophil counts were observed in the 13-week dietary study (≥100 mg/kg/day), in the 26-week oral rat study at all dosage levels (≥20 mg/kg/day) and in the rat carcinogenicity study (≥100 mg/kg/day). Even though the decreased neutrophil count observed in these studies remained within normal range, the relationship between LVFX and neutropenia were further investigated (see Special Studies)

Enzyme Changes:

Increased alanine aminotransferase and alkaline phosphatase were observed at very high doses only (800 mg/kg/day for 4- and 13-week; oral administration)

Urinary Crystals:

Dose-related occurrences of urinary crystals have been observed in the i.v. rat studies with LVFX [this effect was not seen with Ofloxacin.].

These crystals were **not formed in the bladder but rather after micturition and were not associated with any kidney changes** as is the case with ciprofloxacin in which histologic changes in the kidney and increased kidney weight were observed.[69,79]

Arthropathy:

This common finding in juvenile animals was observed **in some but not all** rat studies.

In the oral studies, arthropathy was observed at 800 mg/kg/day for 4 weeks but not at 320 mg/kg/day for 26 weeks.

In the i.v. studies, arthropathy was observed after 60 mg/kg/day for 4 weeks and 90 mg/kg/day for 13 weeks.

B. The DOG:

Clinical Signs:

Reddening of the skin and swelling of auricles and face, decreased spontaenous movement, and prostration were common following i.v. injection of 3 to 10 mg/kg/day LVFX. Similar clinical signs were also observed with ofloxacin.

-In a 4-week infusion study in 7-8 month old dogs, the only changes were histamine-like effects and arthropathy at 10 and 30 mg/kg/day.

In immature dogs (4-5 month old), in addition to the preceding clinical signs, dysstasia [difficulty in standing] at 15 mg/kg/day for 2 weeks, delayed testicular maturation (with decreased testis weight) and erosions of the weight bearing joints (4 mg/kg/day for 2 weeks) have been observed. Effects on the testes have also been observed with quinolone administration.

Other changes observed solely with the immature dogs at 60 mg/kg/day were: increased urine specific gravity, plasma fibrinogen and alkaline phosphatase (15 mg/kg/day), and decreased serum iron concentration. However, most of these changes were within normal range for the species or observed prior to dosing.

In more mature dogs (18 months), the clinical signs associated with i.v. injection such as redness and decreased locomotor activity were still present (10 mg/kg/day for 2 weeks) but there was no effect on testicular weight or articular cartilage at doses up to 30 mg/kg/day for 2 weeks.

C. MONKEYS:

Both oral and i.v. administration of LVFX produced only minor changes in monkeys.

- In the 4-week oral study, monkeys were dosed with 10, 30, or 100 mg/kg/day LVFX. Salivation, diarrhea, slight body weight loss, low urinary pH, unusually large adenal gland (one monkey only) and what appeared to be blood in the urine were observed at 100 mg/kg/day.

- The only finding attributed to oral administration of 62.5 mg/kg/day LVFX for 26 weeks was a decrease in food consumption during the first half of the study.

- A slight decrease in neutrophil count observed in the LVFX-treated males was considered to be a result of a high neutrophil count in one vehicle-control male and not due to drug treatment.
- In a 4-week i.v. study, treatment-related clinical signs were limited to quietness and slight decrease in water consumption (25 and 63 mg/kg/day) and food consumption (63 mg/kg/day) and heavy-lidded eyes (63 mg/kg/day).

The only other finding was decreased promyelocytes in the bone marrow, which in the absence of any associated decrease in other cells in the myeloid series or of peripheral blood effects, was not considered to be toxicologically meaningful.

Comparison of Toxicity [Levofloxacin vs. Ofloxacin]:

- Oral and i.v. administration of LVFX produced toxicity comparable to ofloxacin. Differences in toxicity were minimal and were not considered to be toxicologically meaningful.

- In the **acute toxicity** studies, LVFX was marginally more toxic than ofloxacin when administered orally to mice. However, in all other species and in the i.v. mouse studies, LVFX was comparable to if not slightly **less** toxic (i.v. rat and dog) than ofloxacin (see **Table III-4**).

- In the **multidose** studies, most of LVFX's effects were typical of other quinolones including ofloxacin. Even though there appeared to be more serum biochemical changes in the 26 week oral rat study with LVFX than ofloxacin, these changes were slight and per investigators most likely due to nutritional changes resulting from the pharmacologic effect of antibiotics on the intestinal gut microflora in the rodent (**Tables III-5 and III-6**). These tables present the comparison of LVFX and ofloxacin results from the 4-week and 26-week rat and 4-week monkey studies.

- As with ofloxacin, LVFX was **not nephrotoxic**, exhibited a low potential for **antigenicity**, caused slight **local irritation**, and did not produce **ocular** or **ototoxicity**.

- LVFX produced **phototoxic** reactions in mice and **arthropathic** lesions in juvenile animals but to a lower magnitude as compared to ofloxacin (**Table III-7**).

- **Neutropenia** and **crystalluria**, while not observed with ofloxacin, have been reported for other quinolones.

- LVFX did not exhibit a carcinogenic potential.

- Although LVFX was positive in the in vitro chromosomal aberration and sister chromatid assays and ofloxacin was not, ciprofloxacin was positive in both in vivo and in vitro chromosomal aberration assays indicating that LVFX did not differ significantly from the marketed quinolones.

- The potential reproductive toxicity of both ofloxacin and LVFX were comparable (**Table III-8**)

[see TABLES - pages 67 t0 70]

Table III-4: Comparison of Acute Toxicity (LD_{50} Values) for Levofloxacin and Ofloxacin [a]

Species	Route	Levofloxacin (mg/kg)	Ofloxacin[21,22] (mg/kg)
Mouse	p.o.	1803-1943	3557-5450[b]
	i.v.	244-323	208-233
Rat	p.o.	1478-1754	1737[c]
	i.v.	395-423	273-276
Dog	p.o.	ND	>200
	i.v.	200	>70[d]
Monkey	p.o.	>250[e]	>500 but <1000[f]
	i.v.	>200	ND

[a] LD_{50} values are presented as a range including both male and female values, if both males and females were tested.
[b] The LD_{50} value of 3557 mg/kg was observed in a study that directly compared levofloxacin and ofloxacin in the same study, the higher LD_{50} value (5450 mg/kg) was observed in an earlier study.
[c] This LD_{50} value was observed in a study that directly compared levofloxacin and ofloxacin.[33] Higher LD_{50} values were observed in an earlier study with different experimental conditions, i.e. fasted vs. nonfasted prior to dosing.
[d] One female dog died at 100 mg/kg.
[e] Only one monkey successfully dosed with 500 mg/kg and this monkey survived.
[f] All monkeys (4) died at 1000 mg/kg.
ND = not determined

Table III-5a: Comparison of 4 Week Oral Toxicity in Rats for Levofloxacin and Ofloxacin

Study Type	Levofloxacin (mg/kg)			Ofloxacin[21] (mg/kg)			
Oral Rat	50	200	800	30	90	270	810
Salivation, soft stool, haircoat stain, transient pallor or hypothermia	-	-	+	-	-/+	+	+
↓ fc or bw gain (transient, ♂)[a]	+	+	+	-	-	+	+
↑ wc	-	-	-	-	-	+	+
↓ PMNs[a]	+	+	+ (♀)	+ (♀)	+ (♀)	+ (♀)	+ (♀)
↑ WBC, P, ALT, M:E, ↓ K^+, Cl^-, urea	-	-	+	-	-	-	-
↑ P, ALP	-	-	-	-	-	-	+
↑ occult blood or ↓ urinary Na^+	-	-	-	-	-/+	+	+
↓ heart weight[a]	-	-	+	-	-	-	+
↑ cecal weight	-	+	+	+	+	+	+
articular cartilage lesions	-	-	+	-	-	-	+
Slight vacuolization and minimal hypertrophy of hepatocytes	-	-	+	-	-	-	-

fc = food consumption, bw = body weight, wc = water consumption, PMNs = neutrophils, WBC = white blood cells, P = phosphorus, ALT = alanine aminotransferase, ALP = alkaline phosphatase, M:E = myeloid to erythroid ratio, K^+ = potassium, Cl^- = chloride, Na^+ = sodium
[a] The findings for ofloxacin were not considered to be toxicologically significant and therefore were not discussed in the ofloxacin tablet technical summary but can be found in the individual ofloxacin report (DS-1575) which was submitted with the ofloxacin tablet NDA.

Table III-5b: Comparison of 4 Week Intravenous Toxicity in Rats for Levofloxacin and Ofloxacin

Study Type	Levofloxacin (mg/kg)			Ofloxacin[22] (mg/kg)		
Intravenous Rat	20	60	180	10	32	80
↓ spontaneous activity; blepharoptosis (♂)	-	-	+	-	-	-
↓ fc and bw gain	-	-	+	-	-	-
irritation @ inj. site	-	-	+	-/+	-/+	+
↓ total protein, albumin, A/G ratio, cholinesterase, urinary protein, RBC*	-	-	+	-	-	-
↑ WBC, retics, and fibrinogen*	-	-	+	-	-	-
Crystalluria	-/+	-/+	+	-	-	-
↓ thymus, liver, heart, ovaries, and brain*	-	-	+	-	-	-
↑ cecal weight	-	+	+	ND	ND	ND
arthropathy	-	+	+	-	-	-

* Many of these biochemical findings were due to decreased body weight gain. Hematology findings were related to the irritation at the injection site.

fc = food consumption, bw = body weight, inj. = injection, A/G = albumin/globulin, RBC = red blood cell, WBC = white blood cell, retic = reticulocyte, ND = not determined.

Table III-5c: Comparison of 26 Week Oral Toxicity in Rats for Levofloxacin and Ofloxacin

Study Type	Levofloxacin (mg/kg)			Ofloxacin[21] (mg/kg)			
Oral Rat	20	80	320	10	30	90	270
Salivation, large fecal pellets, soft stool or stained haircoat	-	-	+	-	-	+	+
↑ fc	-	+	+	-	-	-	-
↑ food conversion ratio (♀)	-	-	+	-	-	-	-
↓ fc, bw; ↑ wc	-	-	-	-	-	-	+
↑ ALT (♀), ↑ ALP (♂)	-	-	-	-	-	-	+
↓ PMNs*	+	+	+	-	+(♀)	+(♀)	+(♀)
↑ glucose (♂); ↓ β-glob,. α-glob (♀)[b]	+	+	+	-	-	-	-
↓ triglyceride (♀)	-	-	+	-	-	-	-
↓ Cl^- and total protein (♂); ↑ urinary pH	-	+	+	-	-	-	-
fecal occult blood	-	-	-	-	+(♂)	+	+
↑ lipid droplets adrenal cortex	-	-	-	-	-	-	+
enlargement of cecum or ↑ weight	+	+	+	-	+	+	+
articular degeneration	-	-	-	-	-	+	+

fc = food consumption, bw = body weight, wc = water consumption, ALT = alanine aminotransferase, ALP = alkaline phosphotase, β-glob = β-globulin, α-glob = α-globulin, PMNs = neutrophils, Cl^- = chloride

* The findings for ofloxacin were not considered to be toxicologically significant and therefore were not discussed in the ofloxacin tablet technical summary but can be found in the individual ofloxacin report (DS-1567) which was submitted with the ofloxacin tablet NDA.

[b] β-globulin and α-globulin levels were not measured in the ofloxacin study.

Table III-6: Comparison of 4 Week Oral Toxicity in Monkeys for Levofloxacin and Ofloxacin

Study Type	Levofloxacin (mg/kg)			Ofloxacin [21] (mg/kg)		
Monkey (3/sex/group)	10	30	100	20	60	180
Mortality	-	-	-	-	-	2/6 [a]
Salivation	-	-	+	-	-	-
Diarrhea and/or emesis	-	-	+	-/+	+	+
Slight body weight loss and/or low urinary pH [b]	-	-	+	-	-	+
Blood in urine [b]	-/+	-/+	+	-	-	+
↓ cholesterol and ALP	-	-	-	-	-	+
Minimal to mild karyomegaly of the liver	-	-	-	-	-/+	+

[a] Mortality believed due to electrolyte imbalance because of diarrhea

[b] The findings for ofloxacin were not considered to be toxicologically significant and therefore were not discussed in the ofloxacin tablet technical summary but can be found in the individual ofloxacin report (DS-1568) which was submitted with the ofloxacin tablet NDA.

ALP = alkaline phosphatase

Table III-7a: Comparison of Arthropathy in Juvenile Rats for Levofloxacin and Ofloxacin

Study Type and Length	Levofloxacin (mg/kg)			Ofloxacin[21,22] (mg/kg)			
Oral - 1 week	100	300	900	100	300	900	
Arthropathy	-	+	+	-	+	+	
Oral - 4 week	50	200	800	30	90	270	810
Arthropathy	-	-	+	-	-	-	-/+ [a]
Oral - 26 week	20	80	320	10	30	90	270
Arthropathy	-	-	-	-	-	+	+
Intavenous - 4 week	20	60	180	10	32	80	
Arthropathy	-	+	+	-	-	-	

Table III-7b: Comparison of Arthropathy in Dogs for Levofloxacin and Ofloxacin

Study Oral Administration (1-2 Weeks)	Levofloxacin (mg/kg)				Ofloxacin [21] (mg/kg)			
3-4 month old dogs [a]	5	10	20	40	5	10	20	40
Arthropathy	-	+	+	+	-	+	+	+
12-13 month old dogs [b]	10	40			20	40	80	
Arthropathy	-	+ (1/3)			-	-	-	

[a] 1 week study
[b] Study with levofloxacin was for 1 week and study for ofloxacin was for 2 weeks.

Table III-8: Comparison of Reproductive Toxicity in Rats (Oral Gavage) for Levofloxacin and Ofloxacin

Study Type	Levofloxacin (mg/kg)			Ofloxacin[21] (mg/kg)		
Segment I - Fertility and Reproductive Performance	10	60	360	10	60	360
Effects on mating performance and intrauterine survival	NSF	NSF	NSF	NSF	NSF	NSF
Segment II - Teratology and Embryotoxicity	10	90	810	10	90	810
↑ fetal mortality and ↓ fetal weight	-	-	+	-	-	+
delayed ossification due to maternal toxicity	-	-	+	-	-	+
↓ mean pup weight at birth (♂ and ♀) and on days 63-77 postpartum (♀)	-	-	+	-	-	+
Segment III - Perinatal and Postnatal	10	60	360	10	60	360
Effects on F_1 or F_2 generation	NSF	NSF	NSF	NSF	NSF	NSF

NSF = no significant findings

Comments:

1. The NDS, levofloxacin, is a broad-spectrum, synthetic antibacterial agent belonging to the quinolone class of compounds.

2. Chemically, levofloxacin is the l-isomer of the racemate, ofloxacin (FLOXIN®). Ofloxacin is currently marketed in the U.S. in both oral and parenteral dosage forms.
3. Toxicologically, levofloxacin is generally comparable to the marketed ofloxacin (see above).

4. The proposed maximum human clinical oral or intravenous dose is 1000 mg (500 mg b.i.d.) [equivalent to 20 mg/kg in 50 kg person]. Animal toxicology studies were conducted at multiples of this dose.

5. The nonclinical pharm/tox data submitted in the NDA provide sufficient information to support the safety of this drug.

6. The applicant has initiated a photocarcinogenicity study in a rodent under a phase IV agreement.

7. Labelling with regard to carcinogenesis, mutagenesis, impairment of fertility, pregnancy category has been revised

Recommendation: Approval of the drug.

Key Words: levofloxacin, sparfloxacin, enoxacin, arthropathy.

7/3/96

3-Appendices & Labelling (Original only) **S.R. Joshi, D.V.M.,Ph.D.**

cc:
Orig.NDA
HFD-340
HFD-520
HFD-520/Pharm/Joshi **Concurrence Only**
HFD-520/MO/~~Moteelim~~ HOPKINS **HFD-520/Dep.Dir/L.Gavrilovich**
HFD-520/Chem/Shetty **HFD-520/SPharm/REOsterberg**
HFD-520/Micro/King
HFD-520/CSO/Fogarty
HFD-520 /rd init. by REOsterberg
R/D/4/12/96/FT/6/3/96/7/3/96/SRJ
N-20-634.001

7/3/96

7/5/96

Appendix - 1

Table IV-1: Summary of In Vivo Nonclinical Studies of Absorption, Distribution, Metabolism, and Excretion of Levofloxacin

Ref. No.	Doc ID	Study Type	Species	Strain Sex [N]	Route of Administration	Dose(s) (mg/kg)	Radioactive Dose Solution; ^{14}C-Levofloxacin (μCi/mg)	Vehicle mL/kg	GLP
129	244205:1	A, D, E, PB	Mouse	Slc:ddy Male [28]	p.o.	20	41.55	Aqueous 10 mL/kg	0
130	245002:1	A, D, E	Mouse	Slc:ddy Male [20]	p.o.	600	[a]	0.5% CMC suspension 20 mL/kg	0
131	22254:1	A, D, E	Rat	Slc:SD Male [73]	p.o.	20	4.49, 10.2, 6.09, 1.03	Aqueous 5 mL/kg	0
132	22266:1	A, D, E	Rat	Slc:SD Male [51]	p.o.	5, 80, 320	22.8, 1.44, 0.63, 0.38	Aqueous or 0.5% CMC suspension 5 mL/kg	1
133	22260:1	A, D	Rat	Slc:SD Male [40]	[b]	5, 20	17.8, 3.39	Aqueous 2 mL/kg	2
137	22251:1	A, D, E	Rat	SPF:SD Male [*]	p.o.	20 (21 day)	[a]	Aqueous 5 mL/kg	0
148	28561:1	A, D, E	Rat	SD:CD Female (lactating) [18]	p.o.	20	4.92-37.9	Aqueous[d]	0
147	28560:1	A, D, E, PT	Rat	SD:CD Female (pregnant) [20]	p.o.	20	2.36-9.64	Aqueous[d]	0
151	28722:2	E, I/I	Rat	Slc:SD Male [28]	p.o.	20 (3, 7, 21 day)	[a]	Aqueous 5 mL/kg	0
49	339457:1	TK	Rat	Fisher Male [15] Female [15]	diet	10, 30, 100 (104 weeks)	NA	Diet	1
135	28563:2	A, D, E, PB	Rat	Slc:SD Male [43]	i.v.[c]	20	5.91, 0.99	Aqueous 2 mL/kg	0
136	22256:1	A, D, E	Rat	Slc:SD Male [43]	i.v.	20	3.95, 9.07, 2.40	Aqueous 1 mL/kg	2
138	22265:1	A, D, E	Rat	SPF:SD Male [10]	i.v.	20 (14 day)	[a]	Aqueous 2 mL/kg	0
139	22249:1	A, D, E	Dog	Beagle Male [4]	p.o.	20	[a]	Aqueous 2 mL/kg	0
140	28564:2	A, E, PB	Dog	Beagle Male [6]	i.v.	5 20	1.57 1.00	Aqueous 1 mL/kg	2

[a] Could not be determined from the data provided.
[b] Injected into ligated sections of the stomach and intestines.
[c] Drip infusion for 30 minutes.
[d] Dose volume adjusted for weight.
CODES: A = Absorption Study, D = Distribution Study, E = Excretion Study, PB = Protein Binding Study, PT = Placental Transfer, I/I = Isolation/Identification; WBA = Whole Body Autoradiography; GLP Status, 0 = Non-GLP Study, 1 = USA GLPs, 2 = Japanese GLPs; TK = toxicokinetic

Table IV-1: Summary of In Vivo Nonclinical Studies of Absorption, Distribution, Metabolism, and Excretion of Levofloxacin (Continued)

Ref. No.	Doc ID	Study Type	Species	Strain Sex [N]	Route of Administration	Dose(s) (mg/kg)	Radioactive Dose Solution; ^{14}C-Levofloxacin (μCi/mg)	Vehicle mL/kg	GLP
153	28829:2	I/I	Dog	Beagle Male [4]	p.o	20	a	Aqueous 2 mL/kg	0
153	28829:2	I/I	Monkey	Cynomolgus Male [4]	p.o.	20	a	Aqueous 2 mL/kg	0
141	22250:1	A, D, E	Monkey	Cynomolgus Male [a]	p.o.	20	1.076	Aqueous 2 mL/kg	0
143	22259:1	A, D, E	Monkey	Cynomolgus Female [4]	I.v.	20	1.17 0.45	Aqueous 1 mL/kg	2
142	28562:2	A, E, PB	Monkey	Cynomolgus Female [4]	i.v.[c]	20	a	Aqueous 1 mL/kg	0
47	22372:2	TK	Monkey	Cynomolgus Male [16]/Female [16]	p.o.	10, 25, 62.5 (25 weeks)	a	0.5% CMC suspension	1
48	22390:1	TK	Monkey	Cynomolgus Male [9]/Female [9]	i.v.	10, 25, 63	NA	Sterile Saline 6.3 mL/kg	1
146	28669:2	WBA	Monkey	Squirrel Male [3]	p.o.	20	4.49	Aqueous 2 mL/kg	0

[a] Could not be determined from the data provided.
[b] Injected into ligated sections of the stomach and intestines.
[c] Drip infusion for 30 minutes.
[d] Dose volume adjusted for weight.
CODES: A = Absorption Study, D = Distribution Study, E = Excretion Study, PB = Protein Binding Study, PT = Placental Transfer, I/I = Isolation/Identification; WBA = Whole Blood Antiradiography; GLP Status, 0 = Non-GLP Study, 1 = USA GLPs, 2 = Japanese GLPs; TK = toxicokinetic

Table IV-2: Results of In Vivo Nonclinical ADME Studies

Ref. No.	Document ID No.	Species, Strain, Sex	Dose[a] (mg/kg) Route of Admin.	Assayed Matrix	C_{max}[b] (μg equiv/mL)	T_{max} (h)	$AUC_{(0-24)}$ (μg equiv • h/mL)	$t_{\frac{1}{2}}$ (h)	Tissues of Maximum Concentration	Cumulative % of Administered Radioactivity: Urine	Feces	Total
129	244205:1	Mouse Slc:ddy Male	20 p.o.	Blood	3.93	0.25	10.7	4.87	Kidney>Liver>Spleen>	42.2	50.3	92.6
				Plasma	5.16	0.25	14.4	5.56	Lung			
130	245002:1	Mouse Slc:ddy Male	600 p.o.	Serum	99.2	0.25-1.0	589.2	ND	Bone Marrow>Kidney> Liver	47.6	35.1	82.7
131	22254:1	Rat Slc:SD Male	20 p.o.	Blood	2.51	0.5	10.3	1.71	Kidney>Liver>Trachea>	43.8	56.8	100.6
				Serum	3.23	0.5	13.0	1.87	Salivary Gland			
132	22266:1	Rat Slc:SD Male	5 p.o.	Blood	0.36	0.25	3.0	ND	Kidney>Liver	33.7	61.7	95.4
			80		6.35	0.50	43.8	ND		35.8	58.3	94.1
			320		32.28	2.0	249.8	ND		35.3	58.5	93.7
133	22260:1	Rat Slc:SD Male	5,20[c]	Blood	ND	ND	ND	ND	Jejunum>Duodenum> Colon>Ileum	ND	ND	ND
137	22251:1	Rat SPF:SD Male	20 p.o. (21 day)	Blood	2.96	0.50	7.2[d]	1.8	Kidney>Liver>Salivary Gland>Vein>Spleen; Day 21	32.4 32.1	65.4 63.7	97.8 95.7
147	28560:1	Rat SD:CD Female (pregnant)	20 p.o.	GD 12								
				Blood	2.98	0.50	ND	ND	GD 12 Kidney>Liver>	29.2	51.6	82.0
				Serum	4.06	0.50			Pancreas>Spleen> Salivary Gland			
				GD 19								
				Blood	3.46	0.50	ND	ND	GD 19 Kidney>Liver>	31.5	28.1	63.1
				Serum	5.04	0.50			Salivary Gland>Spleen> Pancreas			
148	28561:1	Rat, Female (Lactating)	20 p.o.	Blood	2.27	0.50	17.7	ND	NA	NA	NA	NA
				Milk	5.81	0.50						

[a] Single dose unless otherwise noted.
[b] Total measurable radioactivity (unless otherwise noted).
[c] Dose administered into ligated sections of the stomach and intestine.
[d] $AUC_{(0-8\ h)}$
[e] Taken at 5 minutes postdose
[f] Percent of parent drug
[g] $AUC_{(0-48\ h)}$
[h] Percent of total sample radioactivity associated with levofloxacin.
[i] Levofloxacin (μg/mL)
[j] Sample taken during the dark cycle
[k] Human data are included for comparison.

Codes:
WBA = Whole Body Autoradiography
NA = Not Applicable
ND = Not Determined
GD = Gestational Day

Table IV-2: Results of In Vivo Nonclinical ADME Studies (Continued)

Ref. No.	Document ID No.	Species, Strain, Sex	Dose[a] (mg/kg) Route of Admin.	Assayed Matrix	C_{max}[b] (μg equiv/mL)	T_{max} (h)	$AUC_{(0\text{-}24)}$ (μg equiv • h/mL)	$t_{½}$ (h)	Tissues of Maximum Concentration	Cumulative % of Administered Radioactivity: Urine	Feces	Total
151	28722:2	Rat Slc:SD Male	20 p.o. (3, 7, 21 day)	Serum, Feces, Urine, Bile	NA	NA	NA	NA	Kidney>Liver>Lung	27.8[f]	52.9[f]	80.7[f]
49	339457:1	Rat, Fisher, Male, Female	10	Serum	0.21 (M)[i,j] 0.18 (F)[i,j]	NA	NA	NA	NA	NA	NA	NA
			30		0.65 (M)[i,j] 0.66 (F)[i,j]							
			100		2.36 (M)[i,j] 2.95 (F)[i,j]							
135	28563:2	Rat Slc:SD Male	20 i.v.-drip infusion	Blood Serum	9.17[e] 10.15[e]	NA NA	10.6 11.1	0.84 0.95	Kidney>Salivary Gland, Liver, Pituitary>Spleen, Trachea, etc.	50.0	51.1	101.1
136	22256:1	Rat Slc:SD Male	20 i.v. bolus	Blood Serum	17.1[e] 17.3[e]	NA NA	16.0 17.7	4.55 5.21	Vein>Kidney>Sciatic Nerve>Skin>Trachea>Liver	51.9	51.8	103.7
138	22265:1	Rat SPF:SD Male	20 i.v. (14 day)	Blood	13.2[e]	NA	13.4[e]	0.75	Kidney>Prostate>Trachea	40.0 40.3	58.7 55.9	98.7 96.1
139	22249:1	Dog Beagle Male	20 p.o.	Blood Serum	6.38 6.57	4 3	110.3[g] 94.1[g]	8.4 8.7	NA NA	52.0	39.4	91.4
140	28564:2	Dog Beagle Male	5 i.v.	Blood Serum	5.55 5.83	NA NA	28.2[g] 28.7[g]	3.51 3.84	NA NA	65.6	22.3	87.8
			20 i.v. bolus	Blood Serum	21.72 24.71	NA NA	186.7[g] 198.0[g]	5.86 5.70	NA NA	66.6	23.7	90.2
153	28829:2	Dog Monkey	20 p.o. 20 p.o.	Urine, Feces	NA	NA	NA	NA	NA	81.7[h] 94.2[h]	84.1[h] 66.0[h]	

[a] Single dose unless otherwise noted.
[b] Total measurable radioactivity (unless otherwise noted).
[c] Dose administered into ligated sections of the stomach and intestine.
[d] $AUC_{(0\text{-}8\ h)}$
[e] Sample taken at 5 minutes postdose
[f] Percent of parent drug
[g] $AUC_{(0\text{-}48\ h)}$
[h] Percent of total sample radioactivity associated with levofloxacin.
[i] Levofloxacin (μg/mL)
[j] Sample taken during the dark cycle
[k] Human data are included for comparison.

Codes:
WBA = Whole Body Autoradiography
NA = Not Applicable
ND = Not Determined
GD = Gestational Day

Table IV-2: Results of In Vivo Nonclinical ADME Studies (Continued)

Ref. No.	Document ID No.	Species, Strain, Sex	Dose[a] (mg/kg) Route of Admin.	Assayed Matrix	C_{max}[b] (μg equiv/mL)	T_{max} (h)	$AUC_{(0-24)}$[c] (μg equiv • h/mL)	$t_{½}$ (h)	Tissues of Maximum Concentration	Cumulative % of Administered Radioactivity		
										Urine	Feces	Total
141	22250:1	Monkey Cynomolgus Male	20 p.o.	Blood	7.76	3	82.2	4.5	NA	84.4	5.0	89.4
				Serum	7.48	3	76.6	4.2				
143	22259:1	Monkey Cynomolgus Female	20 i.v. bolus	Blood	21.97	NA	84.8	3.02	NA	91.4	4.8	96.2
				Serum	23.3	NA	85.3	2.84				
142	28562:2	Monkey Cynomolgus Female	20 i.v.- drip infusion	Blood	21.53	NA	56.6	2.57	NA	86.3	4.1	90.4
				Serum	21.56	NA	57.1	2.60	NA			
48	22390:1	Monkey Cynomolgus Male/Female	10 i.v.	Serum	8.19(M),[e,j] 8.23(F)	NA	NA	NA	NA	NA	NA	NA
			25 i.v.	Serum	21.91(M),[e,j] 20.66(F)[e,j]							
			63 i.v.	Serum	58.69(M),[e,j] 72.26(F)[e,j]							
47	22372:2	Monkey Cynomolgus Male/Female	10 p.o. (24 wk)	Plasma	2.13 (M)[i]	NA	NA	NA	NA	NA	NA	NA
			25 p.o. (24 wk)		2.91 (F)[i] 8.55 (M)[i] 8.48 (F)[i]							
			62.5 p.o. (25 wk)		22.86 (M)[i] 20.35 (F)[i]							

[a] Single dose unless otherwise noted.
[b] Total measurable radioactivity (unless otherwise noted).
[c] Dose administered into ligated sections of the stomach and intestine.
[d] $AUC_{(0-8\ h)}$
[e] Taken at 5 minutes postdose
[f] Percent of parent drug
[g] $AUC_{(0-48\ h)}$
[h] Percent of total sample radioactivity associated with levofloxacin.
[i] Levofloxacin (μg/mL)
[j] Sample taken during the dark cycle
[k] Human data are included for comparison.

Codes:
WBA = Whole Body Autoradiography
NA = Not Applicable
ND = Not Determined
GD = Gestational Day

Table IV-2: Results of In Vivo Nonclinical ADME Studies (Continued)

Ref. No.	Document ID No.	Species, Strain, Sex	Dose[a] (mg/kg) Route of Admin.	Assayed Matrix	C_{max}[b] (μg equiv/mL)	T_{max} (h)	$AUC_{(0\text{-}24)}$[c] (μg equiv • h/mL)	$t_{½}$ (h)	Tissues of Maximum Concentration		Cumulative % of Administered Radioactivity: Urine	Feces	Total
146	28669:2	Monkey Squirrel Male	20 p.o.	WBA	NA	NA	NA	NA	Uveal Tract, Hair Follicles > Thyroid Gland > Trachea, Cartilage > Liver, Kidney		NA	NA	NA
160	21156:1	Human Male[k]	500 p.o.	Plasma									
				(Day 1)	5.19	1.3	42.6	6.5	ND	NA	64	ND	ND
				(Day 10)	5.72	1.1	47.5	6.8	ND		67	ND	ND
161	204120:1	Human Male[k]	500 i.v.	Plasma									
				(Day 1)	6.34	NA	49.6	7.1	ND	NA	60	ND	ND
				(Day 10)	6.40	NA	54.6	7.0	ND		63	ND	ND

[a] Single dose unless otherwise noted.
[b] Total measurable radioactivity (unless otherwise noted).
[c] Dose administered into ligated sections of the stomach and intestine.
[d] $AUC_{(0\text{-}6\ h)}$
[e] Taken at 5 minutes postdose
[f] Percent of parent drug
[g] $AUC_{(0\text{-}48\ h)}$
[h] Percent of total sample radioactivity associated with levofloxacin.
[i] Levofloxacin (μg/mL)
[j] Sample taken during the dark cycle
[k] Human data are included for comparison.

Codes:
WBA = Whole Body Autoradiography
NA = Not Applicable
ND = Not Determined
GD = Gestational Day

Bio

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: August 8, 1996

FROM: Frances V. LeSane
Project Manager
DAIDP/HFD-520
301-827-2125
301-827-2325/2327 FAX

SUBJECT: RE: Telecon 7-31-96 request from Biopharm Reviewer for NDA 20-634 levofloxacin tablets.

TO: Heather L. Jordan
Associate Director
Regulatory Affairs
The R.W. Johnson PHARMACEUTICAL RESEARCH INSTITUTE
908-704-4607
908-722-5113 FAX

Please note the following request in regard to your pending NDA.

Please submit the following as ASCII files for the four month safety report:

1. - The NONMEM input data file(s).

   - The NM-Tran control files for the NONMEM analysis

2. The data files for the NPEM2 analysis of the Pk/PD (Dr. Drusano's analysis).

3. The data files for the Pk/PD (AUC/MIC, C_{Max}/MIC) analysis.

4. The data files for the pk/PD (adverse events) analysis.

If you have any questions, please call me at the above number and I will arrange a telecon with the reviewer.

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: May 17, 1996

FROM: Frances V. LeSane
Project Manager
DAIDP/HFD-520
301-827-2125
301-827-2325/2327 FAX

SUBJECT: Request from Biopharm Reviewer for NDA 20-634 levofloxacin tablets.

TO: Heather L. Jordan
Associate Director
Regulatory Affairs
The R.W. Johnson PHARMACEUTICAL RESEARCH INSTITUTE
908-704-4607
908-722-5113 FAX

Please note the following request in regard to your pending NDA.

1. The status of BE study # LOFBO-PHI-104. We know that you plan to submit it after the analysis have been completed.

2. Please submit the following as ASCII files:

   - The NONMEM input data file(s).

   - The NM-Tran control files for the NONMEM analysis

If you have any questions, please call me at the above number and I will arrange a telecon with the reviewer.

OCT 7 1996

CLINICAL PHARMACOLOGY/BIOPHARMACEUTICS REVIEW

NDA: 20,634
Levofloxacin, 250 & 500 mg tablets

SUBMISSION DATES: Dec. 21, 1995, Feb. 5, 1996, Mar. 20, 1996, May 31, 1996, July 3, 1996, Aug. 2, 1996 & Aug. 23, 1996

R.W. Johnson Pharmaceutical Research Institute
920 Route 202 South, P.O. Box 300
Raritan, NJ 08869

REVIEWER: Funmilayo O. Ajayi, PhD

TYPE OF SUBMISSION: Original NDA **CODE:** 1-S

SYNOPSIS: The application was submitted for levofloxacin which is being proposed for the treatment of adults suffering from infections of the upper and lower respiratory tract, urinary tract, and skin and skin structure caused by susceptible strains of responsible microorganisms.
In support of this application, the sponsor carried out various pharmacokinetic studies that address issues such as drug interactions, systemic availability and disposition of levofloxacin in healthy adults, the elderly, patients with renal impairment, and those with HIV infection. Overall, the pharmacokinetics of levofloxacin is similar to that of the racemic mixture, ofloxacin. There was no evidence of interconversion to the d-isomer (d-ofloxacin) following administration of levofloxacin. The absorption is significantly reduced when administered with aluminum and magnesium containing antacids. Statistically significant increases were observed for $AUC_{0-\infty}$ and $T_{1/2}$ following co-administration of a single 500 mg dose of levofloxacin with cimetidine and probenecid; while CL_R were statistically significantly reduced. No significant drug interaction was observed following co-administration with digoxin, cyclosporine, theophylline or warfarin. The elimination of levofloxacin is mainly affected by the degree of renal function. Thus, dosage adjustment is required in subjects with renal impairment.

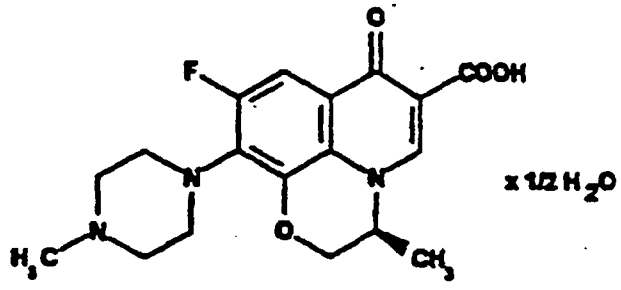
RECOMMENDATION: The information provided in the Human Pharmacokinetics and Bioavailability section of NDAs 20,634 and 20,635 for levofloxacin tablets and IV injection is acceptable because it meets the requirements set forth in 21 CFR 320. The proposed dissolution method, 900 ml of 0.1N HCl in USP Apparatus I at 100 rpm, and specification of NLT [redacted]% of label claim dissolved in [redacted] minutes is acceptable.

TABLE OF CONTENTS

ORGANIZATION OF REVIEW: Following the background is a description of the drug formulation and dissolution method and specification. The summary of the studies is followed by the general comments, labeling comments, and comments to the Firm.

BACKGROUND: Levofloxacin is the levorotatory isomer of the D,L-racemate of ofloxacin and a synthetic, fluorinated carboxyquinolone belonging to the quinolone class of antibacterial agents. Levofloxacin differs from the older generation quinolones such as nalidixic acid by the presence of a fluorine and an N-methylpiperazine substituent. It is chemically distinct from other compounds comprising the newer generation of quinolones with respect to the presence of a benzoxazine ring. Levofloxacin is said to be significantly more soluble than the D-isomer; which should reduce the possibility of crystalluria. It was reported that levofloxacin acts by binding to topoisomerase II (DNA gyrase) and topoisomerase IV which is another enzyme that regulates the superhelicity of DNA, with much greater affinity than the dextro (D-) rotatory species. Levofloxacin has also been shown to be a broad spectrum antibacterial agent, which is active against both conventional and atypical pathogens such as *Mycoplasma pneumoniae* and *Chlamydia pneumoniae*. As at the time of submission of this NDA, levofloxacin is marketed in 4 countries namely Japan, Hong Kong, China, and Korea.

Structure of Levofloxacin



Molecular Formula

$C_{18}H_{20}FN_3O_4 \cdot 1/2H_2O$

Molecular Weight

370.38

FORMULATION: The Tables below shows the components for the 250 mg and 500 mg tablets as well as that for the IV formulation.

Levofloxacin Tablet Strength/Components	mg/Tablet
250 mg: FD-25213-097-AB-22	
Levofloxacin hemihydrate (RWJ-25213-097)	
Hydroxypropyl Methylcellulose 2910, USP	
Crospovidone, NF	
Microcrystalline Cellulose, NF	
Magnesium Stearate, NF	
Polyethylene Glycol 8000, NF	
500 mg: FD-25213-097-AA-22	
Levofloxacin hemihydrate (RWJ-25213-097)	
Hydroxypropyl Methylcellulose 2910, USP	
Crospovidone, NF	
Microcrystalline Cellulose, NF	
Magnesium Stearate, NF	
Polyethylene Glycol 8000, NF	

[a] This excipient is essentially removed during processing.

	mg/unit dose	
Ingredient	FD-25231-097-D-45[a] (25 mg/mL)	(5 mg/mL)
Levofloxacin (hemihydrate)	mg	mg
		-
		mg
	mL	mL

[a] Formula FD-25213-097-D-45 is the proposed commercial formulation for Levofloxacin Injection, 25 mg/ mL, which is the subject of NDA 20-635.

DISSOLUTION: The proposed dissolution method for levofloxacin tablets utilizes USP Apparatus I (basket) containing 900 ml of 0.1 N HCl maintained at 37°C and a rotation of 100 rpm. The dissolution specification (Q) of NLT [redacted]% dissolved in [redacted] minutes is proposed. All through the NDA, the tablets used have all passed the dissolution testing. The sponsor was requested to provide the dissolution of levofloxacin in other media. However, the following response was submitted and constitute the rationale for (a) using the proposed dissolution method and (b) for not making further efforts to evaluate the dissolution profile in other media:

(1) the sponsor prefers the use of similar dissolution method for levofloxacin as for the approved ofloxacin tablets.

(2) the pH-solubility profile for levofloxacin hemihydrate between [redacted] and [redacted] is flat ([redacted] mg/ml). Thus, dissolution testing at any pH within this range is expected to be similar. The solubility of levofloxacin hemihydrate was observed to increase with further increases in pH to a maximum of [redacted] mg/ml at pH [redacted] and minimum pH-solubility profile at pH [redacted]

(3) the publication by Russell *et. al.*, Pharm. Res., 1993 provided a report of the gastric and duodenal pH levels measured in 79 healthy elderly men and women under fasted and fed condition using the Heidelberg capsule technique. Overall, the reported minimal and maximal pH values were 1.1 and 6.7.

ANALYTICAL METHOD: Two validated high performance liquid chromatographic (HPLC) methods that achieved chiral discrimination between D- and L-ofloxacin were employed in the quantitation of levofloxacin in biologic fluids.

SUMMARY OF STUDIES:

1. Pharmacokinetics: Levofloxacin is rapidly and almost completely absorbed following oral administration with an absolute bioavailability of ~ 99% and a mean apparent volume of distribution of ~ 95 L. The peak plasma concentration (C_{max}) in healthy subjects ranges from 7 to 12 μg/ml following a 500 mg oral dose. The mean apparent total clearance and renal clearance following a single or multiple (q.d. or b.i.d) 250 or 500 mg IV or oral dose ranged from [redacted] ml/min and [redacted] ml/min, respectively. Following the above dosing regimen, the mean terminal elimination half-life ranged from approximately 6 to 8 hours. The renal clearance is in excess of glomerular filtration rate suggesting tubular secretion of levofloxacin in addition to glomerular filtration. The residual intra-subject variability was estimated from the NONMEM analysis of

pooled data to be 25% and 18.6% at plasma concentration of 1 μg/ml and ≥ 7 μg/ml, respectively. Inter-subject variability (95% CI) for CL, V and KA are: 21.3 (15.3 - 25.9)%, 24.5 (0 - 35.2)% and 268.5 (0 - 443.7)%, respectively. The inter-subject variability around V and KA can not be adequately estimated because of the lack of enough data points.

1.1 Metabolism and disposition: Levofloxacin is mainly bound to human serum albumin. In-vitro, over a clinically relevant serum/plasma concentration of [redacted] μg/ml, levofloxacin is approximately 24 - 38% bound to serum proteins. It undergoes limited metabolism in humans and is mainly excreted as unchanged drug in urine. Approximately 87% of an administered dose was recovered unchanged in urine in 48 hours; while < 4% of the dose was recovered in 72 hour feces. Desmethyl levofloxacin (M2) and levofloxacin N-oxide (M3) accounted for ~ 1.75 and 1.63% of the dose, respectively. These metabolites were reported to have little relevant pharmacological activity.

1.2 Bioavailability and bioequivalence: The pharmacokinetics of the individual enantiomers of ofloxacin have been compared and reported in the 8/19/94 submission to IND reviewed by Dr. Ette. The results showed similar values for the bioavailability parameters (C_{max}, AUC & Ae) for both levofloxacin and d-ofloxacin.

Following a review of study # M92-035 (RWJPRI) contained in the 7/11/94 submission to IND by Dr. Ette, the 500 mg (hemihydrate levofloxacin, RWJPRI) single clinical tablet was found to be bioequivalent to 5x100 mg (488 mg anhydrous levofloxacin - European formulation, DF). The 500 mg market-image tablet (RWJPRI) was compared to the 500 mg clinical tablet (RWJPRI) in study # LOFBO-PHIO-097 contained in the 5/2/95 submission to IND #s

Dr. Sun's review of the data showed that the market image failed the bioequivalence test because the C_{max} exceeded the 90% CI limit.

In study # HR 355/1/GB/103 (LOFBO-PHIO-100), the 500 mg RWJPRI clinical tablet formulation was compared to the 500 mg HAG tablet and IV formulations. Data from this study demonstrated bioequivalence for the two tablet formulations. In study # LOFBO-PHIO-096 bioequivalence was demonstrated for the RWJPRI 250 mg market-image tablet formulation and 2x125 mg RWJPRI clinical tablet formulation. Study # LOFBO-PHI-104 is a repeated study that compared the 500 mg to-be-marketed formulation to the RWJPRI 500 mg clinical tablet formulation. Results from this study showed that the two tablet formulations are bioequivalent.

Although bioequivalence, as defined by similar rate and extent, can not be proven for a 500 mg dose of levofloxacin given via the IV and oral routes, the degree of exposure (AUC) is comparable following both routes of administration.

1.3 Dose proportionality: The AUC and C_{max} of levofloxacin following single and multiple once daily administration increased linearly over a dose range of 50 mg to 600 mg (study # 91/17). Similarly, these parameters increased proportionally following single and multiple 750 mg and 1 gram oral doses (study # LOFBO-PHIO-093).

1.4 Multiple dosing: The pharmacokinetics of levofloxacin following multiple IV doses (500 mg q 12h - study # L91-054 and 500 mg q24h for 9 days - study # L91-053) was evaluated in normal healthy subjects and reported in a 7/22/94 submission to IND reviewed by Dr. Ette. The extent of accumulation as evaluated from the day10/day1 AUC and C_{max} ratios are 1.06 and 1.14

(study # L91-054) and 0.99 & 1.01 (study # L91-053), respectively. These values were close to the predicted/theoretical of 1.47 for the q.d. and 1.11 for the b.i.d. dosing regimens. The disposition parameters were similar following the two multiple dosing regimen. These results are comparable to those following 500 mg multiple oral doses (study #s K90-077 and K90-014).
The pharmacokinetics of levofloxacin were compared after single and multiple daily or b.i.d. 500 mg oral doses and once daily 750 mg or 1 gram doses in healthy subjects (study # LOFBO-PHIO-093). Overall, a modest accumulation that is predictable from the single dose data was observed and the disposition kinetics of levofloxacin are comparable to those following single oral and IV administration.

1.5 Food effect study: Administration of levofloxacin with food resulted in delayed absorption (60% increase in T_{max}), and slight decrease in the C_{max} (14%) and AUC (10%). Overall, these differences are not of such magnitude that preclude administration of levofloxacin tablets with food [study # HR 355/1/USA/105(LOFBO-PHIO-099)].

1.6 Tissue concentration: The tissue:plasma concentration ratios of levofloxacin were evaluated in study #s LOFBO-PHI-095, HR 355/1/USA/104/GP (N93-069), and HR 355/1/USA/103/GP (N93-070). The tissue:plasma ratio varies from 0.11 to ~ 3 in the cortical and spongiosa bone tissue, blister fluid exudate, and lung tissue.

2. Drug interaction studies:

2.1 Calcium, Aluminum and Magnesium containing antacids: The sponsor proposed identical labeling for levofloxacin dosage and administration as for ofloxacin with respect to interaction with aluminum and magnesium containing antacids in the 8/19/94 submission to IND
reviewed by Dr. Ette. This labeling request was found acceptable following a review of submitted information. However, a review of the literature indicated lack of significant effect of ranitidine (H-2 receptor antagonist) and calcium carbonate on the bioavailability of levofloxacin (Shiba *et.al.*, Antimicrobial Agents and Chemotherapy, 1992; 36, 2270 - 2274). Hence, the proposed labeling should be made to reflect this finding by removing calcium containing antacids from the list of antacids referred to in the labeling.

2.2 Theophylline: The effect of multiple oral dose of levofloxacin (500 mg q12h x 9 doses), at steady-state, on the kinetics of a single 4.5 mg/kg 30-minute I.V. infusion of theophylline was evaluated in 14 healthy males who completed the study (study # LOFBO-PHI-101). The results showed that the pharmacokinetics of a single 4.5 mg/kg I.V. infusion of theophylline were not significantly altered by steady-state levels of levofloxacin. The steady state kinetics of levofloxacin were similar to those observed in studies where multiple 500 mg oral doses of levofloxacin were administered. A similar result was obtained in another study that evaluated the effect of multiple oral doses of 97.6 mg levofloxacin, q8h Days 5 through 9 on the pharmacokinetics of multiple oral doses of 200 mg theophylline administered twice daily on Days 1 - 9 (study # 3355J-MET038; not reviewed).

2.3 Warfarin: The effect of multiple oral dose of levofloxacin (500 mg q12h x 9 doses), at steady-state, on the kinetics of a single 30 mg oral dose of racemic warfarin was evaluated in 16 healthy

male subjects (study # LOFBO-PHI-098). The results showed that the steady-state levels of levofloxacin had no significant effect on the disposition and anticoagulant effect of R- or S-warfarin.

2.4 Cyclosporine: The effect of multiple oral dose of levofloxacin (500 mg q12h x 11 doses), at steady-state, on the kinetics of a single 10 mg/kg oral dose of cyclosporine was evaluated in 14 healthy men and women (N93-059). The results showed that the pharmacokinetics of a single 10 mg/kg oral dose of cyclosporine were not significantly altered by steady-state levels of levofloxacin.

2.5 Digoxin: The effect of multiple oral dose of levofloxacin (500 mg q12h x 11 doses), at steady-state, on the kinetics of a single 0.4 mg oral dose of digoxin was evaluated in 12 healthy men and women (study # LOFBO-PHI-094). The results showed that the pharmacokinetics of a single 0.4 mg oral dose of digoxin were not significantly altered by steady-state levels of levofloxacin. The steady state kinetics of levofloxacin, with and without concomitant digoxin administration, were similar.

2.6 Cimetidine and probenecid: The effect of multiple oral dose of cimetidine (400 mg q12h x 7 days) or probenecid (500 mg q6h x 7 days) on the kinetics of a single 500 mg of levofloxacin, given on Day 4, was evaluated in 12 healthy male subjects (study # HR 355/1/GB/101). There was no statistically significant changes in the C_{max} and T_{max} of levofloxacin following co-administration with cimetidine or probenecid; indicating little or no changes in the rate of absorption. However, statistically significant increases were observed for $AUC_{0-\infty}$ (27% cimetidine, 38% probenecid) and $T_{1/2}$ ($\sim$ 30%). The reductions seen in CL_R were also statistically significant and are 119 ml/min, 91 ml/min and 77 ml/min for levofloxacin alone, with cimetidine and with probenecid, respectively. In general, the observed reductions in CL/F can be attributed to the reductions in CL_R when levofloxacin was co-administered with cimetidine or probenecid.

3. Special population:

3.1 Elderly: The effect of age on the pharmacokinetics of a single 500 mg oral dose of levofloxacin was evaluated in study # N93-024. There was a trend for increased C_{max} and $AUC_{0-\infty}$ with age. The C_{max}, $AUC_{0-\infty}$, Vd/F, T_{max}, CL_R, and CL/F were statistically significantly altered in the elderly. However, differences in total amount excreted (Ae) and T_{max} were not significant. These observed differences were attributable to the differences in renal function. This conclusion is supported by the data from the NONMEM analysis. Thus, dosage adjustment based on age considerations alone is not deemed necessary.

3.2 HIV Patients: The pharmacokinetics of single and multiple oral dosage regimens of levofloxacin was evaluated in HIV seropositive subjects. In study # N93-032, a 750 mg once daily oral dose administered for 14 days followed by 750 mg or 1 gm thrice weekly (t.i.w.) oral doses administered for 2 weeks was evaluated in parallel in patients with CD4 cell counts < 250 and ≥ 250. The differences observed in the kinetics of levofloxacin in the 2 groups was attributed to the differences in the renal function [mean CL_{CR} (range) = 83 (50 - 140) ml/min for patients with CD4 cell count <250; 108 (81 - 182) ml/min for patients with CD4 cell count ≥ 250]. The results indicate a linear relationship in the kinetics of levofloxacin following the 750 mg (q.d. & t.i.w.)

and 1 gm (t.i.w.) doses. Also, there was a reasonable degree of accumulation following the multiple oral doses. Two other studies (K90-024 & K90-086) evaluated the pharmacokinetics of levofloxacin following single and multiple (t.i.d.) 350 mg oral doses for 10 days in HIV patients with and without concurrent therapy with AZT. Results from both studies indicate attainment of steady-state plasma levels within 3 days with minimal accumulation upon multiple dosing. There was an agreement in the observed data points and the simulated plasma concentration profile. The kinetics of levofloxacin does not appear to be affected by concomitant administration of AZT. The kinetics of levofloxacin in the HIV patients are similar to that of healthy subjects. No dosage adjustment is thus necessary in this patient population with or without concomitant therapy with AZT.

3.3 Renal disease: The pharmacokinetics of a single 500 mg oral dose of levofloxacin was evaluated in subjects with varying degrees of renal impairment (study # M92-046). There was a good linear correlation between the degree of renal impairment and the plasma clearance as well as the elimination half-life. Overall, less than 15% of the administered dose of levofloxacin (maximum observed amount = 64 mg, in 1 individual) was removed by hemodialysis or continuous ambulatory peritoneal dialysis (CAPD). Thus, administration of extra dose following hemodialysis is not warranted as these processes do not significantly remove levofloxacin from the body. The following dosage adjustment was recommended for each group following a simulation (superposition method) based on the parameter values obtained in this study:

CrCl > 80 ml/min - 500 mg q12h or q24h
CrCl = 50 - 80 ml/min - 500 mg q24h
CrCl = 20 - 49 ml/min - 500 mg start, followed by 250 mg q24h
CrCl = 10 - 19 ml/min - 500 mg start, followed by 250 mg q48h
Subjects on hemodialysis or CAPD - 500 mg start, followed by 250 mg q48h

3.4 Gender: Results from study # N93-024 revealed statistically significant differences in C_{max}, T_{max}, apparent volume of distribution (Vd/F), $T_{1/2}$, and CL/F but not CL_R and $AUC_{0-\infty}$ between males and females. In general, the C_{max} in females compared to males was 26% higher, T_{max} was increased by 46% (~0.5h), while the Vd/F, $T_{1/2}$ and CL/F were decreased by 15%, 19% and 18%, respectively. The differences in the pharmacokinetic parameters between the genders were no longer statistically significant when the CrCl of each subject was included as a covariate in the ANOVA model. In fact, good correlations were observed between the subject's CrCl and C_{max}, $AUC_{0-\infty}$, CL/F, and CL_R. Although the observed differences between the genders seem unexplainable, it could in part, be attributable to the observed differences in the renal function. This conclusion is supported by the data from the NONMEM analysis which was verified by Dr. Ette. Good correlations were also observed between the C_{max}, Vd/F and each subject's body weight. Data from simulations of the steady-state plasma concentration profiles for females below 50 kg body weight with compromised renal function, using parameter values from NONMEM analysis and the relevant adjusted dosage regimen, indicated a profile within the concentration range (1- 10 μg/ml) seen in normal subjects. Similar differences in the pharmacokinetic parameters were observed in data from studies where males and females were enrolled. However, the magnitude are not high enough to warrant different dosing regimen for females.

3.5 Race: The NONMEM analysis of pooled data from 4 studies indicated similar CL/F and Vd/F for non-white (N=24) and white (N=48) subjects. The NONMEM analysis was reviewed and found acceptable by Dr. Ette.

4. Pharmacokinetic / pharmacodynamic (PK/PD) relationship: A recent 4-month safety update submission contained a report of a multi-center multiple dose study where the pharmacokinetics of levofloxacin was evaluated in hospitalized patients with community acquired infection using population kinetics study design. The relationship between the derived PK parameters (AUC, C_{max}) and clinical outcome, adverse events as well as the microbiological (MIC) outcome was evaluated using logistic regression and Classification And Regression Tree (CART) approach. From a preliminary review, the breakpoint for the C_{max}/MIC ratio was reported by the investigator to be 12.2 for both clinical and microbiological outcomes. Hence, for patients that achieve a C_{max}/MIC ratio of $\geq$ 12.2, the probability of a successful clinical and microbiological outcome is > 95%. The report will be further analyzed when the requested data files become available.

GENERAL COMMENTS (Need Not Be Sent to Firm):

1. Five study protocols (LOFBO-PHIO-094 - levofloxacin/digoxin drug interaction study, LOFBO-PHIO-097 - BE study, LOFBIV-MULT-001 - pharmacokinetics in patients with bacterial infections, LOFBO-PHIO-099 - food and age effect, LOFBO-PHI-101 - levofloxacin/theophylline drug interaction) were reviewed prior to initiation of the studies. The sponsor utilized the comments made by the reviewers of the protocols.

2. Five studies (M92-035 - 500 mg vs. 1x500 mg BE study, L91-053 & L91-054 - single vs. Multiple IV dosing, LOFBO-PHIO-097 - 500 mg market-image vs. Clinical BE study) were reviewed prior to the submission of the NDA.

3. Overall, reports of 40 studies were submitted. Five of these were reviewed prior to the submission of the NDA, while I reviewed 28 studies that were pertinent to the description of the disposition of levofloxacin in healthy subjects and special population as well as describe its drug-drug interaction potential.

LABELING COMMENTS: The following sections of the labeling should be modified as thus edited (in italics):

Dosage and Administration: The following statement should be added:

/Ajayi 9/30/96
Funmilayo O. Ajayi, PhD
Div. of Pharmaceutical Evaluation III

(Clin. Pharm. Biopharm. Briefing - 9/27/96: Lesko, Collins, Fleischer, Albuerne, Hopkins, Huang, Mei-Ling Chen, Pelsor, Lazor, Baweja, Sun, LeSane, Ajayi)

RT initialed by Frank Pelsor, PharmD.....

cc: NDA 20,635 HFD-520 (Clinical Division)
cc: HFD-880 (DPE3,Pelsor,Ajayi).
cc: HFD-870 (Bott)
cc: HFD-340 (Vish)

Appendix I
(Summary of Studies)

STUDY TITLE: A DOUBLE-BLIND STUDY TO EVALUATE THE SAFETY AND PHARMACOKINETICS OF LEVOFLOXACIN 500 MG Q24H VS PLACEBO IN NORMAL SUBJECTS, STUDY # K90-077. **VOLUME 1.63.**

INVESTIGATOR & LOCATION:

OBJECTIVE: To evaluate the safety and pharmacokinetic profiles of levofloxacin under multiple once daily oral dosing.

STUDY DESIGN: Levofloxacin or matching placebo was administered orally to twenty healthy subjects according to a randomized, double-blind, placebo-controlled, parallel design. Ten of the twenty subjects received levofloxacin as levofloxacin hemihydrate, 500 mg per dose; the remaining subjects received placebo. A single dose was given to each subject on Day 1, with a washout period on Days 2 and 3, which was followed by a single daily dose from Days 4 to 10. All doses were administered in the morning with 8 ounces of water; dosing on Days 1 and 10 was conducted with fasted subjects. Subjects were confined to the study site from no less than 12 h prior to administration of the first dose through completion of plasma and urine sampling on Day 13.

FORMULATION: Levofloxacin (RWJ 25213) was provided as white to pale yellowish-white, film-coated tablets containing 100 mg of levofloxacin hemihydrate (FD 25213-B-22, equivalent to 97.6 mg of anhydrous levofloxacin) by The R.W. Johnson Pharmaceutical Research Institute. Identically appearing placebo was also obtained from The R.W. Johnson Pharmaceutical Research Institute (FD 25213-BX-22).

DEMOGRAPHICS: Twenty (20) healthy male subjects participated in this study (Table 1).

SAMPLING: Blood samples were obtained from each subject according to the following time schedule:

Day	Time in Hours	Day	Time in Hours	Day	Time in Hours
1	0	4	72	10	216
	0.5	6	120		216.5
	1	7	144		217
	2	8	168		218
	3	9	192		219
	4				220
	8				224
	12				228
2	24			11	240
	36				252
3	48			12	264
	60				276
				13	288

Urine was collected quantitatively beginning eight hours prior to the first dose and at the following time intervals post-dose: 0-2, 2-4, 4-8, 8-12, 12-24, 24-36, and 36-48 h. Urine was

also collected quantitatively after the last dose on Day 10 at the following time intervals post-dose: 0-2, 2-4, 4-8, 8-24, and 24-48 h.
Fecal samples were also collected *in toto* from all subjects following the initial dose until the morning of Day 3 and also following dosing on Day 10 and continuing until the morning of Day 13. Each sample was weighed, labeled, and frozen. These samples were only to be assayed if plasma and urine data were inconsistent with the dose administered.

ANALYTICAL METHOD: Plasma and urine samples were assayed for levofloxacin according to validated HPLC procedures at The R.W. Johnson Pharmaceutical Research Institute.

The range of detection in plasma was μg/mL whereas the corresponding range in urine was μg/mL.

DATA ANALYSIS: The individual peak concentrations (C_{max}), time to reach C_{max} (T_{max}), and the trough concentrations (C_{min}) on Days 1 and 10 were determined by inspection. The area under the plasma concentration-time curve (AUC), mean residence time (MRT), effective half-life (t½), total body clearance (CL_p/F), and steady-state volume of distribution (VD_{ss}/F) for single-dose (Day 1) and steady-state conditions (Day 10) were determined from the plasma concentration time data.
Steady-state conditions were assessed on Day 10 by evaluating the difference between pre-dose (216 h) concentrations and 24 h post-dose concentrations (240 h).
The plasma concentration versus time profile of each subject during the 13 days of levofloxacin administration was also examined by nonlinear regression. A model assuming two-compartment disposition with first-order absorption and elimination processes was used; computation was performed by means of PCNONLIN (version 4.0).
The percent of dose recovered (Au%) and the renal clearance (Cl_r) after a single dose and at steady state were also determined.
Statistical analyses of pharmacokinetic parameters were conducted using the MINITAB[7] statistical software package. Paired t-tests were used to compare the pharmacokinetic parameter values obtained between Day 1 (single dose) and Day 10 (steady state) of the study. A Type I error rate of 0.05 was used to establish significance.

RESULTS: Mean C_{max} values of levofloxacin after administration of a single 500 mg dose of levofloxacin hemihydrate (Day 1) and a 500 mg dose of levofloxacin hemihydrate at steady-state (Day 10) were 5.19 and 5.72 μg/mL, respectively. The average steady-state plasma levofloxacin concentration during the dosing interval was 1.98 μg/mL (Table 2). The range of the morning pre-dose mean plasma concentrations (C_{min}) from Days 6 to 10 was 0.467 to 0.515 μg/mL. These values indicate that some residual drug was present throughout the dosing interval. Mean AUC_{0-24} values on Days 1 and 10 were 42.6 and 47.5 μg.h/mL, respectively; mean $AUC_{0-\infty}$ values were 47.7 and 53.6 μg•hr/mL, respectively (Table 3). The steady-state volume of distribution was approximately 100 L. On Days 1 and 10, the mean effective elimination half-lives were 6.5 hours and 6.8 hours, respectively.
The difference between single dose $AUC_{0-\infty}$ values and steady state AUC_{0-24} values was not significant (p=0.87). Systemic accumulation of levofloxacin, based on the steady state to single dose ratio of AUC_{0-24}, was marginal but statistically significant (mean accumulation = 11%, p=0.0012).
After single and multiple once-daily 500 mg administrations of levofloxacin hemihydrate, mean (±s.d.) peak urinary concentrations were 751±453 and 552±189 μg/mL, respectively. Corresponding mean urinary recoveries of intact levofloxacin were 64±8% and 67±14% (Table 4). Mean renal clearance values were 7.53±1.80 L/hr following a single dose and 6.97±1.85 L/hr at steady state (p=0.42). Renal clearance accounted for approximately 70% of total plasma clearance.

CONCLUSION: With once-daily oral administration, systemic accumulation was marginal and is approximately 11%. Based on the observed effective t½ values, an accumulation of approximately 9% would occur with once-daily administration. The C_{min} values indicated that some residual drug was present throughout the dosing interval (range: 0.467 to 0.515 µg/mL). Levofloxacin was eliminated primarily by renal excretion at a rate similar to creatinine clearance.

Table 1 : Subject Listing of Baseline Demographic Data (K90-077)

Subject #	Gender	Race	Age (yr)	Weight (lb)
	Male	Cauc.	27	155
	Male	Cauc.	30	194
	Male	Black	26	153
	Male	Cauc.	22	151
	Male	Cauc.	24	166
	Male	Hisp.	19	157
	Male	Cauc.	28	188
	Male	Cauc.	47	190
	Male	Cauc.	22	158
	Male	Cauc.	21	146
	Male	Cauc.	48	212
	Male	Black	35	~~149~~
	Male	Cauc.	20	150
	Male	Cauc.	28	163
	Male	Cauc.	23	178
	Male	Black	22	143
	Male	Cauc.	34	175
	Male	Cauc.	18	137
	Male	Cauc.	22	162
	Male	Cauc.	50	170

Table 2

Individual and Mean Levofloxacin Pharmacokinetic Parameters In Ten Healthy Male Volunteers after Single (Day 1) and Multiple (Day 10) Once-Daily 500 mg Oral Doses of Levofloxacin Hemihydrate Administration (K90-077)

	Day 1						Day 10					
Subject	AUC 0-24H ug.h/mL	AUC 0-inf. ug.h/mL	MRTb h	Effective T1/2 h	CL/F L/h	VDss/F L	AUC 0-24H ug.h/mL	AUC 0-inf. ug.h/mL	MRTb h	Effective T1/2 h	CL/F L/h	VDss/F L
MEAN	42.6	47.7	9.3	6.5	10.5	96.7	47.5	53.6	9.8	6.8	10.5	102
S.D.	6.00	7.59	1.0	0.7	1.75	11.9	6.66	8.59	1.9	1.3	1.47	21.8
C.V.,%	14.1	15.9	11	11	17	12	14	16	19	19	14	21
MAX	50.0	57.2	10.8	7.5	13.1	117	56.4	64.2	14.8	10.3	12.9	151
MIN	35.1	37.3	7.0	4.9	8.54	83.0	37.9	42.0	7.8	5.4	8.7	83.1

Parameters were estimated by model-independent method.

Table 3

Individual and Mean Levofloxacin Pharmacokinetic Parameters in Ten Healthy Male Volunteers After Single (Day 1) and Multiple (Day 10) Once-Daily 500 mg Oral Dosing of Levofloxacin Hemihydrate Administration (K90-077)

Subject	Cmax (µg/mL)		Tmax (hr)		Cmin (µg/mL)[a]		CpssFluctuation	
							ug/mL	Index
	Day 1	Day 10	Day 1	Day 10	Day 1	Day 10	Day 10	
MEAN	5.19	5.72	1.3	1.1	0.459	0.511	1.98	2.6
S.D.	1.21	1.40	0.5	0.4	0.143	0.166	0.28	0.7
C.V.,%	23	24	43	35	31	32	14	27
MAX	7.03	7.97	2.0	2.0	0.691	0.891	2.35	4.3
MIN	3.61	3.77	0.5	0.5	0.243	0.313	1.58	1.8

a.Cmin values were taken at 24-hours.

Table 4

Individual and Mean Urinary Recovery (Au%) and Renal Clearance (CLr) Data Following Single and Multiple Once-Daily 500 mg Oral Doses of Levofloxacin Hemihydrate (K90-077)

	SINGLE-DOSE (DAY 1)			STEADY-STATE (DAY 10)		
Subject	AU% (0-24hr)	Cmax ug/mL	CLr L/h	AU% (0-24hr)	Cmax ug/mL	CLr L/h
MEAN	64	751	7.53	67	552	6.97
S.D.	8	453	1.80	14	189	1.85
C.V.,%	13	60	24	21	34	27
MAX	79	1834	10.6	80	777	10.3
MIN	45	211	4.71	42	266	3.90

Figure 1: Mean Plasma Levofloxacin Concentration versus Time Data Following Single (Day 1) and Multiple (Day 10) Once-Daily 500 mg Oral Doses of Levofloxacin Hemihydrate to Ten Healthy Volunteers (K90-077)

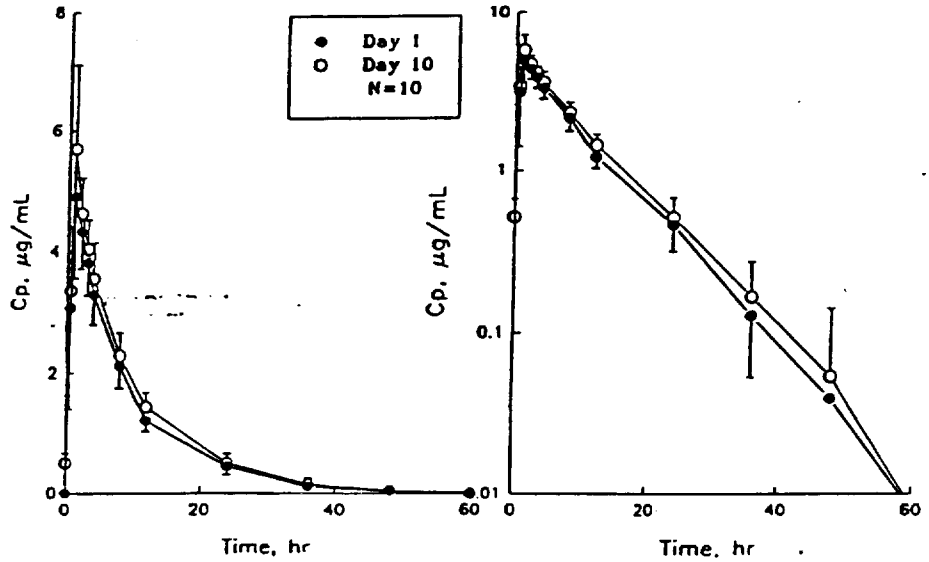
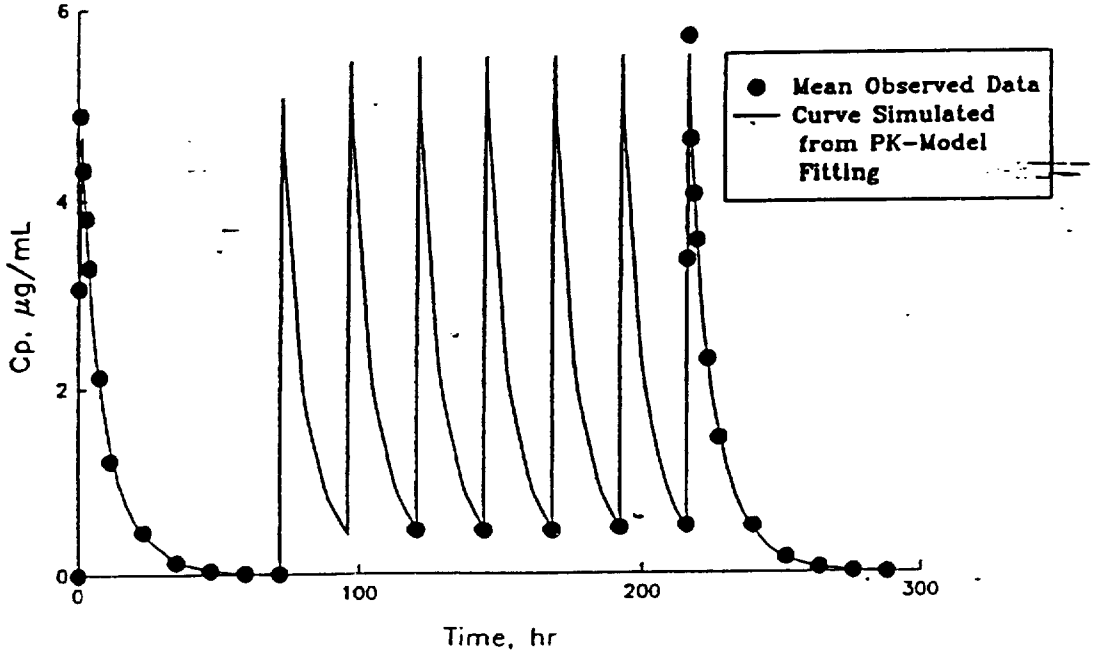


Figure 2: Mean Observed and Predicted Plasma Concentrations of Levofloxacin after Single (Day 1) and Multiple Once-Daily 500 mg Oral Doses of Levofloxacin Hemihydrate to Ten Healthy Subjects (K90-077)



STUDY TITLE: A DOUBLE-BLIND CROSSOVER STUDY OF THE SAFETY AND PHARMACOKINETICS OF MULTIPLE DOSES OF LEVOFLOXACIN 500 MG Q12H VS PLACEBO IN NORMAL SUBJECTS, STUDY # K90-014. **VOLUME 1.64.**

INVESTIGATOR & LOCATION:

OBJECTIVE: To evaluate the safety and pharmacokinetic profiles of levofloxacin under multiple twice daily oral dosing.

STUDY DESIGN: The study was a randomized, double-blind, placebo-controlled, crossover design. Subjects received either levofloxacin (as levofloxacin hemihydrate, 500 mg per dose, equivalent to 500 x 0.976 mg of anhydrous levofloxacin) or placebo during each of the two treatment periods. For Treatment Period I, a single oral dose was given to each subject on Day 1 with a washout period on Days 2-3 and followed by the twice daily oral administrations from Days 4 to 9; a final single oral dose was then administered on Day 10. Following a two day washout period, the alternate treatment was given in the same pattern for Treatment Period II. Dosing on Days 1, 10, 13, and 22 was conducted with subjects in a fasted state. All doses were administered with eight ounces of water. Subjects were confined to the study site from no less than 12 hours prior to administration of the first dose through completion of plasma and urine sampling on Day 25.

FORMULATION: Levofloxacin (RWJ-25213-000) was provided as white to pale yellowish-white, film-coated tablets containing 100 mg of levofloxacin hemihydrate (FD 25213-B-22, equivalent to 97.6 mg of anhydrous levofloxacin) by The R.W. Johnson Pharmaceutical Research Institute. Identically appearing placebo was also obtained from The R.W. Johnson Pharmaceutical Research Institute (FD 25213-BX-22).

DEMOGRAPHICS: Twenty healthy male subjects participated in this study (Table 1).

SAMPLING: Venous blood samples (5 mL) were obtained from each subject according to the following time schedule :

Day	Time in Hours	Day	Time in Hours	Day	Time in Hours
1,13	0	4,16	72	10,2	216
	0.5	6,18	120	2	216.5
	1	7,19	144		217
	2	8,20	168		218
	3	9,21	192		219
	4				220
	8				224
	12				228
2,14	24				240
	36			11,2	252
3,15	48			3	264
	60				276
				12,2	288
				4	
				13,2	
				5	

Urine was collected quantitatively from eight hours prior to the first dose of each treatment period (Days 1 and 13) and at the following time intervals following that dose: 0-2, 2-4, 4-8, 8-12, 12-24, 24-36, and 36-48 hours. Urine was also collected quantitatively after the dose on Days 10 and 22 at the following time intervals post-dose: 0-2, 2-4, 4-8, 8-24, 24-36, and 36-48 hours.
Fecal samples were also collected *in toto* from all subjects through 48 hours post-dose on Days 1, 10, 13, and 22. Each sample was weighed, labeled, and frozen. These samples were only to be assayed if plasma and urine data were inconsistent with the dose administered.

ANALYTICAL METHOD: Plasma and urine samples were assayed for levofloxacin according to validated HPLC procedures at The R.W. Johnson Pharmaceutical Research Institute.

The range of detection in plasma was μg/mL whereas the corresponding range in urine was μg/mL.

DATA ANALYSIS: Levofloxacin absorption and disposition following a single dose and at steady state were evaluated. Steady state conditions on Day 10 were evaluated by determining differences between pre-dose (216 hours) levofloxacin concentrations and post-dose concentrations (228 hours) by subject. Peak plasma concentrations (C_{max}), time to reach C_{max} (T_{max}), and trough concentrations (C_{min}) on Days 1 (single dose) and 10 (steady state) were determined by inspection. The area under the plasma concentration time curve (AUC), the mean residence time (MRT), the effective half-life (T½), the total body clearance (CL_p/F), and the steady-state volume of distribution (VD_{ss}/F) of levofloxacin after a single dose and at steady-state were also estimated.
The plasma concentration data were subsequently fit to a function which described a two compartment system with first-order input and elimination from the central compartment. Data fitting was performed with PCNONLIN (version 4.0) and model selection was based on the Akaike Information Criterion (AIC).
The percent of dose recovered in urine (Au%) and the renal clearance (Cl_r) following a single dose and at steady-state were determined.
Since the ANOVA results confirmed that there were no sequence effects, the pharmacokinetic parameters of levofloxacin for all 20 subjects were grouped for statistical analysis. Paired t-tests were used to compare the pharmacokinetic parameter values between Days 1 (single dose) and 10 (steady state) using the software package, MINITAB. Parameter values were deemed significantly different at α=0.05.

RESULTS: Mean plasma levofloxacin concentrations following single and multiple (steady-state) doses are plotted in Figure 1. Individual and mean pharmacokinetic results are presented in Tables 2 and 3. Day 1 refers to the single levofloxacin dose and Day 10 refers to the 13th levofloxacin dose following multiple Q12H administrations in all subjects. Plasma C_{min} (pre-dose) data indicate that by two days after initiation of the twice daily administration regimen steady-state had been achieved.

Based on C_{min}, the accumulation ratio of levofloxacin following twice daily administration was approximately 2.1 indicating a two-fold increase in plasma levofloxacin concentrations between single dose and steady-state conditions. Based on AUC_{0-12} the accumulation ratio of levofloxacin following twice daily administration was approximately 1.8; again, this suggested a two-fold increase in plasma concentrations between single dose and steady-state conditions. Results of the statistical evaluation on pharmacokinetic parameters are presented in Table 4. Only MRT and T½ possessed significant sequence effects (p=0.024).

Similar values of AUC, MRT, $T_{½}$, CL_p/F, and VD_{ss}/F were obtained from the model-dependent and model-independent methods. Renal clearance accounted for approximately 70% of total plasma clearance.

CONCLUSION: The pharmacokinetic profile of oral levofloxacin following twice daily administration suggested a marginal trend towards nonlinear disposition. Although the mean parameter values on each Study Day were only slightly different, the differences within a given subject ($Value_{Day\ 10}$ - $Value_{Day\ 1}$) maintained a consistent trend. As an example, the mean CL/F values on Study Days 1 and 10 differed by only 15.6%, however, the CL/F for every subject was less on Day 10 than Day 1 (Table 3).

Table 1: Summary of Baseline Demographic Characteristics (K90-014)

	Levofloxacin/Placebooo	Placebo/Levofloxacin
Total Number of	10	10
Sex		
Male	10	10
Female	0	0
Race		
White	7	5
Black	1	2
Hispanic	1	2
Other	1	1
Age (years)		
18 - 25	3	3
26 - 35	4	0
36 - 45	3	5
46 - 55	0	2
N	10	10
Mean	30.7	37.7
Standard Deviation	6.84	11.31
Minimum	23	22
Maximum	41	53

Table 2

Individual and Mean Pharmacokinetic Parameter Values of Levofloxacin in Twenty Healthy Male Volunteers Following Single (Day 1) and Multiple (Days 4 to 10) 500 mg Q12H Oral Doses of Levofloxacin Hemihydrate (K90-014)

Subject	Cmax (µg/mL)		Tmax (hr)		a Cmin (µg/mL)		Cpss ug/mL	Fluctuation Index
	Day 1	Day 10	Day 1	Day 10	Day 1	Day 10	Day 10	
MEAN	5.21	7.80	1.2	1.3	1.41	2.97	4.91	1.02
S.D.	0.91	1.07	0.6	0.6	0.31	0.87	0.98	0.26
C.V.,%	17	14	49	44	22	29	20	26
MAX	6.79	9.56	3.0	3.0	1.95	5.29	7.30	1.60
MIN	3.86	5.02	0.5	1.0	0.86	1.52	2.99	0.53

a. Cmin values were taken at 12 hours.

Table 3

Individual and Mean Pharmacokinetic Parameter Values of Levofloxacin in Twenty Healthy Male Volunteers Following Single (Day 1) and Multiple (Days 4 to 10) 500 mg Q12H Oral Doses of Levofloxacin Hemihydrate (K90-014)

	Day 1						Day 10					
Subject	AUC 0-12H ug.h/mL	AUC 0-inf. ug.h/mL	Effective MRTb h	T1/2 h	CL/F L/h	VDss/F L	AUC 0-12H ug.h/mL	AUC 0-inf. ug.h/mL	Effective MRTb h	T1/2 h	CL/F L/h	VDss/F L
MEAN	32.5	49.6	9.4	6.5	10.2	93.6	59.0	97.6	12.1	8.4	8.61	102
S.D.	4.59	8.80	1.5	1.0	1.93	14.2	11.8	25.4	1.8	1.3	1.82	16.3
C.V.,%	14	18	16	16	19	15	20	26	15	15	21	16
MAX	39.4	66.3	12.0	8.3	14.5	127	87.5	161	15.1	10.5	13.6	135
MIN	23.3	33.6	6.39	4.43	7.36	71.8	35.9	51.2	8.1	5.6	5.57	83.0

Parameters were estimated by model-independent method (moment analysis, Appendix 5).

Table 4.: Analysis of Variance of Pharmacokinetic Parameters

Pharmacokinetic Parameter	P Value: Sequence Effect	P Value: Day 1 vs Day 10[1]
C_{max}	0.685	< 0.001
T_{max}	0.805	0.37
C_{min}	0.129	< 0.001
AUC_{0-12}	0.405	[2]
$AUC_{0-\infty}$	0.165	[2]
MRT_b	0.024	< 0.001
$T½$	0.024	< 0.001
CL/F	0.145	< 0.001
VD_{ss}/F	0.659	< 0.001
AU%(0-8h)	0.973	
AU%(0-24h)	0.588	
CU_{max}	0.798	
CL_r	0.480	0.004

[1] Day 1 (Single-dose) vs. Day 10 (steady-state after multiple-dose)
[2] P value for $AUC_{0-\infty}$(Day 1) vs. AUC_{0-12}(Day 10) is < 0.001

Table 5

Percent Dose Recovered in Urine (AU%) and Renal Clearance (CLr) of Levofloxacin in Twenty Healthy Male Volunteers Following Single (Day 1) and Multiple (Day 10) 500 mg Q12H Oral Doses of Levofloxacin Hemihydrate (K90-014)

Subject	SINGLE-DOSE (DAY 1)				STEADY-STATE (DAY 10)			
	AU%		Cmax	CLr	AU%		Cmax	CLr
	(0-8hr)	(0-24hr)	ug/mL	L/h	(0-8hr)	(0-24hr)	ug/mL	L/h
MEAN	37	63	588	7.24	55	107	767	6.24
S.D.	8	11	241	2.11	6	18	221	1.53
C.V.,%	21	17	41	29	10	17	29	25
MAX	46	74	994	11.9	66	141	1054	10.0
MIN	15	27	198	2.98	46	80	292	3.71

Fig 1: Mean (±s.d.) Plasma Levofloxacin Concentration versus Time Data Following Single (Day 1) and Multiple (Days 4 to 10) 500 mg Q12H Oral Doses of Levofloxacin Hemihydrate to Twenty Healthy Males (K90-014)

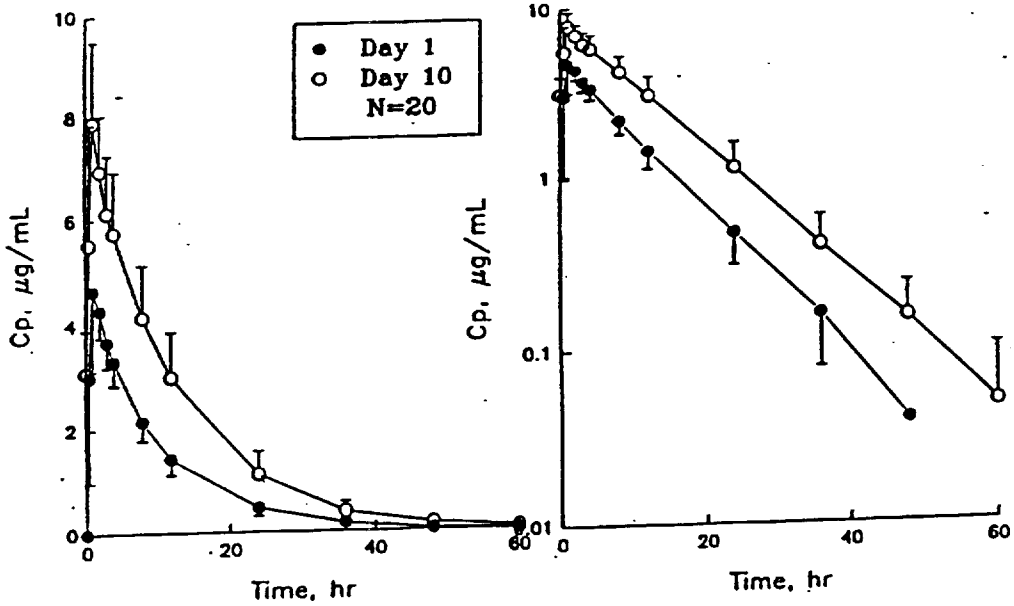
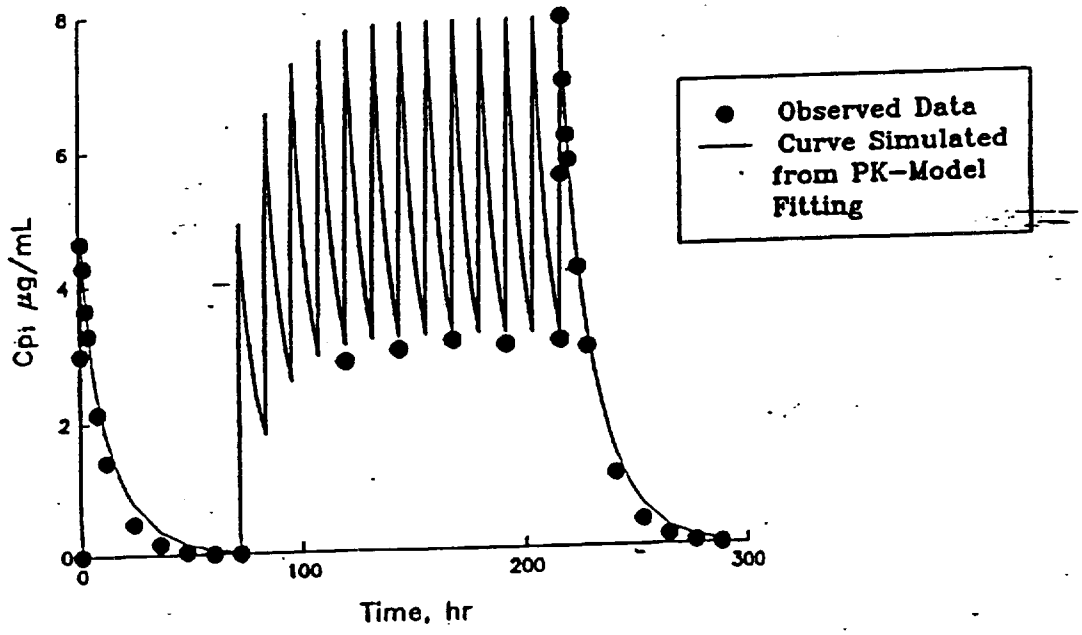


Fig 2: Observed Mean and Predicted Plasma Concentration of Levofloxacin Following Single (Day 1) and Multiple (Days 4 to 10) 500 mg Q12H Oral Doses of Levofloxacin Hemihydrate to Twenty Healthy Males (K90-014)



Title: **Safety and Pharmacokinetics of DR-3355 Administered Once Daily for Seven Days to Healthy Human Volunteers**

Protocol Number: 91/17 VOLUME 1.68.

Investigator and Location:

Study Design: This is a study designed to compare the pharmacokinetics and safety of three doses of DR-3355 following once daily oral administration for 7 days. Subjects received 150 mg, 300 mg and 600 mg once daily on Days 1-7 of Week 1, Week 4 and Week 7, respectively, with pharmacokinetic analysis on Days 1 and 7 of each of the three weeks.

Demographics: A total of 13 healthy male volunteers (aged 19-39, mean 25.6, years) participated in the study.

Sampling: Blood samples were taken at 0, 0.25, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12 and 24 hours on Days 1 and 7 and, on Day 7 only, at 36 and 48 hours after dosing.

Analytical Method:: DR-3355 concentrations in plasma and urine were determined by

DR-3355 levels in plasma were determined using HPLC with fluorescence detection. The detection limit of the HPLC method was 0.01 µg/mL for plasma and 1.0 µg/mL for urine.

Results: Plasma data were used to fit exponential curves and the pharmacokinetic parameters of terminal elimination half-life, terminal elimination rate constant, distribution half-life, absorption half-life, absorption rate constant, mean residence time, volume of distribution and total clearance were extracted from the fitted curves. C_{max} (maximum plasma concentration), C_{min} (concentration at time 0 hours, pre-dose), T_{max} and AUC represent the observed values for individual subjects, and were not derived from fitted curves.

Conclusion: There were dose linear relationships between dose and C_{min}, C_{max}, $AUC_{(0\text{-}24\ h)}$, $AUC_{(0\text{-}48\ h)}$, mean plasma level at steady state, distribution half-life, and volume of distribution on Days 1 and 7.

The mean values of the pharmacokinetic parameters on Day 1 and Day 7 are presented below.

	Cmax (µg/mL)			Tmax (h)			AUC (0-24) (µg.h/mL)		
	Day 1	Day 7	P Value	Day 1	Day 7	P Value	Day 1	Day 7	P Value
150 mg od	2.21	2.31	NS	0.75	0.86	NS	10.07	10.85	NS
300 mg od	4.25	4.17	NS	1.04	1.08	NS	21.65	25.10	0.001
600 mg od	8.10	9.84	NS	1.00	0.91	NS	45.66	52.58	0.03

NS - not significant

The mean accumulation ratio (Cmax Day 7/Cmax Day 1) was 1.04 for 150 mg once daily dosing, 0.99 for 300 mg once daily dosing and 1.21 for 600mg once daily dosing.

	Mean residence time (hours)			Total clearance (0-24 h) (mL/min)		
	Day 1	Day 7	P Value	Day 1	Day 7	P Value
150 mg od	8.38	8.55	NS	232.44	223.40	NS
300 mg od	8.59	9.17	0.04	216.30	186.42	<0.001
600 mg od	9.00	8.97	NS	208.98	178.80	0.03

The Day 7 (0-48 h) mean pharmacokinetic parameters are presented in the following tables:

	Cmin (µg/mL)	Cmax (µg/mL)	Tmax (h)	AUC (0-48) (µg.h/mL)	Mean plasma level at steady state (µg/mL)	Distribution half-life (alpha) (h)
150 mg od	0.11	2.31	0.86	11.84	0.49	0.77
300 mg od	0.22	4.17	1.08	27.38	1.14	0.87
600 mg od	0.59	9.84	0.91	57.40	2.39	0.44

	Terminal Elim half-life (h)	Elim rate constant (h^{-1})	Abs half-life (h)	Abs rate constant (h^{-1})	Mean residence time (h)	VD (L/kg)	Total clearance (mL/min)
150 mg od	7.41	0.094	0.26	3.36	9.13	1.85	218.34
300 mg od	7.33	0.095	0.24	3.59	9.54	1.56	183.18
600 mg od	7.07	0.099	0.20	3.72	9.21	1.46	176.32

The distribution constants between the peripheral and central compartment (K_{21}) and the central and peripheral compartment (K_{12}) and the volumes of distribution of the central and peripheral compartments were also calculated from data from the fitted mean curves for Day 7.

	K_{21} (h^{-1})	K_{12} (h^{-1})	V_1 (L)	V_2 (L)
150 mg od	0.352	0.452	44.78	57.51
300 mg od	0.325	0.448	33.85	46.66
600 mg od	0.359	0.970	18.92	51.05

Figure 1: Mean Plasma Concentrations
150 mg od

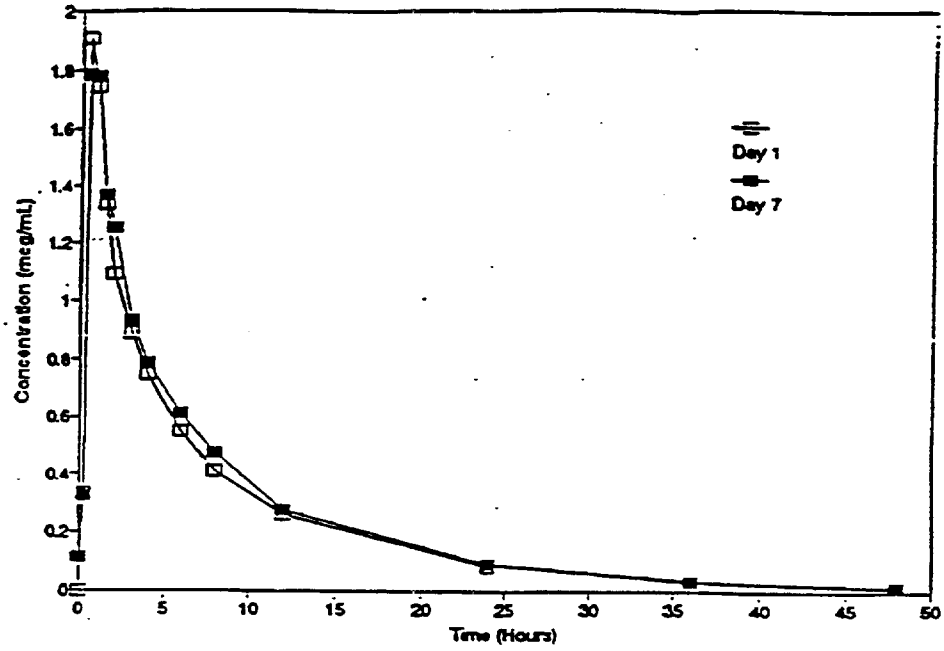


Figure 2: Mean Plasma Concentrations
300 mg od

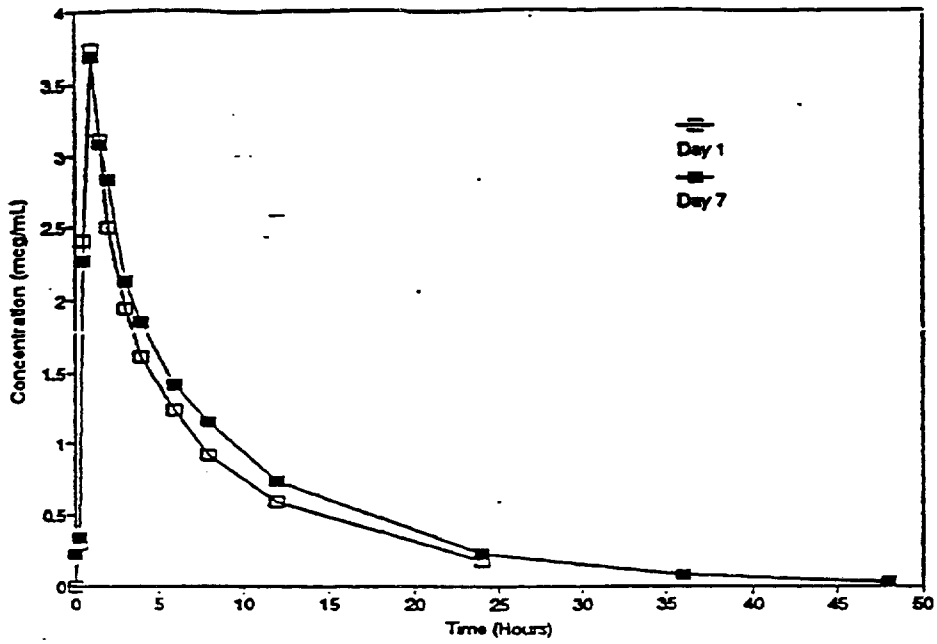


Figure 3: Mean Plasma Concentrations
600 mg od

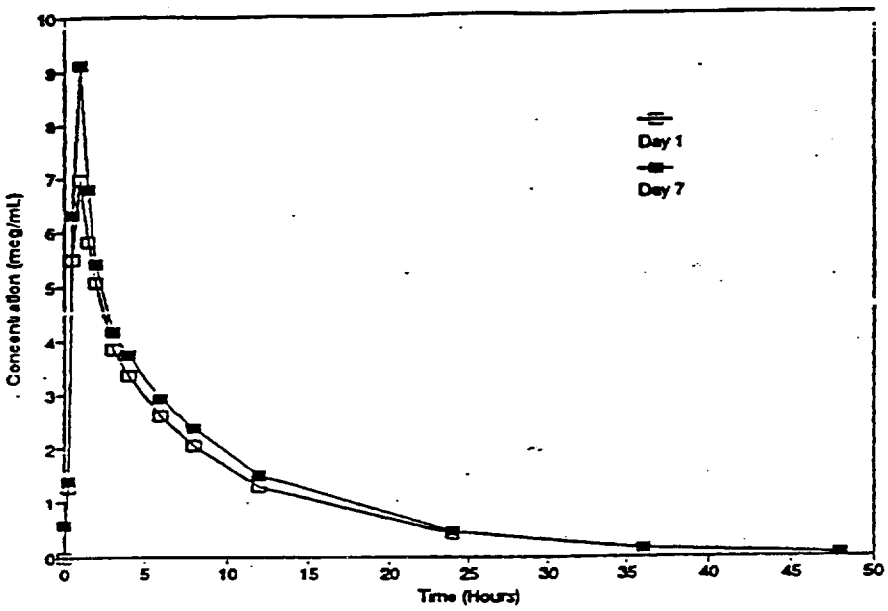
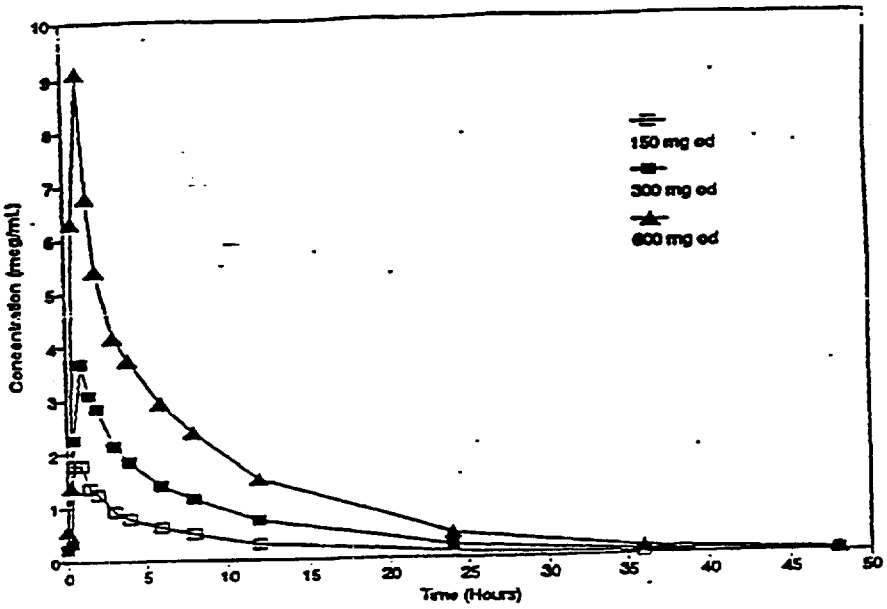
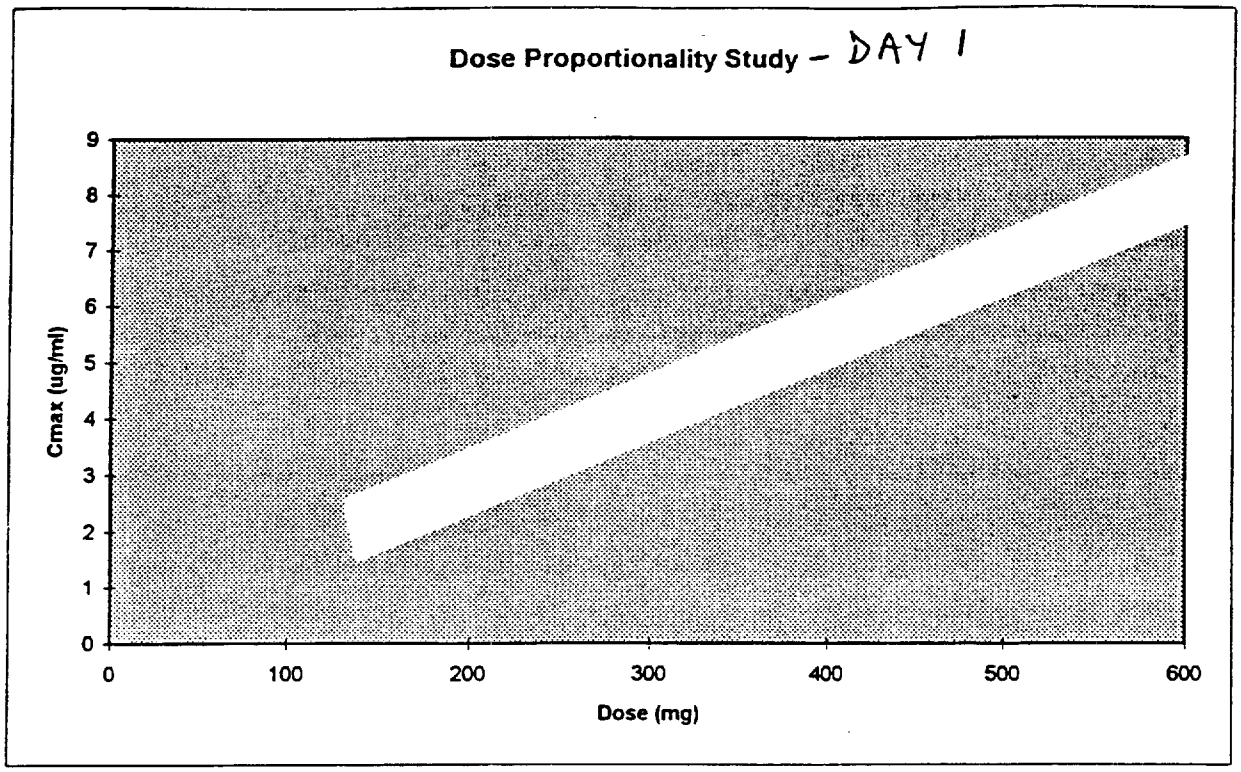
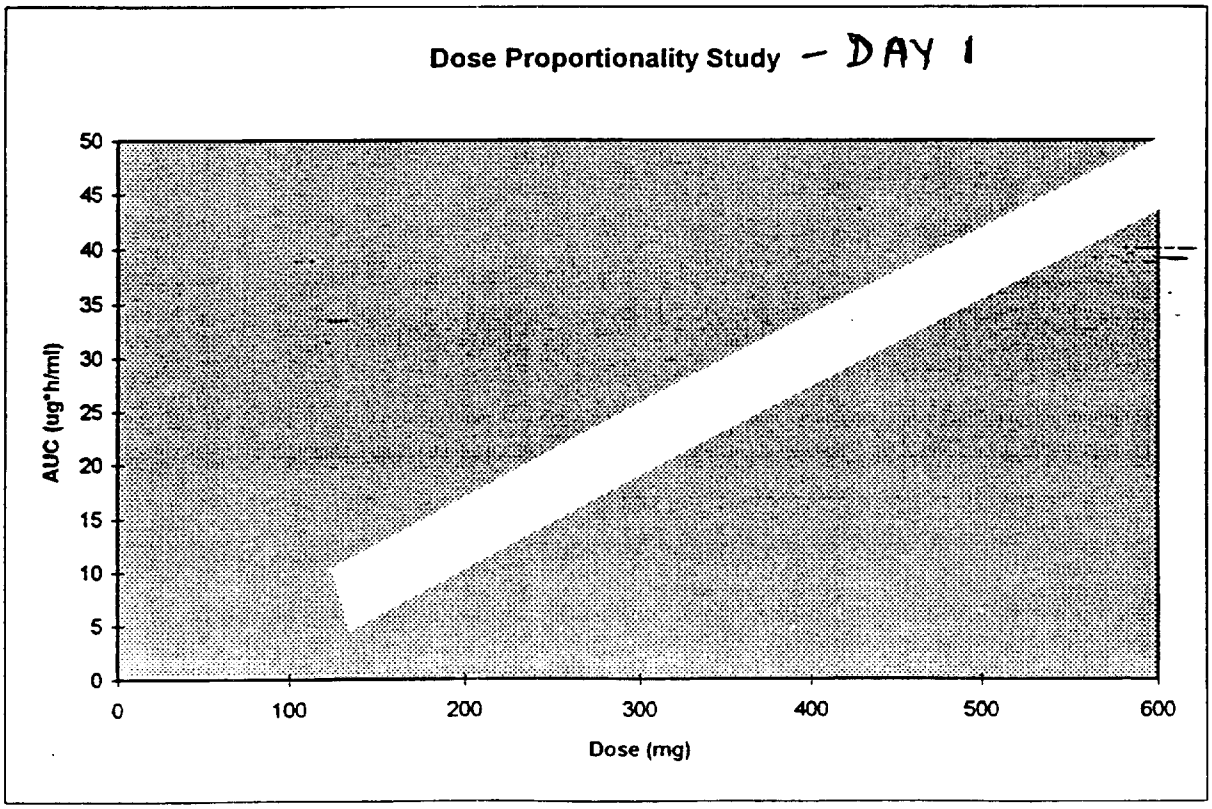


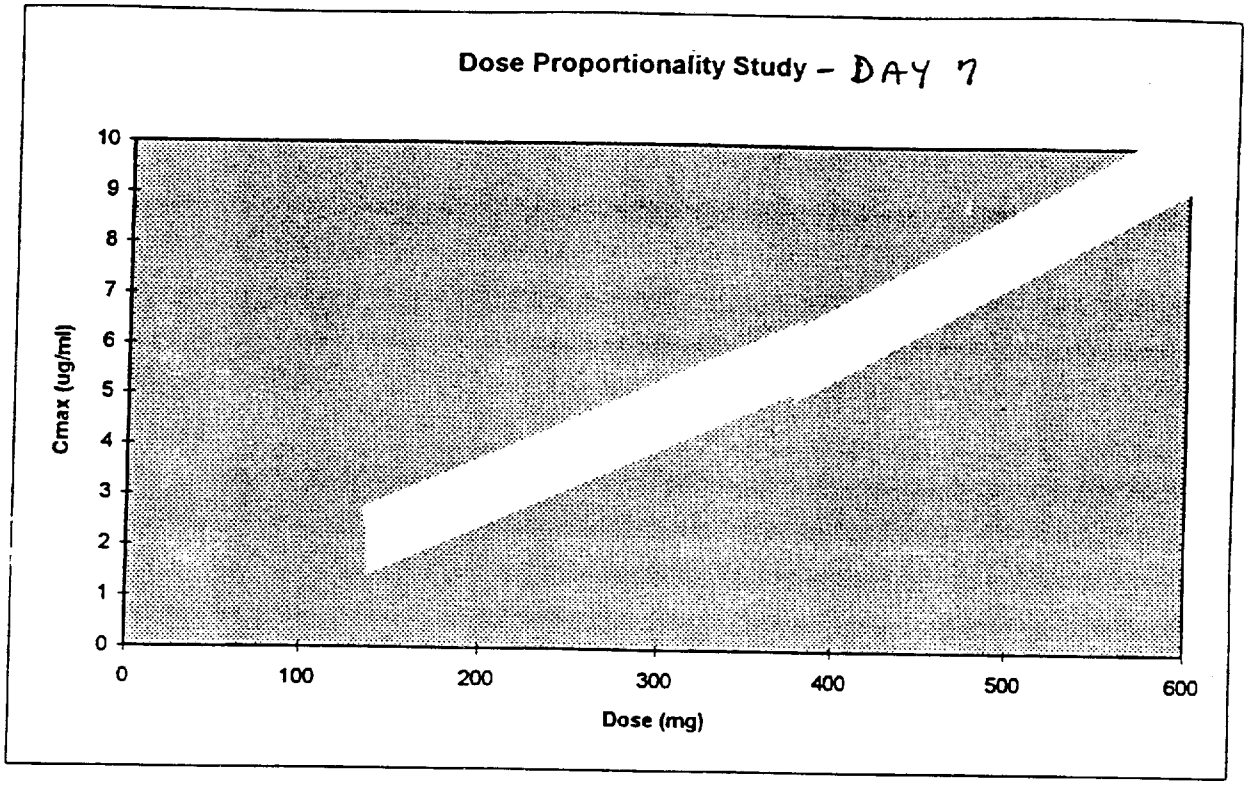
Figure 4: Mean Plasma Concentrations
Day 7

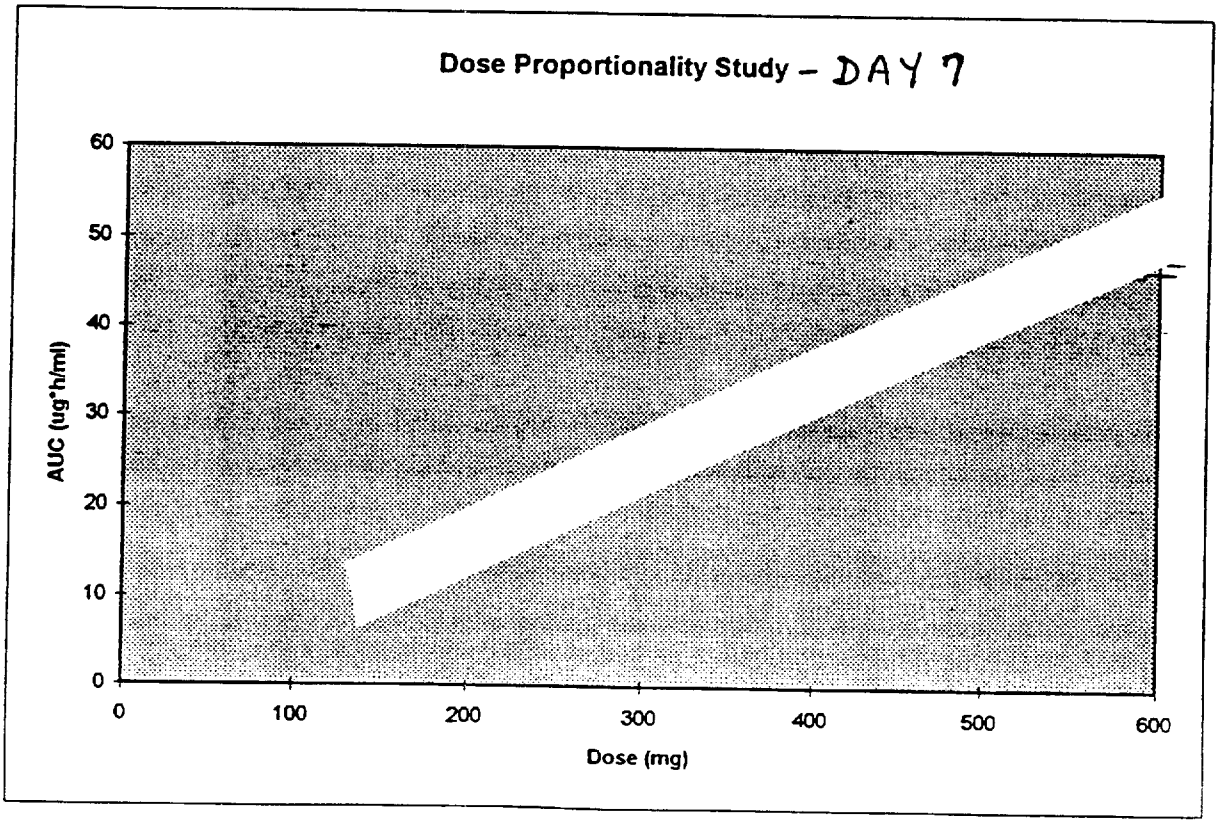


Dose proportionality study






Dose Proportionality Study – DAY 7
Cmax (ug/ml)
0
1
2
3
4
5
6
7
8
9
10
0
100
200
300
400
500
600
Dose (mg)


Dose Proportionality Study – DAY 7
AUC (ug*h/ml)
0
10
20
30
40
50
60
0
100
200
300
400
500
600
Dose (mg)

TITLE OF STUDY: DOUBLE-BLIND EVALUATION OF THE SAFETY AND PHARMACOKINETICS OF ORAL DOSES OF LEVOFLOXACIN 750 MG AND 1 G ADMINISTERED DAILY FOR SEVEN DAYS COMPARED TO PLACEBO IN HEALTHY SUBJECTS. (PROTOCOL LOFBO-PHI0-093) VOLUME 1.65 - 1.66.

PRINCIPAL INVESTIGATOR:

OBJECTIVES: The objective of this study was to evaluate the safety and pharmacokinetics of levofloxacin in healthy subjects after single and multiple once-daily oral doses of 750 mg and 1 g of levofloxacin given for 7 days.

STUDY DESIGN: Sixteen healthy male subjects were enrolled in this Phase I, randomized, double-blind, placebo-controlled, parallel group study. Subjects were randomly assigned to the levofloxacin treatment group (10 subjects) or the placebo group (six subjects). The study consisted of two periods. In Period 1, subjects received a 750-mg dose of levofloxacin or placebo on Day 1, followed by a once-daily 750-mg dosing of levofloxacin or placebo on Days 4 to 10. In Period 2, 3 days after the last dose of levofloxacin or placebo in Period 1, subjects received a 1-g dose of levofloxacin or placebo on Day 1 (Day 14 of the study), followed by once-daily 1-g dosing of levofloxacin or placebo on Days 4 to 10 (Days 17 to 23 of the study). The 750-mg dose consisted of one 500-mg (FD 25213-097-G-22, Batch No. 5324) and two 125-mg (FD 25213-097-H-22, Batch No. R5520) levofloxacin tablets. For the 1-g dose, levofloxacin was administered as two 500-mg (FD 25213-097-G-22, Batch No. 5324) levofloxacin tablets. All doses of study drug were administered with 240 mL of water under fasting conditions.

SAMPLING: In each treatment period, venous blood samples (5-mL) were drawn from each subject immediately prior to dosing on Days 1, 5, 6, 7, 8, 9, and 10 and at 0.5, 1, 1.5, 2, 3, 4, 8, 12, 24, 36, 48, 60, and 72 hours after dosing on Days 1 and 10; urine was collected quantitatively beginning 8 hours prior to the first dose on Day 1 and during the following time periods after dosing on Days 1 and 10: 0-2, 2-4, 4-8, 8-12, 12-24, 24-48, and 48-72 hours.

ANALYTICAL METHOD: Plasma and urine samples were assayed for levofloxacin according to a validated HPLC procedure at

DEMOGRAPHICS: The demographic and baseline characteristics for the subjects in the levofloxacin treatment group and the placebo group are presented in Table 1.

TABLE 1: Demographic and Baseline Characteristics

(All Subjects Enrolled in Study LOFBO-PHI0-093)

	Levofloxacin (N=10)	Placebo (N=6)	Total (N=16)
Race			
Caucasian	10	5	15
Hispanic	0	1	1
Age			
Mean ± SD	26.3 ± 6.0	35.2 ± 10.5	29.6 ± 8.8
Range			
Weight (lbs)			
Mean ± SD	170.8 ± 30.7	176.2 ± 29.9	172.8 ± 29.5
Range			
Height (in)			
Mean ± SD	70.6 ± 2.9	70.6 ± 3.4	70.6 ± 3.0
Range			

RESULTS: Steady-state plasma concentrations of levofloxacin were attained on Day 10 of both treatment periods. The mean (± SD) levofloxacin pharmacokinetic parameter values determined from the first and last doses of each treatment period are summarized in Table 2.

Levofloxacin was rapidly absorbed and extensively distributed after 750-mg and 1-g single oral doses. Approximately 75% of the dose was recovered in 72-h urine collection. Ratios of the mean levofloxacin pharmacokinetic parameter values for the two dose levels are summarized in Table 4. Based on the mean ratio of the disposition parameters and the confidence intervals, the pharmacokinetics of levofloxacin were consistent at the two dose levels.

On once-daily multiple dosing, plasma concentrations of levofloxacin increased. The degree of accumulation was similar for the two dose levels. The mean ± SD ratios of C_{max} (Day 10/Day 1) were 1.22 ± 0.25 and 1.34 ± 0.16 for the 750-mg and 1-g dose, respectively. The corresponding values for AUC were 1.27 ± 0.11 and 1.24 ± 0.06. As observed with the single dose data, the pharmacokinetics of levofloxacin were consistent at steady state for the two dose levels.

CONCLUSION: The pharmacokinetics of levofloxacin in healthy subjects following 750-mg and 1-g single and daily multiple oral doses appear to be similar based on comparable clearance, volume of distribution and plasma elimination half-life estimates and the urinary excretion of unchanged drug. The study evaluated single and multiple once-daily dose pharmacokinetics of levofloxacin at doses higher than the therapeutic dose of 500 mg. Pharmacokinetics were comparable for 750-mg and 1-g doses, both under single and multiple once-daily dose conditions. The pharmacokinetics at the higher doses are also comparable to those at 500-mg dose level (Table 5).

TABLE 2: Summary of Levofloxacin Pharmacokinetic Parameter Estimates[a]

(Study LOFBO-PHI0-093)

	Levofloxacin 750 mg (N=10)		Levofloxacin 1 g (N=10)	
	Day 1 (single dose)	Day 10 (steady state)	Day 1 (single dose)	Day 10 (steady state)
C_{max}, µg/mL	7.13 ± 1.44	8.60 ± 1.86	8.85 ± 1.86	11.8 ± 2.52
	(6.24-8.02)	(7.45-9.76)	(7.70-10.0)	(10.2-13.4)
T_{max}, h	1.9 ± 0.7	1.4 ± 0.5	1.7 ± 0.4	1.7 ± 0.6
	(1.5-2.3)	(1.1-1.7)	(1.4-1.9)	(1.3-2.1)
AUC[b], µg·h/mL	82.2 ± 14.3	90.7 ± 17.6	111 ± 20.8	118 ± 18.9
	(73.3-91.0)	(79.9-102)	(98.1-124)	(106 -130)
CL/F, mL/min	157 ± 27.8	143 ± 29.1	156 ± 33.5	146 ± 28.8
	(139-174)	(125-161)	(135-177)	(128 -163)
Cu,max[c], µg/mL	403 ± 249	822 ± 437	667 ± 286	992 ± 377
	(249-558)	(552-1093)	(490-844)	(758-1226)
Ae[d], % dose	75 ± 6	79 ± 5 (94 ± 8[e])	73 ± 8	71 ± 5 (87 ± 9[e])
	(71-78)	(75-82[f])	(68-78)	(68-74[f])
CL_R, mL/min	118 ± 27.8	116 ± 28.1	113 ± 25.8	106 ± 22.9
	(101-135)	(98.4-133)	(97-129)	(91.4-120)
ke, h^{-1}	0.093 ± 0.016	0.081 ± 0.014	0.091 ± 0.017	0.083 ± 0.022
	(0.083-0.103)	(0.072-0.090)	(0.080-0.102)	(0.070-0.097)
$t_{½}$, h	7.7 ± 1.3	8.8 ± 1.5	7.9 ± 1.5	8.9 ± 2.5
	(6.8-8.5)	(7.8-9.7)	(6.9-8.8)	(7.3-10.5)
Vd/F, L	90.3 ± 14.0	99.5 ± 15.8	96.4 ± 21.9	105 ± 26.5
	(81.6-99.0)	(89.7-109)	(82.8-110)	(88.5-121)

[a] Data are presented as mean ± SD (lower to upper limit of 95% confidence interval), N=10

[b] AUC = $_{0-}$ for Day 1 (single dose) and 0-24 h for Day 10 (steady-state AUC for the 24-h dosing interval)

[c] Peak urinary levofloxacin concentration

[d] Ae = 0-72 h for Day 1 (single dose) and 0-24 h for Day 10 (steady-state AUC for the 24-h dosing interval)

[e] Ae (0-72 h)

[f] Ae (0-24 h)

TABLE 3: Pharmacokinetic Profiles of Levofloxacin: Single Doses (488-1000 mg)

Study	Dose (mg)	T_{max} (h)	C_{max} (µg/mL)	Mean C_{max} (Per 100-mg dose)	$AUC_{0-\infty}$ (µg·h/mL)	Mean $AUC_{0-\infty}$ (Per 100-mg dose)
LOFBO-PHI0-093[a]	750 mg	1.9 ± 0.7	7.13 ± 1.44	0.95	82.2 ± 14.3	11.0
LOFBO-PHI0-093	1000 mg	1.7 ± 0.4	8.85 ± 1.86	0.89	111 ± 20.8	11.1
K90-077[b]	488 mg	1.3 ± 0.5	5.19 ± 1.21	1.06	47.7 ± 7.59	9.77
Study	Dose (mg)	$T_{½}$[c] (h)	Au_{0-72h} % Dose	CL/F (mL/min)	CL_R (mL/min)	Vd/F (L)
LOFBO-PHI0-093	750 mg	7.7 ± 1.3	75 ± 6	156 ± 27.8	118 ± 27.8	90.3 ± 14.0
LOFBO-PHI0-093	1000 mg	7.9 ± 1.5	73 ± 8	156 ± 33.5	113 ± 25.6	96.4 ± 21.9
K90-077	488 mg	[d]	[e]	10.5 ± 1.8[f]	7.53 ± 1.80[g]	97 ± 12

[a] Current study, N=10; [b] N=10; [c] Terminal half-life.

[d] The terminal half-life was not determined in the K90-077 study; however, the effective half-life was calculated to be 6.5 ± 0.7 h.; [e] Not available; [f] 10.5 L/h = 175 mL/min; [g] 7.53 L/h = 126 mL/min; Data are mean ± SD.

TABLE 4: Ratios of the Levofloxacin Pharmacokinetic Parameter Estimates[a]: 1-g Doses vs. 750-mg Dose (Study LOFBO-PHI0-093)

	Single Dose	Multiple Dose
C_{max}, µg/mL	1.25 ± 0.21	1.40 ± 0.27
	(1.13-1.38)	(1.23-1.57)
T_{max}, h	0.95 ± 0.40	1.28 ± 0.47
	(0.70-1.20)	(0.98-1.57)
AUC[b], µg·h/mL	1.35 ± 0.14	1.31 ± 0.16
	(1.27-1.44)	(1.21-1.41)
CL/F, mL/min	0.99 ± 0.10	1.03 ± 0.12
	(0.93-1.06)	(0.95-1.10)
Cu,max[c],µg/mL	2.02 ± 1.12	1.50 ± 0.96
	(1.33-2.72)	(0.91-2.10)
Ae[d], % dose	0.98 ± 0.12	0.91 ± 0.06
	(0.90-1.05)	(0.87-0.95)
CL_R, mL/min	0.97 ± 0.15	0.92 ± 0.09
	(0.88-1.06)	(0.86-0.98)
ke, h^{-1}	0.98 ± 0.06	1.02 ± 0.16
	(0.95-1.01)	(0.92-1.12)
$t_{½}$, h	1.02 ± 0.06	1.00 ± 0.16
	(0.99-1.06)	(0.91-1.10)
Vd/F, L	1.06 ± 0.11	1.05 ± 0.19
	(1.00-1.13)	(0.93-1.17)

[a] Data are presented as mean ± SD (lower to upper limit of 95% confidence interval), N=10

[b] AUC = $_{0-\infty}$ for single dose and 0-24 h for multiple once-daily doses

[c] Peak urinary levofloxacin concentration; [d] Ae = 0-72 h for single dose and 0-24 h for multiple once-daily doses

TABLE 5: Pharmacokinetic Profiles of Levofloxacin: Multiple Once-daily Doses at Steady State (488-1000 mg)

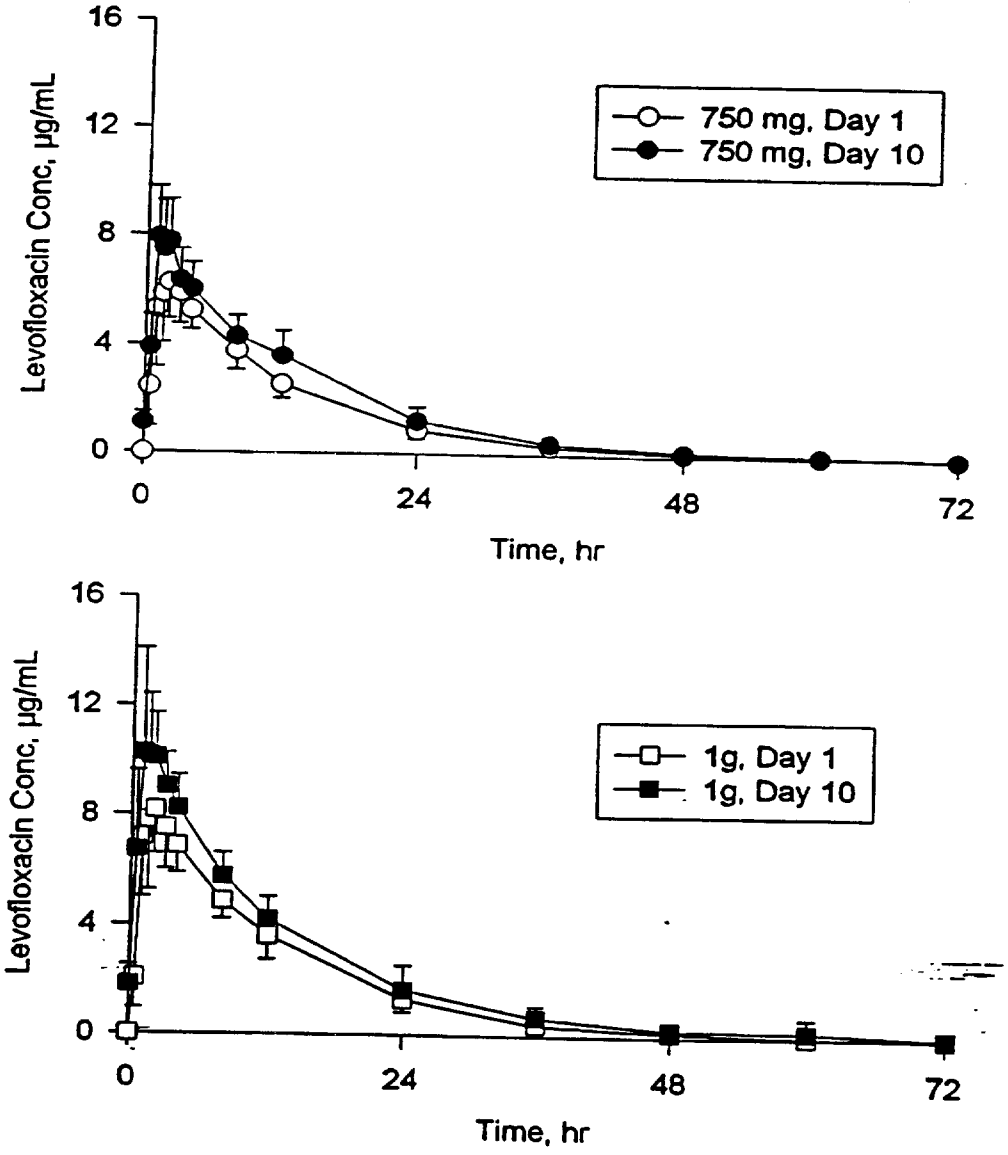
Study	Dose (mg)	T_{max} (h)	C_{max} (µg/mL)	Mean C_{max} (Per 100 mg dose)	AUC_{0-} (µg·h/mL)	Mean AUC_{0-} (Per 100 mg dose)
LOFBO-PHI0-093[a]	750 mg	1.4 ± 0.5	8.60 ± 1.86	1.15	90.7 ± 17.6	12.1
LOFBO-PHI0-093	1000 mg	1.7 ± 0.6	11.8 ± 2.52	1.18	118 ± 18.9	11.8
K90-077[b]	488 mg	1.1 ± 0.4	5.72 ± 1.40	1.17	47.5 ± 6.7	9.73
Study	Dose (mg)	$T_{½}$[c] (h)	Au_{0-72h} % Dose	CL/F (mL/min)	CL_R (mL/min)	Vd/F (L)
LOFBO-PHI0-093	750 mg	8.8 ± 1.5	79 ± 5	143 ± 29.1	113 ± 28.3	99.5 ± 15.8
LOFBO-PHI0-093	1000 mg	8.9 ± 2.5	71 ± 5	146 ± 28.8	104 ± 24.5	105 ± 26.5
K90-077[b]	488 mg	[d]	67 ± 14	10.5 ± 1.5[e]	6.97 ± 1.85[f]	102 ± 22

[a] Current study, N=10; [b] N=10; [c] Terminal half-life.

[d] The terminal half-life was not determined in the K90-077 study; however, the effective half-life was calculated to be 6.8 ± 1.3 h.

[e] 10.5 L/h = 175 mL/min; [f] 6.97 L/h = 116 mL/min; Data are mean ± SD.

FIGURE 1: Mean (± SD) Plasma Levofloxacin Concentrations - Time Profile in 10 Healthy Male Subjects Following 750-mg and 1-g Single and Multiple Once-Daily Doses (Study LOFBO-PHI0-093)



TITLE	Investigation of the absolute bioavailability of two levofloxacin (HR 355) clinical tablet formulations and their bioequivalence in healthy volunteers. Volume 1.54 - 1.55.
INVESTIGATOR, STUDY SITE	
ANALYTICAL SITE	
STUDY OBJECTIVE	To determine the absolute bioavailability and bioequivalence of two levofloxacin (HR 355) clinical tablet formulations, manufactured by and by R.W. Johnson Pharmaceutical Research Institute.
STUDY MEDICATION AND DOSAGE	500 mg levofloxacin i.v. (batch 1), single constant rate infusion over 60 minutes. 500 mg levofloxacin tablet (batch 12), single dose 500 mg levofloxacin tablet (batch R5826), single dose (R.W. Johnson PRI).
STUDY DESIGN	Open, randomised, three-way cross-over design. The three trial periods were separated by drug-free periods of 7 days each.
STUDY POPULATION	Eighteen healthy male subjects, aged between 18 and 60 years, body weight within -15% to +10% of normal weight according to Broca.
ANALYTICAL METHODS	Concentrations of levofloxacin in serum and urine: HPLC. 1.7 ml serum or 5 ml urine was required for each assay, with respective limits of quantification 20 ng/ml and 5 µg/ml.
DATA ANALYSIS	**Pharmacokinetics** Descriptive statistics, non-linear least-squares regression. Variables: <u>Serum</u> Maximum concentration in serum (C_{max}), time to maximum concentration (t_{max}), area under the serum concentration-time data pairs (AUD), AUD with extrapolation to infinity (AUDC), ratio of C_{max} and AUDC (C_{max}/AUDC), apparent terminal half-life ($t_{½z}$), relative total clearance (CL_{tot}/f) and mean time (MT_{res}; MT_{total}). <u>Urine</u> Total urinary excretion (Ae(0-72h)), average renal clearance (CL_{ren}), fractional renal clearance ($CL_{ren,f}$). Urinary creatinine excretion (0-24, 24-48, 48-72h) (for compliance). **Comparison of pharmacokinetic variables** ANOVA, non-parametric analysis (of t_{max}), 90% confidence intervals on original (urine data) or ln-transformed (serum) data.

RESULTS

Serum levofloxacin pharmacokinetic variables

Variable	Levofloxacin i.v.(HAG)	Levofloxacin p.o.(HAG)	Levofloxacin p.o.(PRI/J+J)
C_{max} (µg/ml)	8.51(15.2)	7.19(24.5)	7.36(19.1)
Range	6.17-10.4	4.48-10.9	4.57-10.4
t_{max} (h)	1.00#	1.25#	1.00#
Range			
AUDC (µg*h/ml)	49.6(11.3)	51.4(15.9)	49.6(10.1)
Range			
C_{max}/AUDC (1/h)	Not applicable	0.14(22.1)	0.15(17.4)
Range		0.09-0.21	0.10-0.20
$t_{½,z}$ (h)	6.97(9.24)	6.98(10.8)	6.88(12.3)
Range			

Median value

Point estimates and 90% confidence intervals (in brackets) for the respective ratios "test/reference", based on ln-transformed data analysis:

Variable	Levofloxacin p.o.(HAG)/ Levofloxacin i.v.(HAG)	Levofloxacin p.o. (PRI/J+J)/ Levofloxacin i.v.(HAG)	Levofloxacin p.o.(PRI/J+J)/ Levofloxacin p.o.(HAG)
C_{max}	-	-	104% (93-115%)
t_{max}	-	-	0.00h(-0.38-0.25h)*
AUDC	103% (99-107%)*	100% (96-104%)*	97% (94-101%)
C_{max}/ AUDC	-	-	107% (97-118%)
$t_{½,z}$	100% (96-105%)	98% (94-103%)	98% (94-103%)

* Point estimate and 90% confidence interval (in brackets) for the median difference between treatments, from non-parametric analysis

• Absolute bioavailability (AB)

Pharmacokinetics in urine

The table below shows the mean values, coefficients of variation (CV%) and ranges of the urinary recovery of levofloxacin (0-72h) and average renal clearance.

Urinary levofloxacin pharmacokinetic variables

Variable	Levofloxacin i.v.(HAG)	Levofloxacin p.o.(HAG)	Levofloxacin p.o.(PRI/J+J)
Ae(0-72h)(mg) Range	392(8.84)	401(7.45)	390(7.58)
Ae(0-72h) (% of dose) Range	78.5(8.84)	80.2(7.45)	78.0(7.58)
CL_{ren} (ml/min) Range	133(14.7)	133(17.5)	133(15.5)

Point estimates and 90% confidence intervals (in brackets) for the respective ratios "test/reference", based on untransformed data analysis:

Variable	Levofloxacin p.o.(HAG)/ Levofloxacin i.v.(HAG)	Levofloxacin p.o.(PRI/J+J)/ Levofloxacin i.v.(HAG)	Levofloxacin p.o.(PRI/J+J)/ Levofloxacin p.o.(HAG)
Ae(0-72h)	102% (99-105%)*	99% (96-102%)*	97% (94-100%)
CL_{ren}	100% (95-104%)	100% (95-104%)	100% (95-104%)

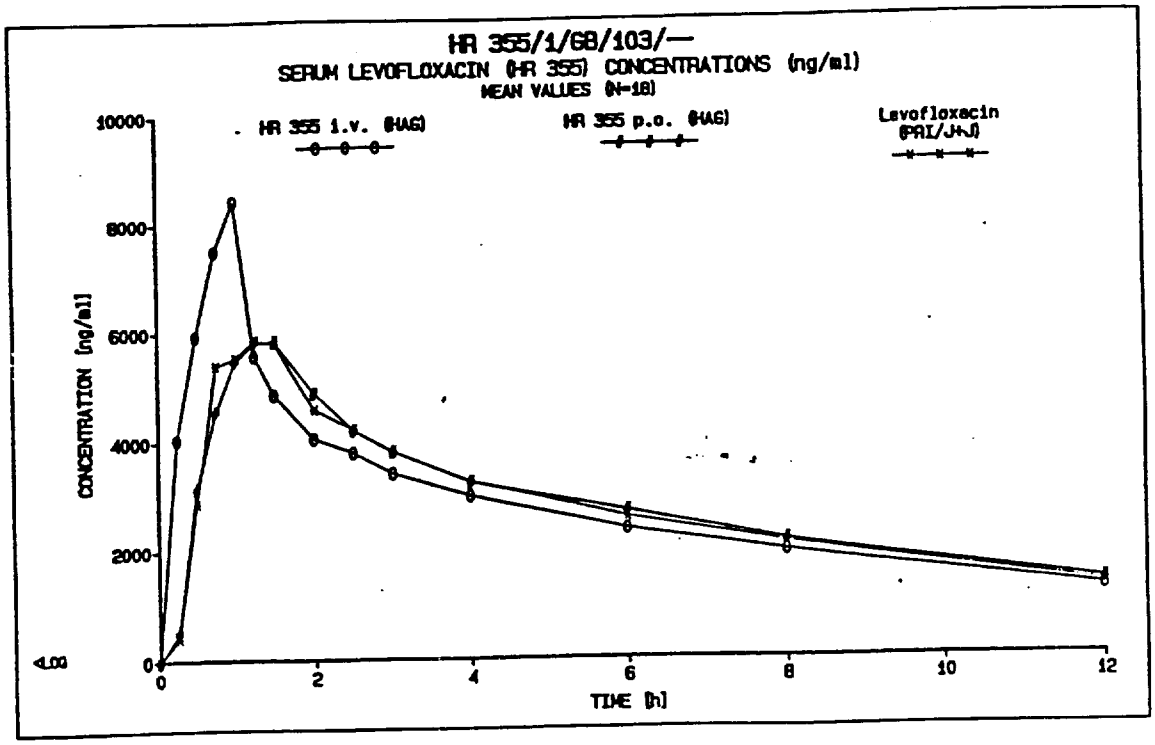
* Absolute bioavailability (AB)

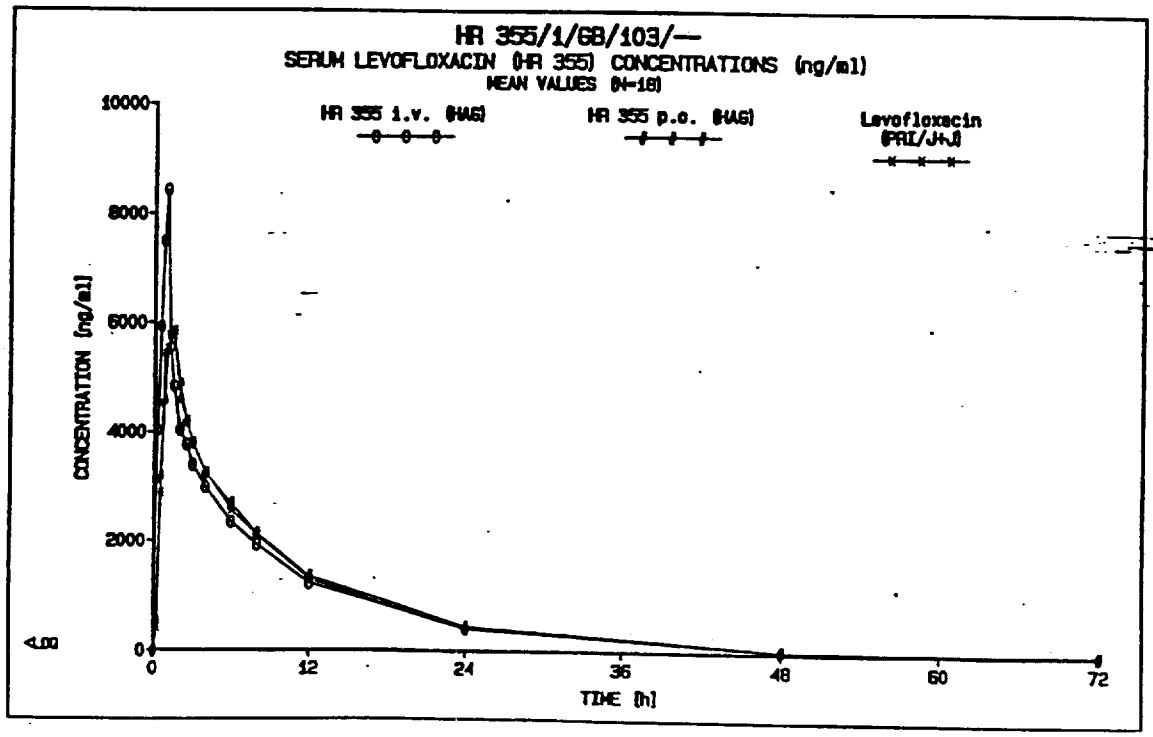
COMMENTS/ CONCLUSIONS

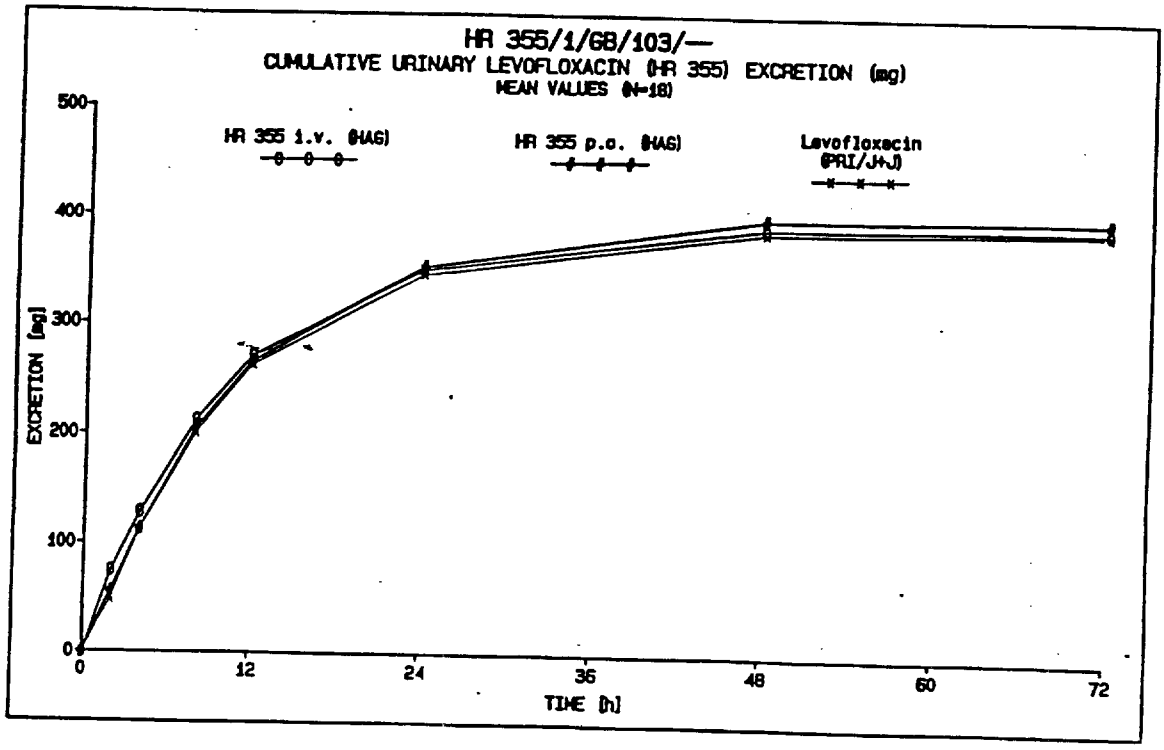
- The absolute bioavailability of levofloxacin p.o. (HAG) was 103% and of levofloxacin p.o.(PRI/J+J), 100%, apparently due to rapid and complete absorption of levofloxacin from the two tablet formulations.
- The two tablets are bioequivalent with regard to the rate and extent of absorption of levofloxacin.
- The mean Ae(0-72h) (% of dose) values for levofloxacin i.v. (HAG), levofloxacin p.o. (HAG) and levofloxacin p.o.(PRI/J+J) were 78.5, 80.2 and 78.0%, respectively.
- Administration of levofloxacin in either tablet formulation or as an infusion, was clinically well tolerated.

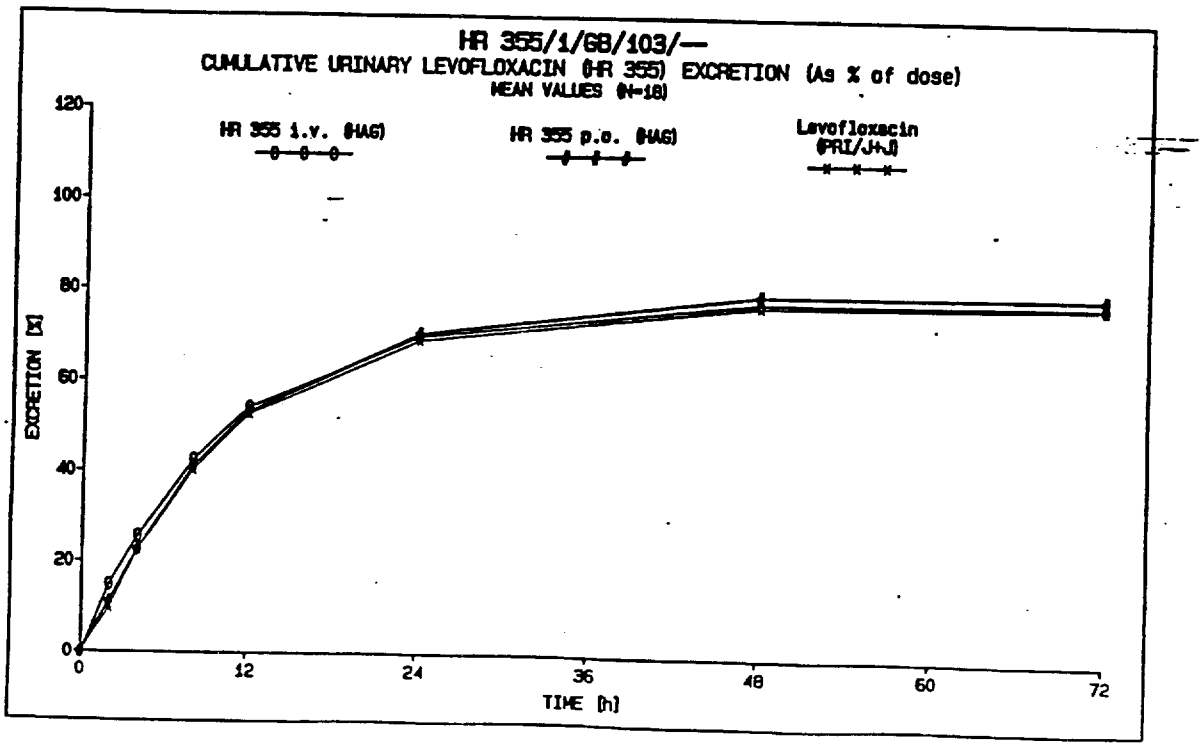
HR 355/1/GB/103/—
DEMOGRAPHIC DATA AND BODY SURFACE AREA (BSA)

SUBJECT NO.	Age	Weight (kg)	Height (cm)	BSA (m**2)	Race	Sex
	28.000	91.800	176.000	2.082	White	Male
	24.000	76.500	180.000	1.959	White	Male
	33.000	80.400	181.000	2.009	White	Male
	26.000	81.000	193.000	2.111	White	Male
	28.000	88.300	183.000	2.107	White	Male
	32.000	87.000	183.000	2.094	White	Male
	32.000	70.900	169.000	1.812	White	Male
	41.000	73.300	178.000	1.908	White	Male
	46.000	77.000	165.000	1.844	White	Male
	48.000	80.000	170.000	1.915	White	Male
	37.000	68.000	170.000	1.788	White	Male
	32.000	75.000	181.000	1.950	White	Male
	43.000	78.000	180.000	1.975	White	Male
	27.000	75.500	188.000	2.010	White	Male
	44.000	68.000	175.000	1.826	White	Male
	36.000	71.000	173.000	1.844	White	Male
	42.000	77.200	173.000	1.911	White	Male
	28.000	82.700	181.000	2.033	White	Male
	36.000	81.000	177.000	1.983	White	Male
MEAN	34.895	78.032	177.684	1.956		
SD	7.340	6.532	6.872	.103		
GEOM MEAN	34.172	77.776	177.559	1.953		
GEOM SD	1.234	1.087	1.039	1.054		
CV%	21.035	8.371	3.868	5.274		
SEM	1.684	1.499	1.577	.024		
MIN	24.000	68.000	165.000	1.788		
MAX	48.000	91.800	193.000	2.111		
MEDIAN	33.000	77.200	178.000	1.959		
n	19	19	19	19	19	19


HR 355/1/GB/103/—
SERUM LEVOFLOXACIN (HR 355) CONCENTRATIONS (ng/ml)
MEAN VALUES (N=18)
HR 355 i.v. (HAG)
HR 355 p.o. (HAG)
Levofloxacin (PRI/J+J)
CONCENTRATION (ng/ml)
10000
8000
6000
4000
2000
0
0
2
4
6
8
10
12
TIME (h)
4.00


HR 355/1/GB/103/—
SERUM LEVOFLOXACIN (HR 355) CONCENTRATIONS (ng/ml)
MEAN VALUES (N=18)
HR 355 i.v. (HAG)
HR 355 p.o. (HAG)
Levofloxacin (PRI/J+J)
CONCENTRATION (ng/ml)
10000
8000
6000
4000
2000
0
0
12
24
36
48
60
72
TIME (h)
4.00


HR 355/1/GB/103/—
CUMULATIVE URINARY LEVOFLOXACIN (HR 355) EXCRETION (mg)
MEAN VALUES (N=18)
HR 355 i.v. (HAG)
HR 355 p.o. (HAG)
Levofloxacin (PRI/J+J)
EXCRETION [mg]
500
400
300
200
100
0
0
12
24
36
48
60
72
TIME [h]


HR 355/1/GB/103/—
CUMULATIVE URINARY LEVOFLOXACIN (HR 355) EXCRETION (As % of dose)
MEAN VALUES (N=18)
HR 355 i.v. (HAG)
HR 355 p.o. (HAG)
Levofloxacin (PRI/J+J)
EXCRETION [%]
120
100
80
60
40
20
0
0
12
24
36
48
60
72
TIME [h]

TITLE OF STUDY: COMPARATIVE BIOAVAILABILITY OF LEVOFLOXACIN FROM A 125 MG CLINICAL TABLET AND A 250 MG MARKET-IMAGE TABLET ADMINISTERED AS A 250 MG SINGLE ORAL DOSE IN THE FASTED STATE TO HEALTHY MALE SUBJECTS.
LOFBO-PHI0-096 **Volume 1.58**

PRINCIPAL INVESTIGATOR:

OBJECTIVES: The objective of this study was to compare the bioavailability of levofloxacin from the 125 mg clinical tablet and 250 mg market-image tablet formulations of levofloxacin when administered at the same dose as a single dose.

STUDY DESIGN: This was a Phase I, randomized, open-label, complete two-way crossover study. Sixteen healthy male volunteers between the ages of 19 to 40 were enrolled. The subjects received each of the following two treatments separated by a 1-week washout period.

Treatment A: Each subject received a 250 mg oral dose of levofloxacin as two 125 mg clinical tablets of levofloxacin (Formula No. FD-25213-097-H-22, Batch No. R5737) administered with 240 mL of water after a 10-hour overnight fast.

Treatment B: Each subject received a 250 mg oral dose of levofloxacin as one 250 mg market-image tablet of levofloxacin (Formula No. FD-25213-097-AB-22, Batch No. R5902) administered with 240 mL of water after a 10-hour overnight fast.

SAMPLING: Serial venous blood samples (5 mL) were drawn from each subject at 0 (predose), 0.5, 1, 1.5, 2, 3, 4, 5, 6, 8, 12, 24, 30, and 36 hours after levofloxacin dosing. Urine samples were collected quantitatively during the following time periods: predose (-2 to 0 hour), 0-12, 12-24, and 24-36 hours postdose.

ANALYTICAL METHOD: Plasma and urine samples were analyzed for levofloxacin concentrations using a validated HPLC method.

DEMOGRAPHICS: Sixteen healthy male subjects were enrolled in the study as specified in the protocol (Table 1).

RESULTS: The mean (SD) levofloxacin pharmacokinetic parameters for the two treatments and the results of ANOVA and the two one-sided test for bioequivalence are summarized in Table 2.

Levofloxacin was rapidly absorbed after oral administration. Peak levofloxacin plasma concentrations were reached within approximately 1.5 hours in most cases. Levofloxacin plasma C_{max} were 2.95 ± 0.46 and 2.80 ± 0.43 µg/mL for the clinical tablet and market-image tablet, respectively. The corresponding AUC (0-∞) were 26.5 ± 3.8 and 27.2 ± 3.9 h· µg/mL. The urinary recovery of the levofloxacin dose in the 36-hour interval was 84.5 ± 8.6% for the clinical tablet and 87.7 ± 5.6% for the market-image tablet.

Statistical comparisons of the parameters for the 125 mg clinical tablet and 250 mg market-image tablet by ANOVA showed no statistically significant difference between the two formulations for log-transformed C_{max}, AUC (0-*), and AUC (0-∞). The two one-sided

test showed that the 90% confidence intervals for the ratio of the market-image tablet to the clinical tablet fell within the region of bioequivalence (80 to 125%) for C_{max}, AUC (0-*), and AUC (0-∞). The two tablet formulations were, thus, found to be bioequivalent.

CONCLUSION: The results of this study demonstrate the bioequivalence of one 250 mg market-image tablet and two 125 mg clinical tablets.

Single-dose administration of 250 mg levofloxacin as either the clinical tablet (2 x 125 mg) or the market-image tablet (1 x 250 mg) was found to be well-tolerated.

Table 1: Demographic and Baseline Characteristics
(All Subjects Enrolled in Study LOFBO-PHI0-096)

	Levofloxacin Market-Image Tablet/Clinical Tablet (N=8)	Levofloxacin Clinical Tablet/Market-Image Tablet (N=8)	Total (N=16)
Race			
Caucasian	4	6	10
Hispanic	2	2	4
Black	2	0	2
Age (years)			
Mean (SD)	24.8 (4.5)	29.5 (6.9)	27.1 (6.2)
Range			
Weight (lbs)			
Mean (SD)	162.6 (15.5)	158.7 (13.1)	160.7
Range			
Height (in)			
Mean (SD)	69.8 (1.7)	70.4 (2.5)	70.1 (2.1)
Range			

NOTE: This study enrolled only men.

Table 2: Levofloxacin Pharmacokinetic Parameters (Study LOFBO-PHI0-096)

Parameter	Clinical Tablet (Treatment A)		Market-Image Tablet (Treatment B)		% Difference[a]	ANOVA[b]	Two One-Sided Test[c]
C_{max} (µg/mL)	2.95	(0.46)	2.80	(0.43)	-5.1	NS	EQ
T_{max} (h)	1.33	(0.65)	1.57	(0.96)	+18.0	–	–
AUC (0-*)[d] (h· µg/mL)	25.1	(3.7)	25.9	(3.8)	+3.2	NS	EQ
AUC (0-∞) (h· µg/mL)	26.5	(3.8)	27.2	(3.9)	+2.6	NS	EQ
k_e (h^{-1})	0.098	(0.009)	0.097	(0.011)	-1.0	–	–
$t_{½}$ (h)	7.12	(0.72)	7.27	(0.85)	+2.1	–	–
CL/F (mL/min)	160	(22)	156	(20)	-2.5	–	–
A_e (% of dose)	84.5	(8.6)	87.7	(5.6)	+3.8	–	–
CL_R (mL/min)	141	(23)	142	(21)	+0.7	–	–

[a] With respect to Treatment A, [B-A]/A x 100
[b] ANOVA results on log-transformed parameters; NS = difference between means is not statistically significant (p>0.05).
[c] Two one-sided test results on log-transformed parameters, EQ = 90% confidence interval is within the 80 to 125% limits of the reference mean.
[d] AUC (0-*) calculated to last concentration above quantification limit.

Table 3: ANOVA Results, Bioequivalence Study Degrees of freedom (df), the value of the test statistic (F), and p-values from the ANOVA Model (Study LOFBO-PHI0-096)

	Group Effect			Period Effect			Treatment Effect		
Parameter	df	F	p-value	df	F	p-value	df	F	p-value
C_{max}	1,13	2.36	0.148	1,13	0.49	0.498	1,13	0.96	0.345
AUC (0-*)	1,13	1.06	0.323	1,13	0.34	0.569	1,13	1.36	0.264
AUC (0-∞)	1,13	0.95	0.348	1,13	0.17	0.688	1,13	0.80	0.386

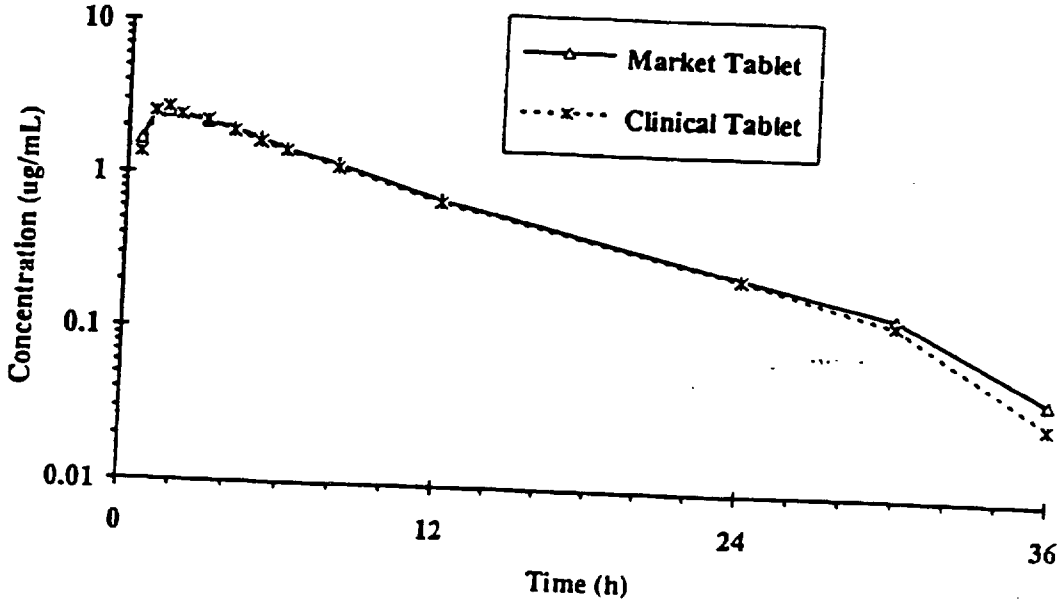
* AUC from time 0 to the last measurable concentration

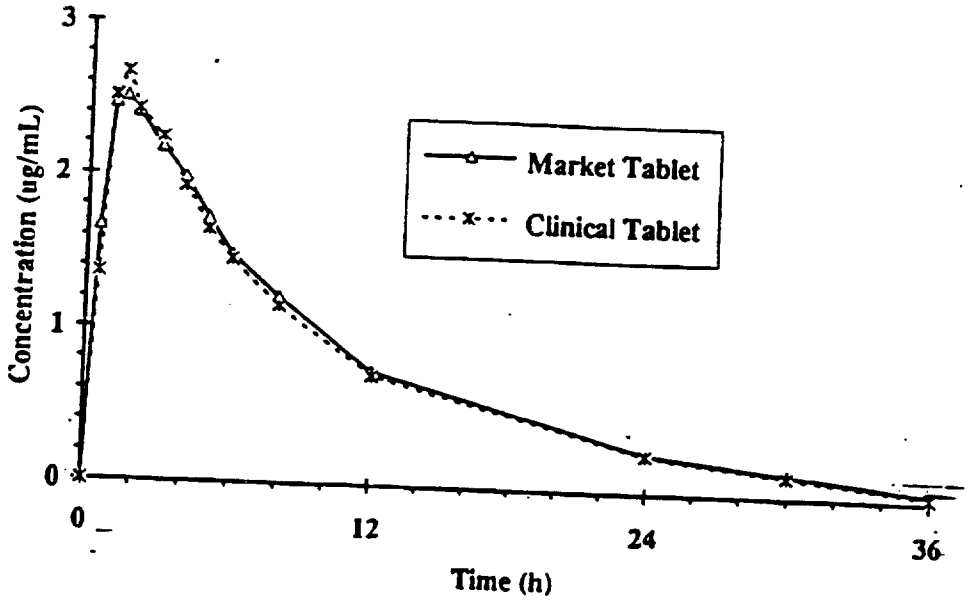
Table 4: 90% Confidence Interval for C_{max}, AUC (0-*), and AUC (0-∞) (Study LOFBO-PHI0-096)

			Geometric Mean			90% CI	
Parameter	RMSE	df	Clinical Tablet[a] (Treatment A)	Market-Image Tablet (Treatment B)	Ratio (%)	Lower Limit (%)	Upper Limit (%)
C_{max} (µg/mL)	0.145	1,13	2.91	2.76	94.9	86.4	104.3
AUC (0-*) (h· µg/mL)	0.070	1,13	24.98	25.73	103.0	98.5	107.8
AUC (0-∞) (h· µg/mL)	0.075	1,13	26.37	27.02	102.5	97.6	107.6

[a] The clinical tablet was the reference and the market-image tablet was the test formulation.

Figure 1: Mean Levofloxacin Plasma Concentration vs. Time Profiles
(Study LOFBO-PHI0-096)





TITLE OF STUDY: COMPARATIVE BIOAVAILABILITY OF LEVOFLOXACIN FROM A 500 MG CLINICAL TABLET, A 500 MG MARKET-IMAGE TABLET, AND A 500 MG MARKET-IMAGE INTRAVENOUS SOLUTION, EACH ADMINISTERED AS A SINGLE 500 MG DOSE IN THE FASTED STATE TO HEALTHY MALE SUBJECTS.

STUDY #: LOFBO-PHI-104 **VOLUMES 4.1 & 4.2**

PRINCIPAL INVESTIGATOR:

OBJECTIVES: The objective of this study was to compare the bioavailability of levofloxacin from the RWJPRI 500 mg clinical tablet, the RWJPRI 500 mg market-image tablet, and a 500 mg dose of a 5 mg/mL dilution of the RWJPRI market-image 25 mg/mL intravenous formulation following single dose intravenous infusion administration.

STUDY DESIGN: This was a Phase I, open-label, randomized, complete three-way crossover study. The subjects were randomized to one of six treatment sequence groups and received each of the following three treatments separated by a 1-week washout period.

Treatment A: Each subject received a 500 mg oral dose of levofloxacin administered as one RWJPRI 500 mg clinical tablet (Formula No. FD-25213-097-G-22, Batch No. R6008) with 240 mL water following a 10-hour overnight fast.

Treatment B: Each subject received a 500 mg oral dose of levofloxacin administered as one RWJPRI 500 mg market-image tablet (Formula No. FD-25213-097-AA-22, Batch No. R5903) with 240 mL water following a 10-hour overnight fast.

Treatment C: Each subject received a 500 mg intravenous infusion dose of levofloxacin (Formula No. FD-25213-097-D-45, Batch No. 5270) administered over 60 minutes as a 5 mg/mL dilution of the RWJPRI market-image intravenous formulation following a 10-hour overnight fast.

DEMOGRAPHICS: Twenty-four healthy male subjects aged 19 to 40 years were enrolled but 23 completed the study (Table 1). Subject 122 was discontinued after completing two treatment periods (market-image tablet and i.v. infusion treatments) because of a protocol violation (the subject donated blood between the second and third periods of the study).

SAMPLING: Serial venous blood samples (5 mL) were drawn from each subject at: 0 (predose), 0.5, 1, 1.5, 2, 3, 4, 5, 6, 8, 12, 24, 30, and 36 hours postdose. Urine was collected quantitatively during the following intervals: -8 to 0 (predose), 0 to 12, 12 to 24, and 24 to 36 hours postdose.

ANALYTICAL METHOD: Plasma and urine levofloxacin concentrations were determined by validated HPLC methods at the R.W. Johnson Pharmaceutical Research Institute, Raritan, N.J.

DATA ANALYSIS: The plasma and urine concentration data for levofloxacin were analyzed by model independent methods . Statistical comparisons were performed using SAS software, and bioequivalence comparisons were performed on log-transformed data using the two, one-sided test.

RESULTS: The mean levofloxacin pharmacokinetic parameters determined for the three treatments are summarized in Table 2. The results of the two, one-sided test for bioequivalence are summarized in Tables 3 to 5. The mean levofloxacin plasma concentration:time curves for the 23 subjects who completed the study for the three treatments are shown in Figure 1.

The results show that levofloxacin was rapidly absorbed from the oral tablets with mean T_{max} values of 1.37 and 1.57 hours for the market-image and clinical tablets, respectively. Levofloxacin was also completely absorbed from both tablet formulations with mean absolute bioavailability ≥99%.

Bioequivalence comparisons by the two, one-sided test on log-transformed data (90% confidence interval approach) for the market-image tablet with reference to the clinical tablet showed that the two treatments were equivalent for both C_{max} and AUC (0-∞).

Statistical comparisons for bioequivalence on log-transformed AUC (0-∞) data by the two, one-sided test showed that the extent of absorption for both the clinical and the market-image oral tablets were equivalent to that from the intravenous infusion. As expected, C_{max} values for the clinical and market-image tablets were not equivalent to C_{max} from the intravenous infusion by the two, one-sided test on log-transformed data. However, these differences between oral and intravenous treatments around peak concentrations were not great and were short-lived, with mean plasma concentrations nearly superimposable in the post-peak, distribution-elimination phase.

CONCLUSION: The results from this study show that the RWJPRI market-image 500 mg levofloxacin tablet is bioequivalent to the RWJPRI 500 mg clinical tablet. In addition, both the 500 mg levofloxacin clinical and market-image tablets were equivalent to the 500 mg levofloxacin one-hour intravenous infusion with respect to the extent of absorption. Absorption of levofloxacin from the tablet dosage forms was rapid and complete, with absolute bioavailability ≥99%.

Figure 1: Mean Levofloxacin Plasma Concentration: Time Profiles For 23 Healthy Male Subjects Following Single 500 mg Doses of the Clinical Tablet, the Market-Image Tablet, and the I.V. Infusion
(Study LOFBO-PHI-104)

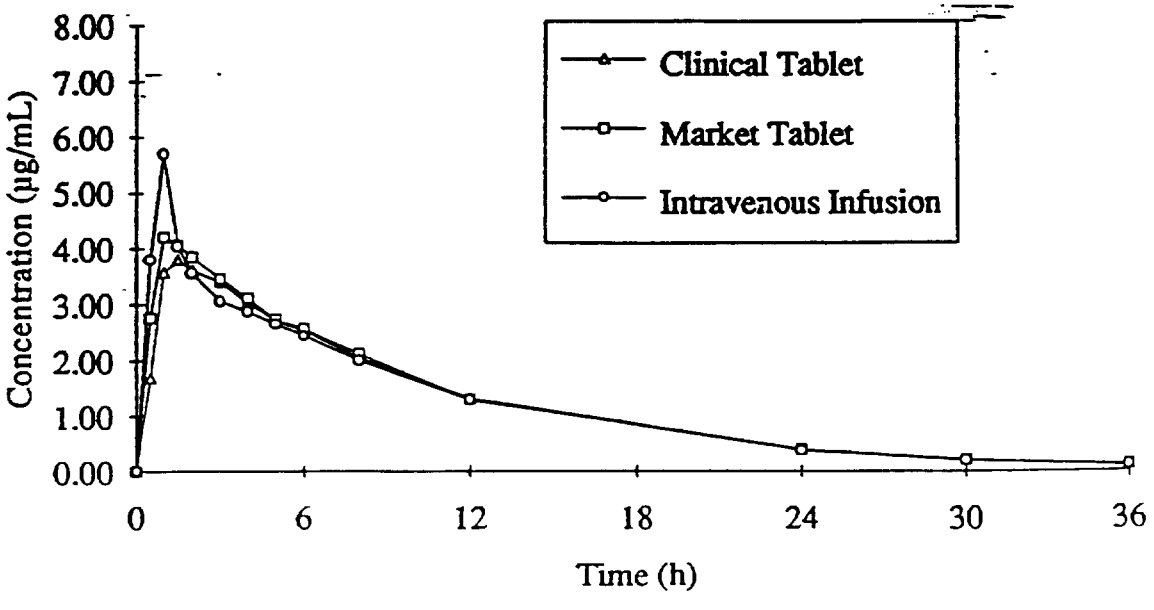


Table 1: Demographic and Baseline Characteristics
(All Subjects Enrolled in Study LOFBO-PHI-104)

	All Subjects (N=24)	Subjects Used For Pharmacokinetic Analysis (N=23)
Race		
Black	1	1
Caucasian	17	16
Hispanic	6	6
Age (years)		
Mean±SD	25.3±6.0	25.0±6.1
Range		
Weight (lbs)		
Mean±SD	168.5±18.5	169.6±18.1
Range		
Height (in)		
Mean±SD	69.8±2.2	69.8±2.2
Range		

NOTE: All subjects enrolled in this study were men.

Table 2: Summary of Levofloxacin Pharmacokinetic Parameters
(Study LOFBO-PHI-104)

Parameter	Clinical Tablet	Market-Image Tablet	Intravenous Infusion
C_{max} (μg/mL)	4.51(0.9)[a]	4.80(1.0)	5.70(0.8)
T_{max} (h)	1.57(0.8)	1.37(0.8)	1.00(0.0)
AUC (0-*) (μg•h/mL)	41.9(7.0)	43.4(6.5)	42.8(7.2)
AUC (0-∞) (μg•h/mL)	43.2(7.1)	44.7(6.7)	44.0(7.3)
F	0.99(0.1)	1.03(0.1)	NA
k_e (h^{-1})	0.102(0.01)	0.102(0.01)	0.104(0.01)
$t_{½}$ (h)	6.8(0.6)	6.9(0.6)	6.7(0.7)
CL (mL/min)	NA	NA	195(35)
CL/F (mL/min)	199(37)	191(28)	NA
A_e (% Dose)[b]	99(20)	102(17)	107(16)
V_{ss} (L)	NA	NA	105(16)
$MRT_{i.v.}$ (h)	NA	NA	9.0(0.8)
$t_{½,eff}$ (h)	NA	NA	6.2(0.5)

[a] Data are the mean (SD) for 23 subjects completing the study
[b] N=20
C_{max} The peak plasma concentration
T_{max} The time of peak plasma concentration
AUC (0-*) AUC from time zero to the time of the last measurable concentration
AUC (0-∞) AUC from time zero to infinity
F Absolute bioavailability
k_e The elimination rate constant
$t_{½}$ The elimination half-life
CL/F Clearance/bioavailability, oral clearance
CL Clearance following intravenous administration
A_e The amount of levofloxacin excreted in urine to 36 hours as % Dose
V_{ss} The steady-state volume of distribution determined from the i.v. treatment
$MRT_{i.v.}$ The mean residence time determined from the i.v. treatment
$t_{½,eff}$ The effective dosing half-life determined from the i.v. treatment
NA Not applicable

Table 3: Summary of Two, One-Sided Test Results on Log-Transformed Data, Market-Image Tablet vs. Clinical Tablet (Study LOFBO-PHI-104)

Parameter	Treatment A Clinical Tablet	Treatment B Market Tablet	% Difference in Means [a]	Two, One-sided Test Result [b]
C_{max} (µg/mL)	4.51(0.9)[c]	4.80(1.0)	+ 6.4	EQ
AUC (0-∞) (µg•h/mL)	43.2(7.1)	44.7(6.7)	+ 3.5	EQ

[a] With respect to Treatment A, (B-A)•100%/A
[b] Two, one-sided test results on log-transformed parameters, EQ = 90% confidence interval within 80 to 125% limits with respect to the reference mean.
[c] Mean (SD)

Table 4: Summary of Two, One-Sided Test Results on Log-Transformed Data, Market-Image Tablet vs. I.V. Infusion (Study LOFBO-PHI-104)

Parameter	Treatment B Market Tablet	Treatment C I.V. Infusion	% Difference In Means [a]	Two One-Sided Test Result [b]
C_{max} (µg•mL)	4.80(1.0)[c]	5.70(0.8)	- 15.8	NEQ[d]
AUC (0-∞) (µg•h/mL)	44.7(6.7)	44.0(7.3)	+ 1.6	EQ

[a] With respect to Treatment C, (B-C)/C•100%
[b] Two, one-sided test results on log-transformed parameters, EQ = 90% confidence interval within 80 to 125% limits with respect to the reference mean, NEQ = 90% confidence interval outside the 80 to 125% limits with respect to the reference mean.
[c] Mean (SD)
[d] 90% confidence interval bounds = 77.2 to 89.3

Table 5: Summary of Two, One-Sided Test Results on Log-Transformed Data, Clinical Tablet vs. I.V. Infusion (Study LOFBO-PHI-104)

Parameter	Treatment A Clinical Tablet	Treatment C I.V. Infusion	% Difference In Means [a]	Two One-Sided Test Result [b]
C_{max} (µg/mL)	4.51 (0.9)[c]	5.70 (0.8)	- 20.9	NEQ[d]
AUC (0-∞) (µg•h/mL)	43.2 (7.1)	44.0 (7.3)	- 1.8	EQ

[a] With respect to Treatment C, (A-C)•100%/C
[b] Two, one-sided test results on log-transformed parameters, EQ = 90% confidence interval within 80 to 125% limits with respect to the reference mean, NEQ = 90% confidence interval outside the 80 to 125% limits with respect to the reference mean.
[c] Mean (SD)
[d] 90% confidence interval bounds = 72.4 to 83.8

TABLE 6

Parameter	Root MSE	Group Sequence Effect F	df	p-value	Period Effect F	df	p-value
AUC (0-∞)	0.081	0.86	5,17	0.530	3.60	2,42	0.036
C_{max}	0.147	0.57	5,17	0.722	5.04	2,42	0.011

For the comparison of the market-image tablet to clinical tablet, the 90% confidence intervals were as follows:

Parameter	Mean Clinical Tab	Mean Market Tab	Ratio (%)	90% CI Lower(%)	Upper(%)
AUC (0-∞)	42.40	44.05	103.88	99.77	108.16
C_{max}	4.41	4.70	106.57	99.05	114.65

For the comparison of the market-image tablet to the market-image intravenous solution, the 90% confidence intervals were as follows:

Parameter	Mean I.V.	Mean Market Tab	Ratio (%)	90% CI Lower(%)	Upper (%)
AUC (0-∞)	43.29	44.05	101.74	97.71	105.93
C_{max}	5.66	4.70	83.00	77.15	89.29

For the comparison of the clinical tablet to the market-image intravenous solution, the 90% confidence intervals were as follows:

Parameter	Mean I.V.	Mean Clinical Tab	Ratio (%)	90% CI Lower(%)	Upper (%)
AUC (0-∞)	43.29	42.40	97.94	94.06	101.97
C_{max}	5.66	4.41	77.88	72.39	83.79

FIGURE 2: Dissolution Profiles for Levofloxacin 500 mg Clinical Tablets, Formula No. FD-25213-097-G-22, Batch No. R6008
(Study LOFBO-PHI-104)

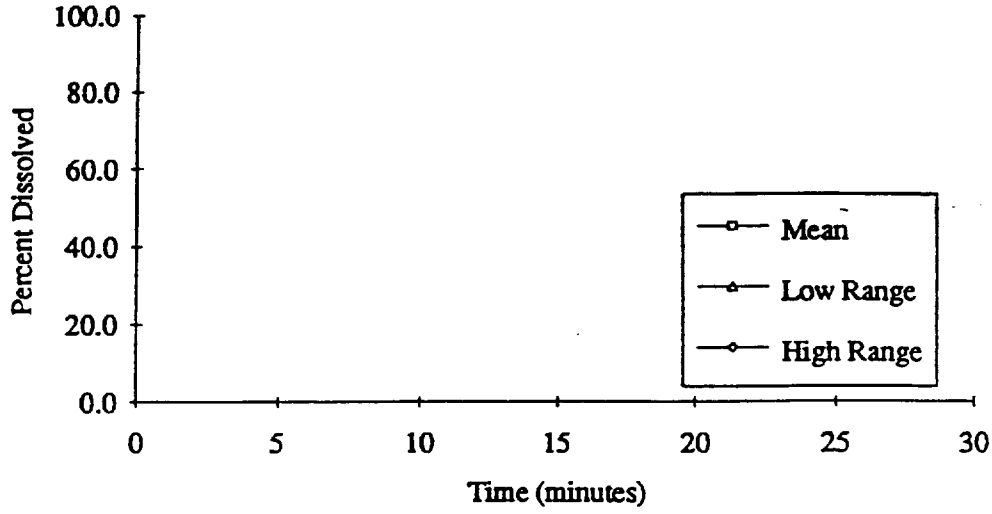
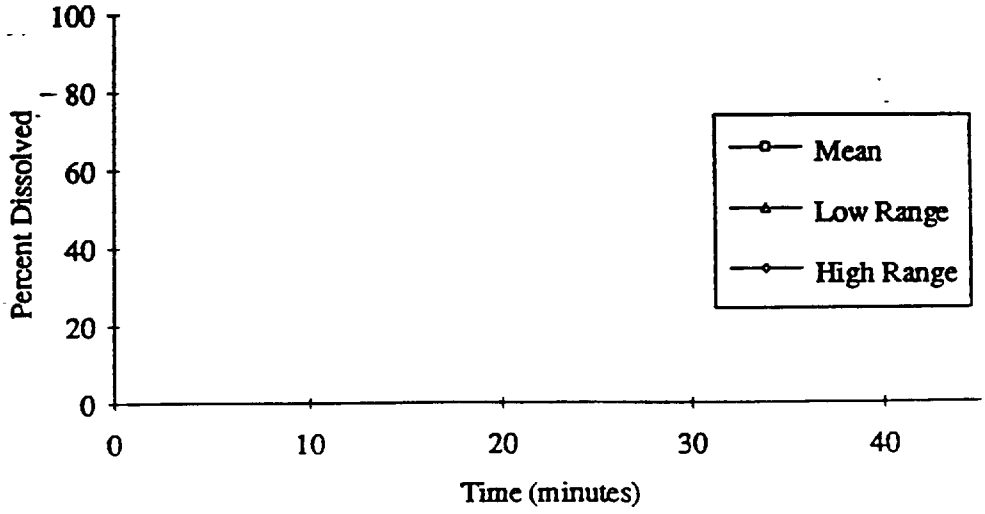


FIGURE 3: Dissolution Profiles for Levofloxacin 500 mg Market-Image Tablets, Formula No. FD-25213-097-AA-22, Batch No. R5903
(Study LOFBO-PHI-104)



TITLE	Assessment of the Effect of Food and Carafate® (Sucralfate) on Levofloxacin After a Single Oral Dose of 500 mg in Healthy, Young Male and Female Subjects (HR 355/1/USA/105). **Volume: 1.59 - 1.60.**
INVESTIGATOR AND STUDY SITE	
STUDY OBJECTIVES	The purpose of this study was to determine the effect of food (immediately before levofloxacin dosing) and sucralfate (1 gm given 2 hours after levofloxacin dosing) on the pharmacokinetics of a single, oral 500-mg tablet of levofloxacin.
STUDY MEDICATION	Single doses of 500-mg anhydrous levofloxacin as a tablet (Batch no.R5903) Single doses of 1-gm sucralfate (Carafate®) as a tablet (Batch no.K24009)
STUDY DESIGN	This was a single-dose, open-label, randomized, three treatment period, six sequence, cross-over, two Latin-square study in young healthy subjects (12 males and 12 females). Each subject received a single dose of one 500-mg levofloxacin tablet (with 240 mL of water) under each of the following conditions: Fasted — fasted without sucralfate, Fed — immediately after a standardized breakfast without sucralfate, or Sucralfate — fasted with 1-gm sucralfate (2 hours after levofloxacin administration and with 240 mL of water). The three treatments were separately administered on Days 1, 8, and 15. Subjects were confined for at least 12 hours before and 48 hours after dosing. During confinement, the subjects were placed on a fixed diet, which included a 10-hour fast before levofloxacin dosing.
STUDY POPULATION	Twenty-four healthy subjects (12 male and 12 female) between 18 and 40 years of age (Table 1) were enrolled.

SAMPLING

On Days 1, 8, and 15, venous blood samples were collected before levofloxacin dosing (Hour 0) and at Hours 0.5, 0.75, 1, 1.5, 2, 3, 4, 6, 8, 12, 16, 24, 30, 36, and 48 postdose. When sucralfate was administered, the 2-hour blood sample was to be taken immediately before the sucralfate dose.

Urine samples (for assessment of levofloxacin levels) were collected at the following time intervals: Hours -2 to 0 (before dosing), 0 to 4, 4 to 8, 8 to 12, 12 to 24, and 24 to 48.

ANALYTICAL METHOD

Concentrations of levofloxacin in plasma and urine were determined by high performance liquid chromatography with ultraviolet detection.

DATA ANALYSIS

The single dose pharmacokinetics of levofloxacin were determined. Plasma and urine concentrations of levofloxacin were measured before dosing and at selected times after dosing. C_{max}, T_{max}, AUC_{last}, Beta, $t_{½}$, AUC_{inf}, AUC_{24}, CL_{tot}/f, Ae_{24}, and CL_r were estimated, using the noncompartmental method, from the plasma and urine data of each individual subject.

The main analysis in this report was to compare the values for C_{max}, $t_{½}$, AUC_{last}, AUC_{inf}, and T_{max} of levofloxacin under (1) fed versus fasted conditions and (2) sucralfate versus fasted conditions. Repeated-measures analysis of variance was performed to compare $t_{½}$, rank T_{max}, and log transformed C_{max}, AUC_{last}, and AUC_{inf} data. An effect was considered significant whenever $p < 0.05$. Schuirmann's two one-sided tests procedure was employed to construct 90% confidence intervals for the ratio of the mean parameter values ($t_{½}$, log C_{max}, and log AUCs) between two treatments. Equivalence was concluded if the obtained confidence interval fell within the range of 80% to 125% for C_{max} and AUCs and 80% to 120% for $t_{½}$ (as used for bioequivalence studies).

TABLE 1: DEMOGRAHICS.

		Age (years)		Weight (lb)		Height (in)	
Group	N	Mean	Range	Mean	Range	Mean	Range
Males	12	23.3		160		70.0	
Females	12	25.8		133		65.9	
Total	24	24.5		146		68.0	

RESULTS: The individual plasma concentration profiles showed very little difference among the three treatments. The only consistent effect of food in most of the subjects was that the absorption was slightly delayed (lengthened T_{max}) and the maximum concentration was slightly lowered (reduced C_{max}) by food compared with the fasted condition (Table 2).

AUC_{last}, AUC_{inf}, $t_{½}$, T_{max}, and C_{max} were not considered to have any significant gender by treatment interaction ($p \geq 0.05$ after round-off of the ANOVA results). Consequently, the dosing recommendations for food and sucralfate interactions developed from the pooled data will apply to both genders. However, irrespective of treatment, there were significant ($p < 0.05$) gender differences in C_{max}, $t_{½}$, and T_{max}. The mean values of C_{max} were higher in the female subjects than in the male subjects for all three treatments. The mean terminal half-life was shorter in the female (~6 hours) than in the male (~7 hours) subjects. The gender differences observed in C_{max} and $t_{½}$ may be due to a smaller mean volume of distribution in females as a result of a smaller mean body weight (133 lb for females versus 160 lb for males). In spite of these differences, the AUC_{last} and AUC_{inf} values were not statistically significantly different between genders.

CONCLUSION: The absorption of levofloxacin is slightly delayed by food; however, there is no substantial change in bioavailability of levofloxacin when administered with food. Similarly, the bioavailability of levofloxacin is not significantly affected when sucralfate is given 2 hours after levofloxacin dose.

TABLE 2: Comparison of the Pharmacokinetic Parameters of Levofloxacin Under Fasted and Fed Conditions

		Fasted		Fed		Point	Confidence
Parameter	Units	Mean	SD	Mean	SD	Estimate[a]	Limits[a]
C_{max}	ng/mL	5930	1260	5090	880	0.86	(0.79, 0.94)
T_{max}	hour	1.0[b]	(0.8, 4.0)[b]	2.0[b]	(0.5, 4.0)[b]	p = 0.0023[b]	
AUC_{last}	ng·hour/mL	49400	7900	44400	6100	0.90	(0.87, 0.94)
AUC_{inf}	ng·hour/mL	50500	8100	45600	6100	0.91	(0.87, 0.94)
$t_{½}$	hour	6.22	1.56	6.45	1.93	1.04	(0.92, 1.15)

Analyses of C_{max} and AUCs are based on log transformation.

[a] Point estimate and 90% confidence limits are presented for the ratio of fed condition to fasted condition, using the least squares means from the ANOVA model.

[b] Median (minimum, maximum); p-value for the comparison between the means of the rank T_{max} values.

TABLE 3: Comparison of the Pharmacokinetic Parameters of Levofloxacin Under Fasted and Sucralfate Conditions

Parameter	Units	Fasted		Sucralfate		Point Estimate[a]	Confidence Limits[a]
		Mean	SD	Mean	SD		
C_{max}	ng/mL	5930	1260	6690	3220	1.06	(0.98, 1.15)
T_{max}	hour	1.0[b]	(0.8, 4.0)[b]	1.0[b]	(0.8, 2.0)[b]	p = 0.0481[b]	
AUC_{last}	ng·hour/mL	49400	7900	46900	8500	0.95	(0.91, 0.98)
AUC_{inf}	ng·hour/mL	50500	8100	47900	8400	0.95	(0.91, 0.98)
$t_{½}$	hour	6.22	1.56	6.06	1.39	0.97	(0.86, 1.09)

Analyses of C_{max} and AUCs are based on log transformation.

[a] Point estimate and 90% confidence limits are presented for the ratio of sucralfate condition to fasted condition, using the least squares means from the ANOVA model.

[b] Median (minimum, maximum); p-value for the comparison between the means of the rank T_{max} values.

TABLE 4

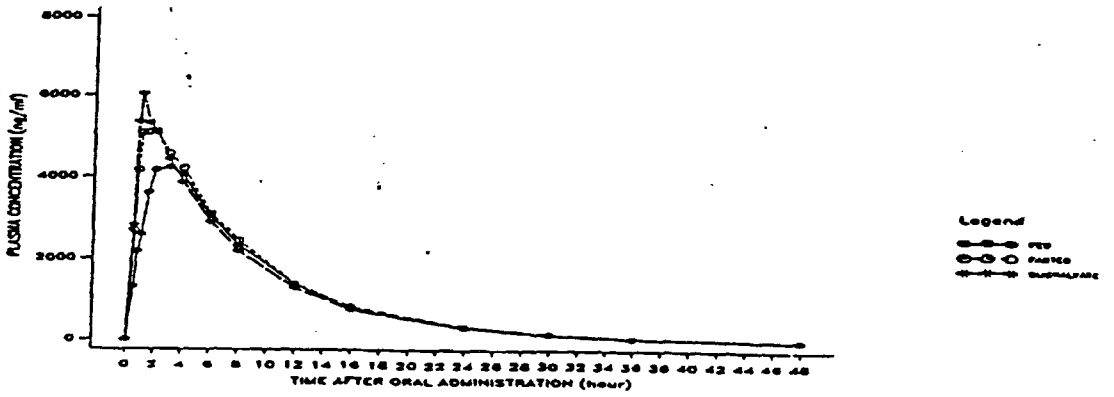
DEMOGRAPHIC DATA - SUMMARY

TREATMENT	N	AGE (yr)		WEIGHT (lb)		HEIGHT (in)		SEX		RACE			
		Mean	SD	Mean	SD	Mean	SD	Male	Female	White	Black	Oriental	Hispanic
Fed-Fasted-Sucralfate	4	25.0	5.83	150	50.3	67.8	6.50	2	2	3	0	1	0
Fasted-Fed-Sucralfate	4	22.3	3.50	138	5.92	68.3	3.86	2	2	3	0	0	1
Fed-Sucralfate-Fasted	4	26.3	7.18	150	18.1	67.8	3.46	2	2	2	1	0	1
Fasted-Sucralfate-Fed	4	22.3	4.03	153	15.9	69.3	2.75	2	2	4	0	0	0
Sucralfate-Fed-Fasted	4	29.3	6.80	147	17.1	68.8	3.59	2	2	1	0	0	3
Sucralfate-Fasted-Fed	4	22.3	3.86	141	22.2	66.8	3.40	2	2	3	0	1	0
Total	24	24.5	5.48	146	23.3	68.0	3.75	12	12	16	1	2	5
Male	12	23.3	5.48	160	19.7	70.0	2.76						
Female	12	25.8	5.39	133	18.1	65.9	3.55						

355/1/USA/105/--/Levofloxacin

FIGURE 1a

MEAN PLASMA CONCENTRATION OF LEVOFLOXACIN
FOLLOWING ORAL ADMINISTRATION OF 500 mg OF LEVOFLOXACIN
ALL SUBJECTS



HR 355/1/USA/105/--/Levofloxacin

FIGURE 1b

MEAN PLASMA CONCENTRATION OF LEVOFLOXACIN
FOLLOWING ORAL ADMINISTRATION OF 500 mg OF LEVOFLOXACIN

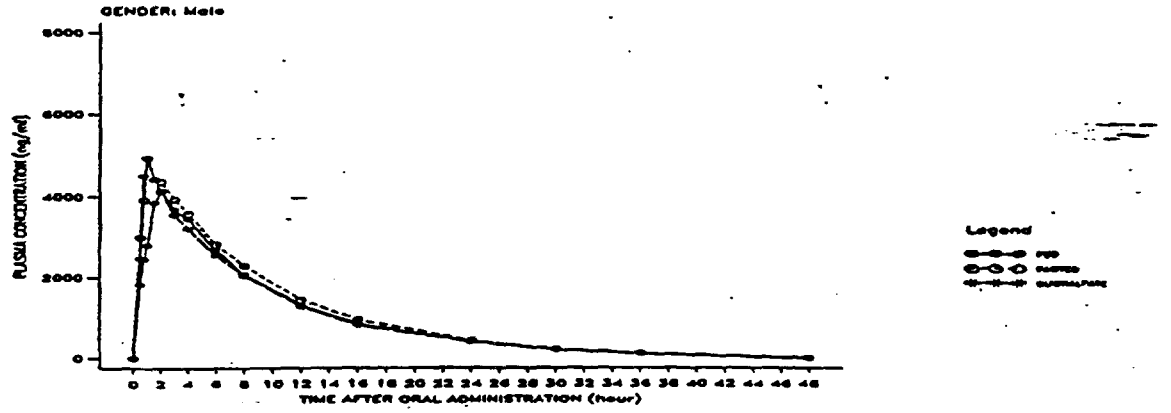
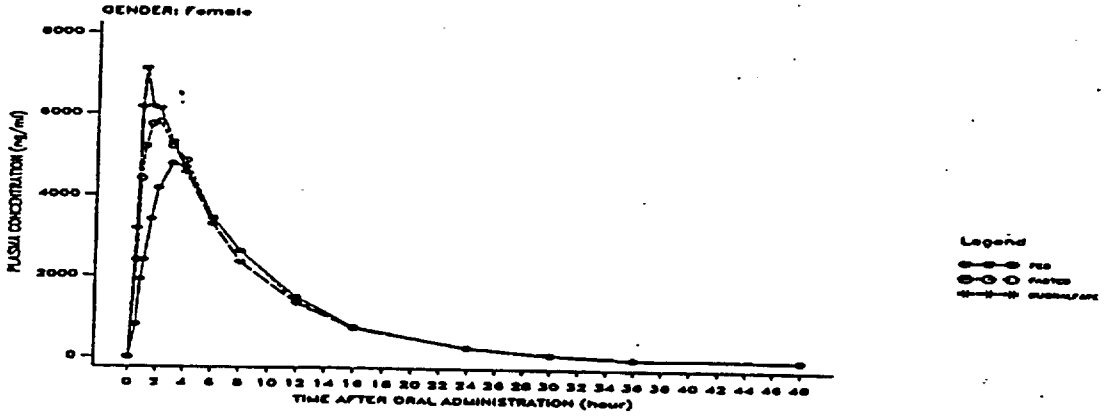


FIGURE 1.c

MEAN PLASMA CONCENTRATION OF LEVOFLOXACIN
FOLLOWING ORAL ADMINISTRATION OF 500 mg OF LEVOFLOXACIN



HR 355/1/USA/105/--/Levofloxacin

FIGURE 2.c

MEAN CUMULATIVE AMOUNT OF LEVOFLOXACIN IN URINE
FOLLOWING ORAL ADMINISTRATION OF 500 mg OF LEVOFLOXACIN
ALL SUBJECTS

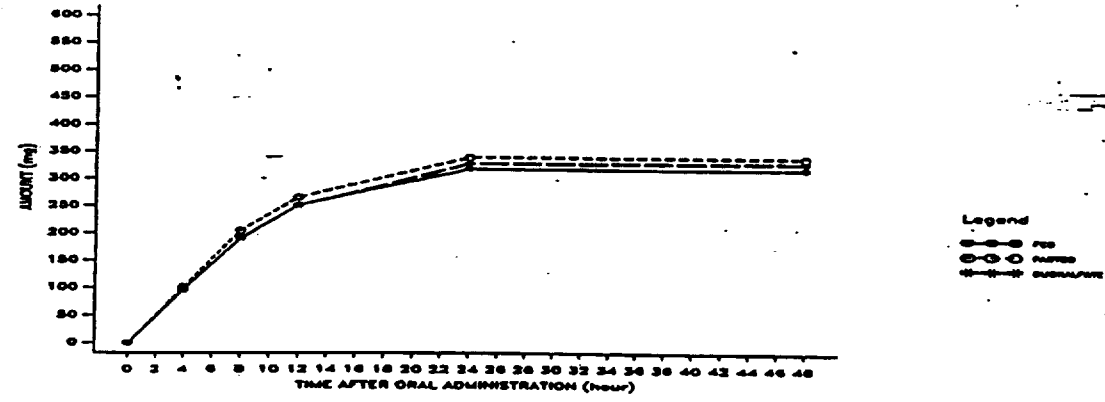
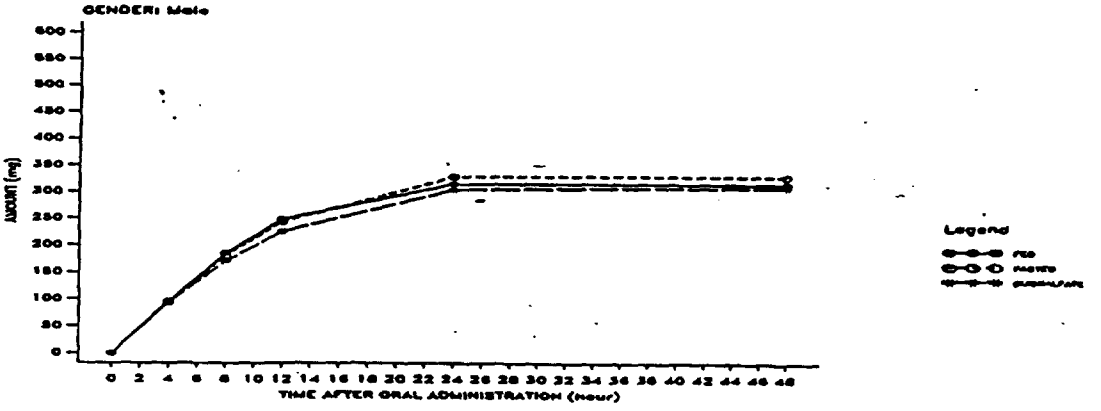


FIGURE 2b

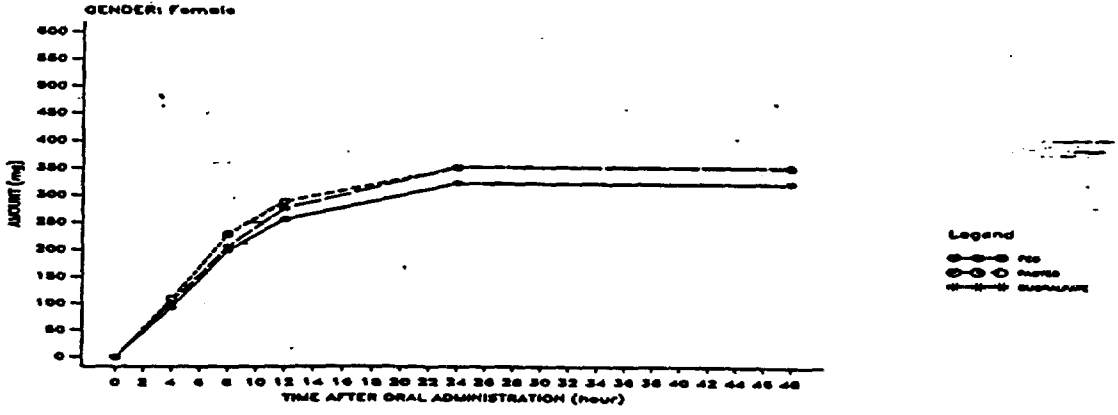
-MEAN CUMULATIVE AMOUNT OF LEVOFLOXACIN IN URINE
FOLLOWING ORAL ADMINISTRATION OF 500 mg OF LEVOFLOXACIN



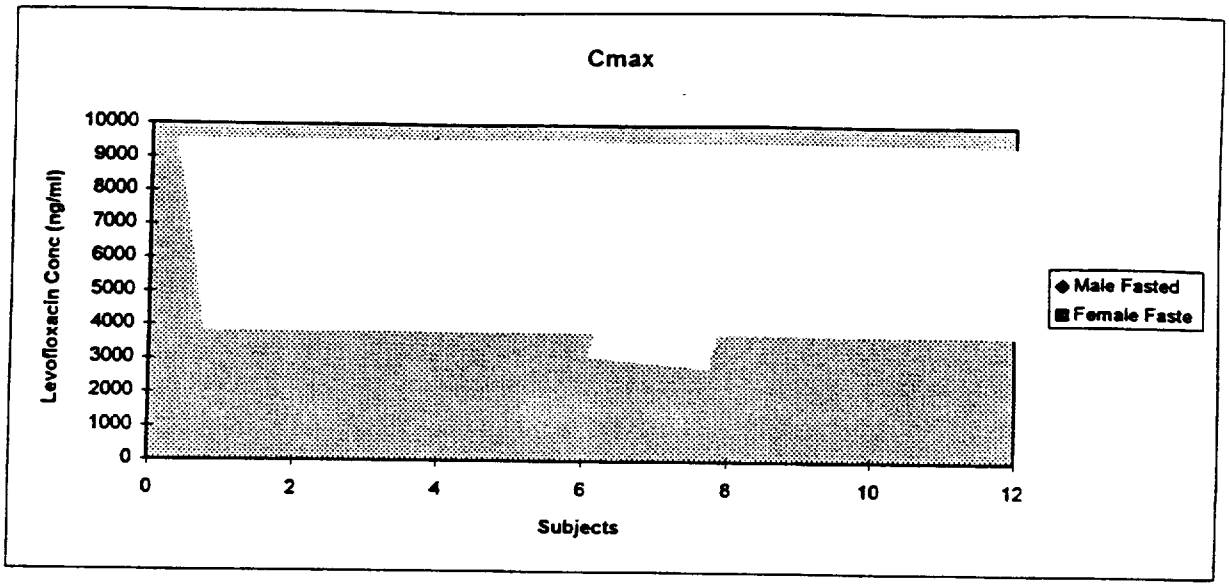
HR 355/1/USA/105/--/Levofloxacin

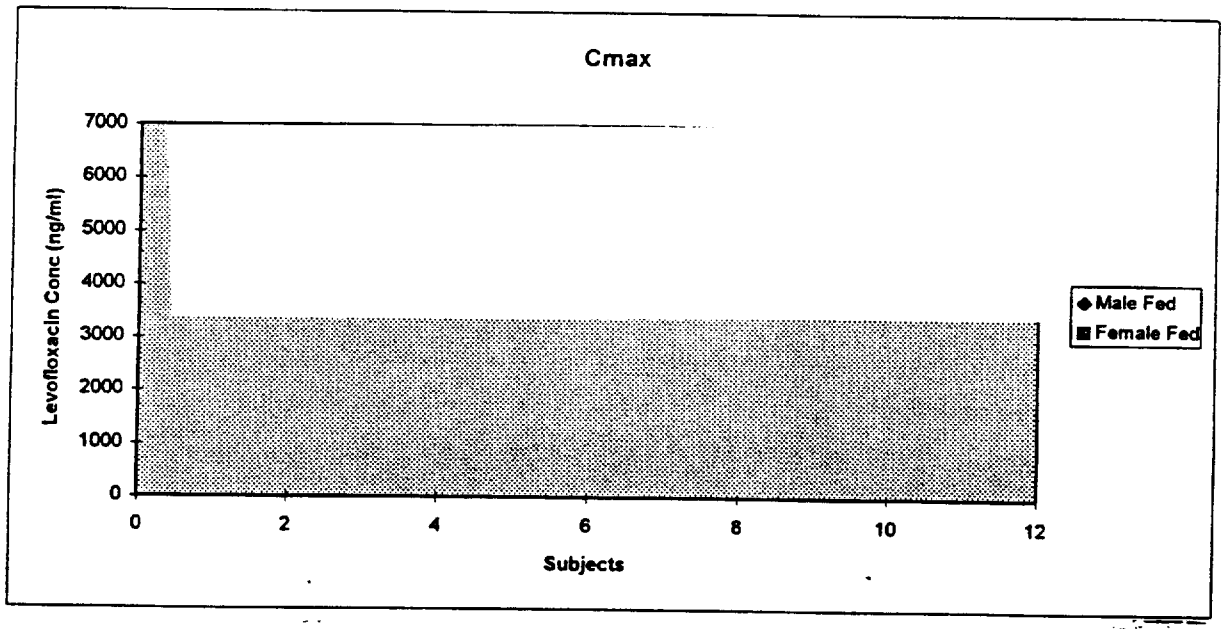
FIGURE 2c

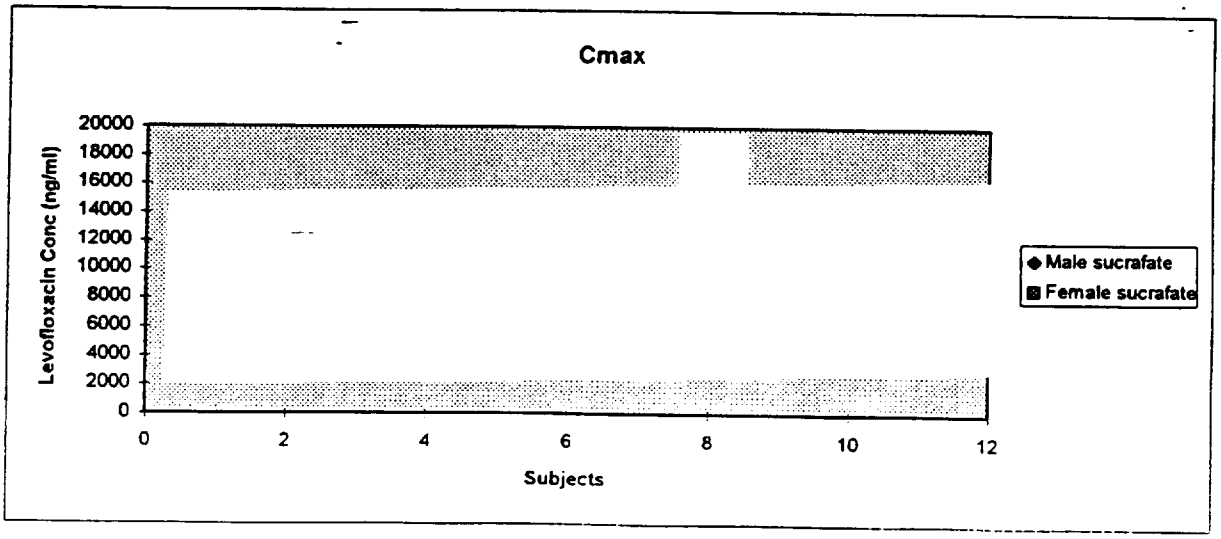
-MEAN CUMULATIVE AMOUNT OF LEVOFLOXACIN IN URINE
FOLLOWING ORAL ADMINISTRATION OF 500 mg OF LEVOFLOXACIN



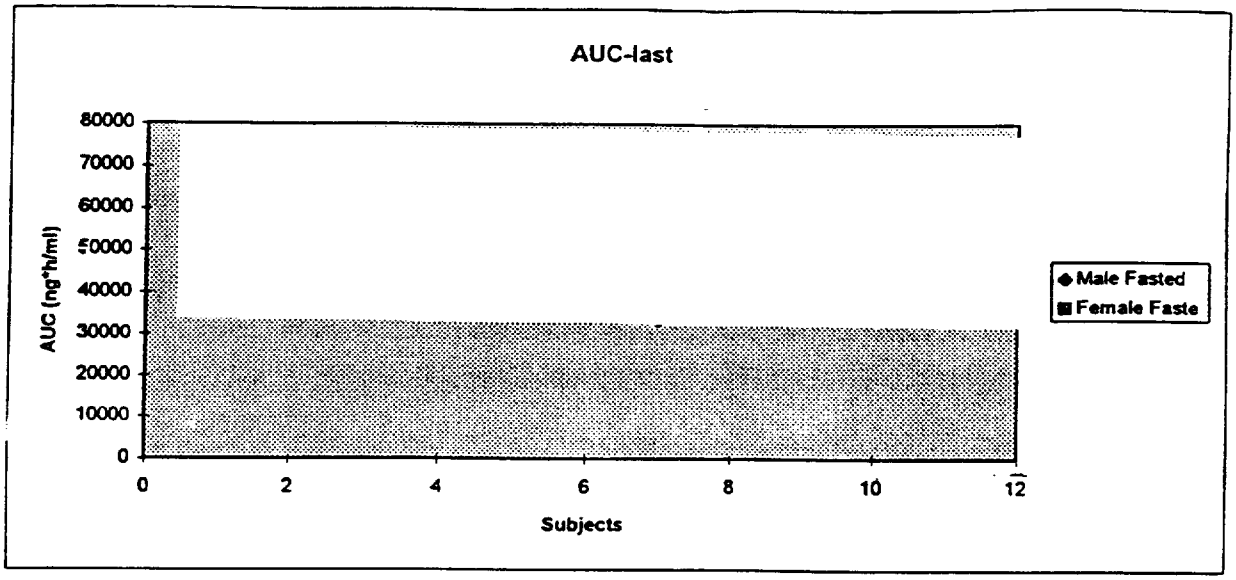
Food effect study

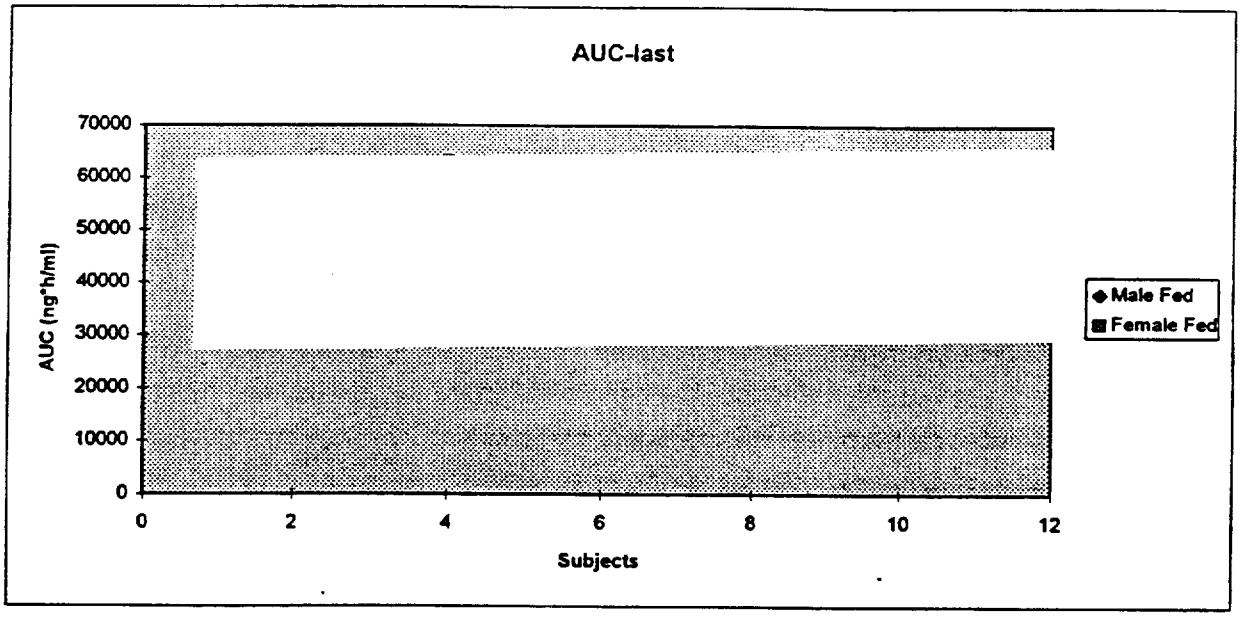


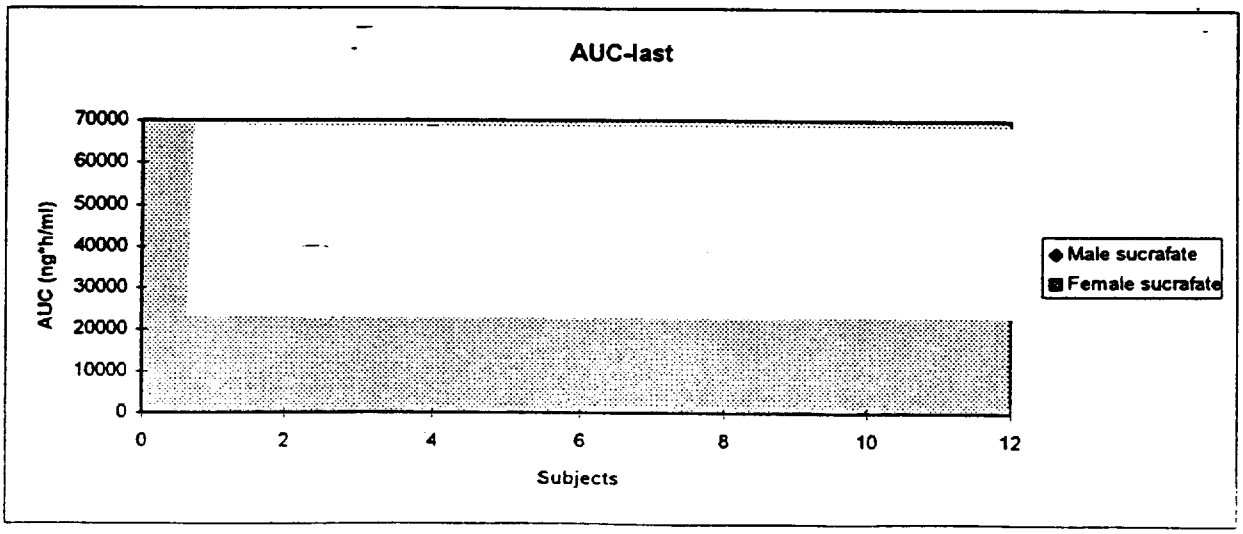




Food effect study







ATTACHMENTS:

3.4.3 General Restrictions on Subjects

The subjects were not to take any nontrial medication (including over-the-counter remedies) in the two weeks before and throughout the study without consulting the investigator in advance. Subjects were to abstain from strenuous physical activity, smoking, alcohol, any medications, and stimulating beverages containing xanthine derivatives (eg, tea, coffee, and Coca Cola-like drinks) from 48 hours before until 48 hours after each levofloxacin administration.

Prior to the day of study drug administration the subjects were admitted into the study site. Subjects were permitted to move about within the trial area. Subjects remained in the clinic under medical supervision until 48 hours after levofloxacin administration.

3.4.4 Dietary Restrictions

On Days -1, 7, and 14 (the days before each dosing day), subjects checked into the clinic where they received a standard diet. Beginning at 10 PM subjects were required to fast for 10 hours before study drug administration. During the fasting period, water was permitted ad lib up to one hour before administration of the study drug.

On Days 1, 8, and 15, dosing began at 8 AM. The subjects who received study drug without food were administered 240 mL water (at ambient temperature) with their levofloxacin and, if given, sucralfate doses. Subjects who received the treatments under fed conditions were served a standard, high fat breakfast (two eggs fried in butter, two strips of bacon, one serving of hash brown potatoes, two slices of toast with butter, and 180 mL of whole milk). Subjects had thirty minutes to finish the entire breakfast, then immediately received their medication with 240 mL of water (at ambient temperature). Lunch and dinner were served at 4 and 9.5 hours postdose (12:00 PM and 5:30 PM). A standard snack was served at 13.5 hours postdose (9:30 PM). Meals were standardized according to the type and quantities of food ingested by subjects.

No additional water or fluids (except for that described above) was allowed from 1 hour predose to 4 hours postdose. Water and liquids consumed with meals and during the study days were to range from 2 to 2.5 L per day.

TITLE OF STUDY: AGE AND GENDER EFFECT ON THE PHARMACOKINETICS OF A SINGLE 500 MG ORAL DOSE OF LEVOFLOXACIN IN HEALTHY SUBJECTS.

Study #: N93-024; **Volume 1.74**

INVESTIGATOR AND LOCATION:

OBJECTIVES: The objective of this study was to evaluate the influence of age and gender on the pharmacokinetics of levofloxacin in subjects receiving a single oral 500-mg dose of levofloxacin.

STUDY DESIGN: This was a Phase I, single-dose, parallel group study. Subjects entered the study unit the evening prior to drug administration (Day 0). Subjects fasted overnight for at least eight hours prior to the morning dose. Water was permitted *ad lib.* up until two hours prior to dosing. On the morning of Study Day 1 at approximately 8 a.m., a levofloxacin 500-mg tablet was given to each subject with 240 mL (8 ounces) of tap water at ambient temperature. A standard breakfast was served two hours after the dose. Subjects were confined to the study unit during the entire study period.

DEMOGRAPHICS: Twenty-four healthy men and women were enrolled with six in each of groups (Table 1).

FORMULATION: levofloxacin 500-mg tablet (Formula No. FD-25213-097-G-22, Batch No. 5324) was used.

SAMPLE COLLECTION: Serial venous (5 mL) blood samples were drawn from each subject at the following times: 0 (predose), 0.5, 1.0, 1.5, 2.0, 2.5, 3, 4, 6, 8, 12, 24, and 36 hours postdose. Urine was collected quantitatively during the following time periods: predose, 0-4, 4-8, 8-12, 12-24, and 24-36 hours postdose.

ASSAY: Plasma and urine samples were assayed for levofloxacin according to a validated HPLC procedure at The methods for quantitating levofloxacin concentrations in plasma and urine utilized reverse phase liquid chromatography with UV detection. The quantitation range in plasma was μg/mL in urine. Calibration curves were constructed by linear regression of peak height ratio (drug/internal standard) to nominal concentration; the regression was weighted by the inverse of the concentration squared. The internal standard was ciprofloxacin.

DATA ANALYSIS: Pharmacokinetic parameters estimated included the area under the plasma concentration-time curve (AUC_{0-t}) as measured by the trapezoidal summation method; mean residence time (MRT) calculated as ($AUMC_{0-\infty}/AUC_{0-\infty}$); apparent total body clearance (CL/F); renal clearance (CLr), the apparent volume of distribution (Vd/F). The peak concentrations of drug in plasma (C_{max}) and the time to reach C_{max}, (T_{max}), were estimated by visual inspection of the plasma drug concentration versus time data.

Analysis of variance models were used to study the effects of age group and gender on the pharmacokinetic parameters (C_{max}, T_{max}, $AUC_{0-\infty}$, Vd/F, $T_{½}$, CL/F, Au, and CLr). The analysis of variance model was based on a 2X2 factorial design and included terms for the two main effects (age group and gender) and the age group by gender interaction term. All tests were performed at a 5% level of significance.

The parameters, C_{max}, $AUC_{0-\infty}$, CL/F, and CLr, were further analyzed taking into consideration the subject's prestudy creatinine clearance values (CLcr). Analysis of variance models were fitted to the total body clearance and renal clearance data with the creatinine clearance as a covariate and age group, gender, and age group by gender interaction as factors. Analysis of variance models were fitted to the AUC and C_{max} data with the inverse of the creatinine clearance as a covariate and age group, gender, and age group by gender interaction as factors. All tests were performed at a 5% level of significance.

RESULTS: The mean (±SD) pharmacokinetic parameters determined from this study are summarized in Table 2. Data are grouped according to the gender (males vs. females) and the age (young vs. elderly) of the subjects:

In these four groups of subjects, mean peak plasma concentrations were reached at approximately 1.5 hours after dosing; renal clearance of levofloxacin accounted for approximately 77% of total body clearance and approximately 76% of the dose was recovered in urine over the 36 hours of collection.

Statistically significant differences in C_{max}, Vd/F, $AUC_{0-\infty}$, $T_{½}$, CL/F, and CLr between the young and the elderly were observed. In the elderly, C_{max} increased approximately 26% (calculated from the mean values of 12 subjects); Vd/F decreased 18%; $AUC_{0-\infty}$ increased 57%; $T_{½}$ increased 27%, CL/F decreased 34%, and CLr decreased 35%. The difference in Au and T_{max} between the young and the elderly was not significant.

Statistically significant differences in C_{max}, T_{max}, Vd/F, $T_{½}$, and CL/F between males and females were observed. Compared to the males, the C_{max} in females was 26% higher; time to reach peak plasma concentration was delayed by about 0.5 hour (Δ=46%); Vd/F was about 15% lower; $T_{½}$ was shorter by approximately 1.4 hours (Δ=19%); and CL/F was 18% lower. The differences in Au, $AUC_{0-\infty}$, and CLr between males and females were not significant. The T_{max} was significantly different between males and females; however, the difference is only 0.5 hour.

Good correlations were observed between the C_{max} and Vd/F of levofloxacin with the subject's body weight. Good correlations were also observed between the C_{max}, AUC, CL/F, and CLr of levofloxacin with the subject's Clcr. Body weight was not correlated with $T_{½}$ or CL/F of levofloxacin.

The differences in the pharmacokinetics (C_{max}, $AUC_{0-\infty}$, CL/F, and CLr) of levofloxacin between the young and the elderly or between males and females became statistically insignificant when the subject's renal function (as indicated by creatinine clearance, CLcr) was included as a covariate in the ANOVA model. CLcr (estimated according to subject's serum creatinine concentration, body weight, age, and gender) was an index for subject's renal function. The adjusted means of pharmacokinetic parameters after adjustment for subject's renal function (CLcr) are summarized in Table 3.

Table 1: Demographic and Baseline Characteristics
(All Subjects Enrolled in Study N93-024)

	Young Males 18-40 years (N=6)	Elderly Males ≥65 years (N=6)	Young Females 18-40 years (N=6)	Elderly Females ≥65 years (N=6)
Race				
Caucasian	1	6	3	6
Black	3	0	3	0
Hispanic	2	0	0	0
Age				
Mean	29.5	69.0	25.3	71.3
Range				
Body Weight (kg)				
Mean	77.1	84.7	70.7	60.0
Range				
Serum Creatinine (mg/dL)				
Mean	1.18	1.28	1.05	0.97
	1.1-1.4	1.1-1.6	0.9-1.3	0.9-1.1
Clcr[a]				
Mean	99.3	65.4	93.8	50.8
Range				

[a] Creatinine clearance (estimated according to subject's serum creatinine concentration, body weight, age, and gender).

Table 2: Summary of Levofloxacin Pharmacokinetic Parameters

(All Subjects Enrolled in Study N93-024)

	Males[a] (n=12)	Females[b] (n=12)	Young[c] (n=12)	Elderly[d] (n=12)
C_{max}[e], µg/mL	5.52±1.07	6.96±1.57	5.52±1.02	6.96±1.60
T_{max}[f], h	1.2±0.4	1.7±0.5	1.5±0.6	1.4±0.5
Vd/F[g], L/kg	1.11±0.19	0.94±0.14	1.13±0.18	0.92±0.12
$AUC_{0-\infty}$[h], µg·h/mL	54.4±18.9	67.7±24.2	47.5±9.8	74.7±23.3
$T_{½}$[i], h	7.5±2.1	6.1±0.8	6.0±0.9	7.6±2.0
Au[j], % Dose (0-36 h)	75±14	77±7	77±10	75±11
CL/F[k], mL/min	166±44	136±44	182±35	121±33
CLr[l], mL/min	126±38	106±40	140±33	91±29

[a] Males (young and elderly)

[b] Females (young and elderly)

[c] Young (males and females), age: 18-36 years

[d] Elderly (males and females), age: 66-80 years

[e] Peak plasma concentration

[f] Peak time

[g] Apparent volume of distribution per kg of body weight

[h] Area under plasma concentration-time curve

[i] Terminal plasma elimination half-life

[j] Percent of dose recovered in urine

[k] Apparent total body clearance

[l] Renal clearance

Table 3: Adjusted Mean[a] of Pharmacokinetic Parameters after Adjustment for Subject's Renal Function (CLcr)

	Males	Females	Young	Elderly
C_{max}	5.77	6.71	6.26	6.22
AUC	60.6	61.6	66.0	56.2
CL/F	160	143	157	146
CLr	120	112	117	115

[a] The adjusted means were obtained as the predicted values of the pharmacokinetic parameters corresponding to an average creatinine clearance value.

CONCLUSION: The consistency of T_{max} and Au among the age groups (young, elderly) and the gender groups (males, females) indicates that the bioavailability (rate and extent) of levofloxacin was not affected by either age or gender. The observed differences in the pharmacokinetics of levofloxacin between the age groups (young versus elderly) and the gender groups (males versus females) were attributable to the differences in renal function of the subjects.

TABLE 4 : Statistical Evaluation of Pharmacokinetic Parameters:
Results from the analysis of variance without adjustment for prestudy creatinine clearance (N93-024)

Parameter	Source	DF	Effect MS	Error MS	F Value	p-value
C_{max}	SEX*AGE_GRP	1, 20	3.792	1.173	3.23	0.087
	SEX	1, 21	12.413	1.298	9.56	0.006
	AGE_GRP	1, 21	12.499	1.298	9.63	0.005
T_{max}	SEX*AGE_GRP	1, 20	0.010	0.244	0.04	0.838
	SEX	1, 21	1.760	0.233	7.57	0.012
	AGE_GRP	1, 21	0.010	0.233	0.04	0.835
AUC_{0-}	SEX*AGE_GRP	1, 20	131.602	292.219	0.45	0.510
	SEX	1, 21	1061.340	284.570	3.73	0.067
	AGE_GRP	1, 21	4417.307	284.570	15.52	0.001
Vd/F	SEX*AGE_GRP	1, 20	0.026	0.016	1.64	0.216
	SEX	1, 21	0.175	0.016	10.74	0.004
	AGE_GRP	1, 21	0.258	0.016	15.83	0.001
$T_{½}$	SEX*AGE_GRP	1, 20	2.602	1.800	1.45	0.243
	SEX	1, 21	12.495	1.839	6.80	0.017
	AGE_GRP	1, 21	15.477	1.839	8.42	0.009
Au (% Dose)	SEX*AGE_GRP	1, 20	0.375	124.858	<0.01	0.957
	SEX	1, 21	15.042	118.931	0.13	0.726
	AGE_GRP	1, 20	22.042	118.931	0.19	0.671
CL/F	SEX*AGE_GRP	1, 20	0.265	1003.751	<0.01	0.987
	SEX	1, 21	5394.541	955.966	5.64	0.027
	AGE_GRP	1, 21	22370.064	955.966	23.40	<0.001
CLr	SEX*AGE_GRP	1, 20	22.815	953.278	0.02	0.879
	SEX	1, 21	2331.693	908.971	2.57	0.124
	AGE_GRP	1, 21	14261.325	908.971	15.69	0.001

TABLE 5 Statistical Evaluation of Pharmacokinetic Parameters:
Results from the analysis of variance with adjustment for prestudy creatinine clearance (N93-024)

Parameter	Source	DF	Effect MS	Error MS	F Value	p-value
C_{max}	SEX*AGE_GRP	1, 19	1.290	1.087	1.19	0.290
	SEX	1, 20	4.177	1.097	3.81	0.065
	AGE_GRP	1, 20	0.002	1.097	<0.01	0.963
$AUC_{0-\infty}$	SEX*AGE_GRP	1, 19	143.105	133.382	1.07	0.313
	SEX	1, 20	4.302	133.868	0.03	0.860
	AGE_GRP	1, 20	164.823	133.868	1.23	0.280
CL/F	SEX*AGE_GRP	1, 19	211.139	851.770	0.25	0.624
	SEX	1, 20	1317.615	819.738	1.61	0.219
	AGE_GRP	1, 20	127.566	819.738	0.16	0.697
CLr	SEX*AGE_GRP	1, 19	79.154	837.423	0.09	0.762
	SEX	1, 20	270.505	799.509	0.34	0.567
	AGE_GRP	1, 20	6.412	799.509	0.01	0.930

TABLE 6 Statistical Evaluation of Pharmacokinetic Parameters:
Percent differences in the mean pharmacokinetic parameters and the results from ANOVA modeling (N93-024)

	Age Group by Gender Interaction	Young vs. Elderly			Males vs. Females		
		% Difference	Age Effect w/o CLcr	Age Effect with CLcr	% Difference	Gender Effect w/o CLcr	Gender Effect with CLcr
C_{max}	NS	26	S	NS	26	S	NS
T_{max}	NS	-3	NS	--	46	S	--
Vd/F	NS	-18	S	--	-15	S	--
$AUC_{0-\infty}$	NS	57	S	NS	24	NS	NS
T½	NS	27	S	--	-19	S	--
Au (% Dose)	NS	-3	NS	--	3	NS	--
CL/F	NS	-34	S	NS	-18	S	NS
CLr	NS	-35	S	NS	-16	NS	NS

S - denotes significant at 5% level.
NS - denotes not significant at 5% level.

Figure 1: Mean (±SD) Plasma Levofloxacin Concentrations in the Age Groups (Young and Elderly) After Receiving a Single Oral Dose of Levofloxacin 500 mg Tablet (Study N93-024)

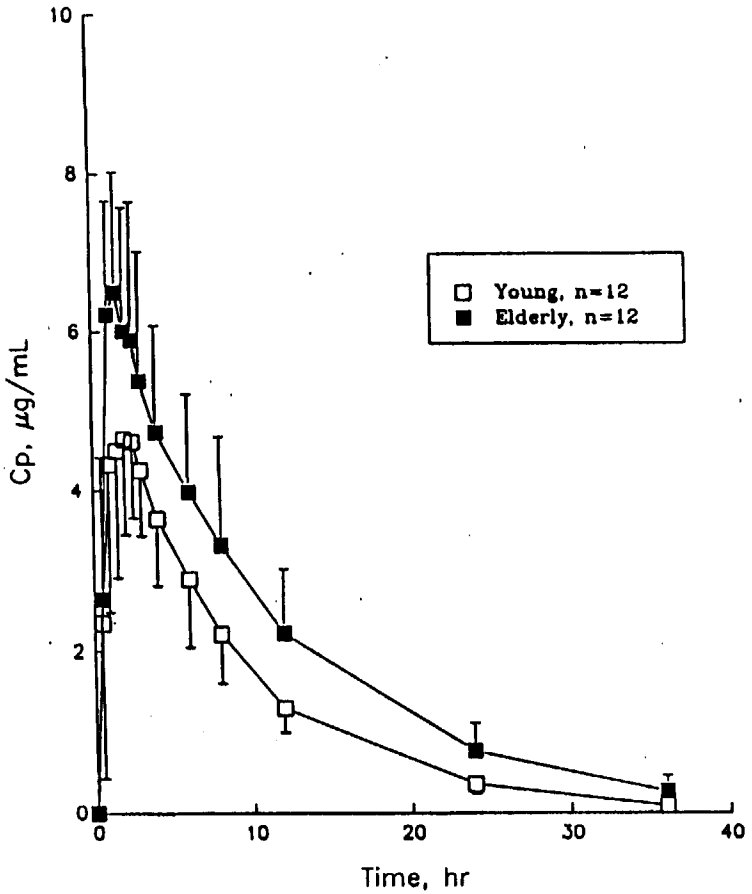


Figure 2: Mean (±SD) Plasma Levofloxacin Concentrations in the Gender Groups (Males and Females) After Receiving a Single Oral Dose of Levofloxacin 500 mg Tablet (Study N93-024)

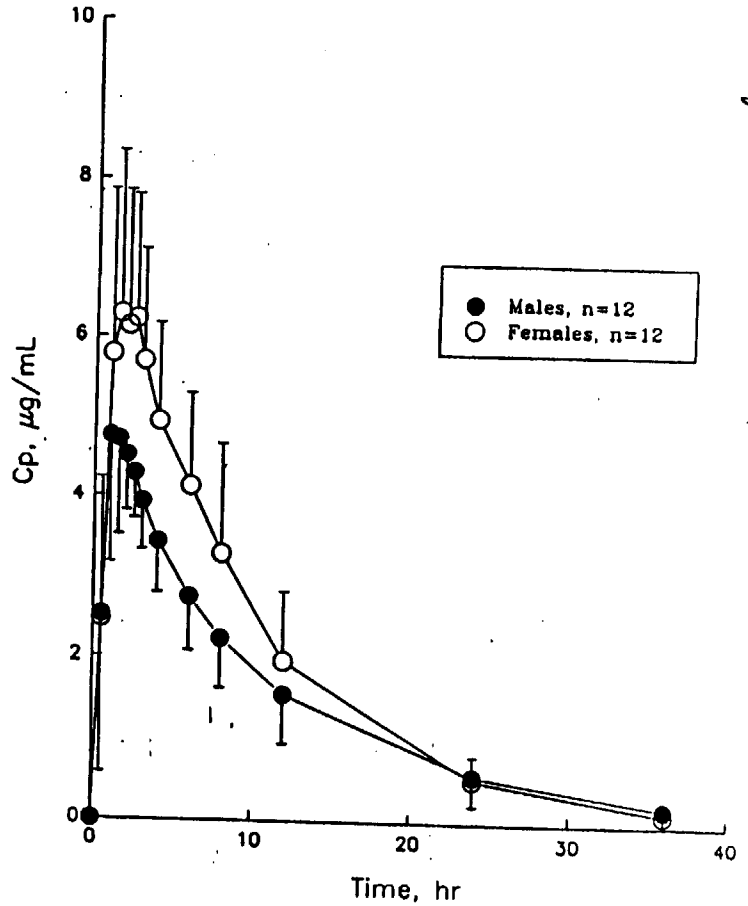


Figure 3: Total Body Clearance (CL/F) of Levofloxacin vs. Subject's Creatinine Clearance (CLcr) in Four Groups (Young Male, Elderly Male, Young Female, Elderly Female) Receiving a Single Oral Dose of Levofloxacin 500 mg Tablet (Study N93-024)

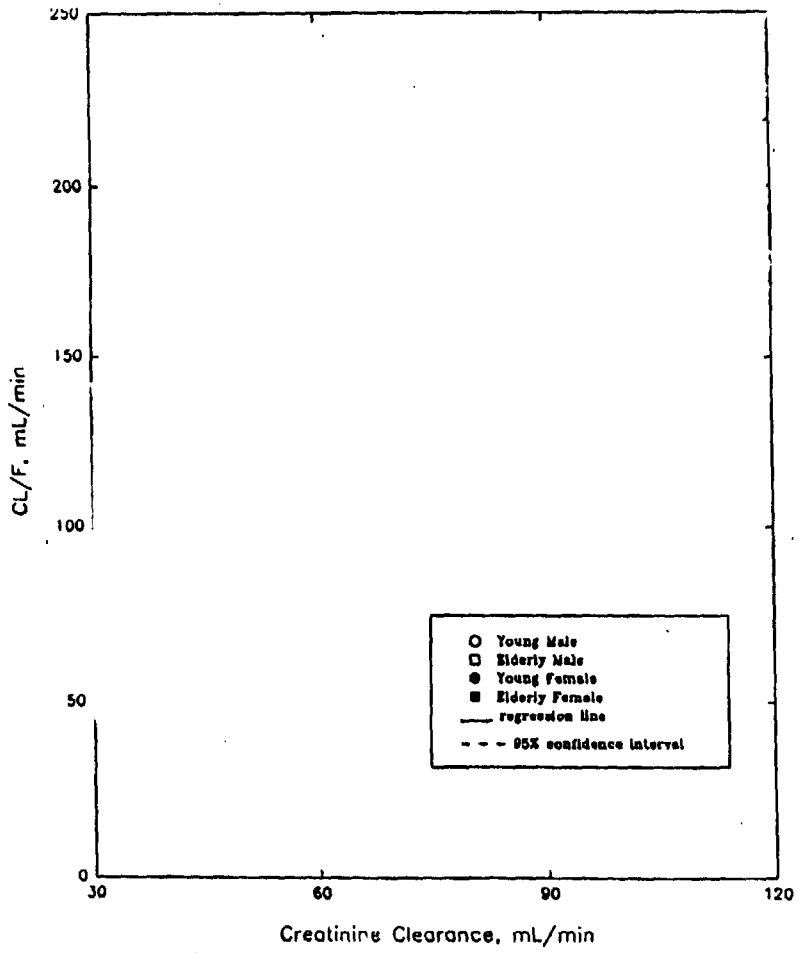


Figure 4: Renal Clearance (CLr) of Levofloxacin vs. Subject's Creatinine Clearance (CLcr) in Four Groups (Young Male, Elderly Male, Young Female, Elderly Female) Receiving a Single Oral Dose of Levofloxacin 500 mg Tablet (Study N93-024)

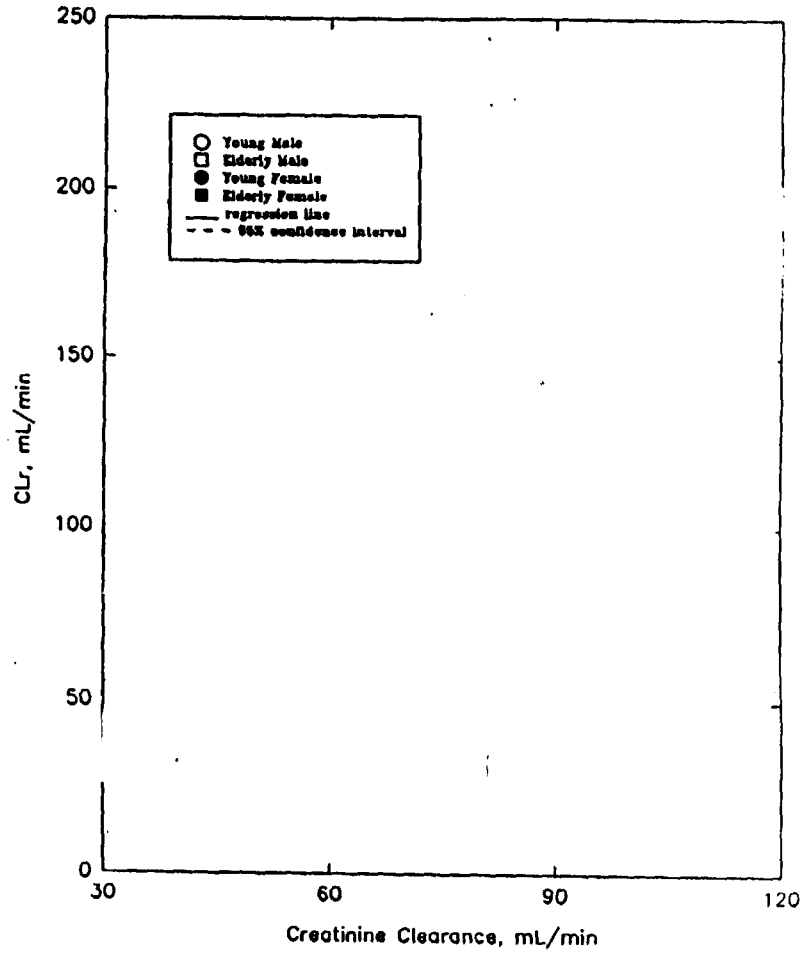


Figure 5

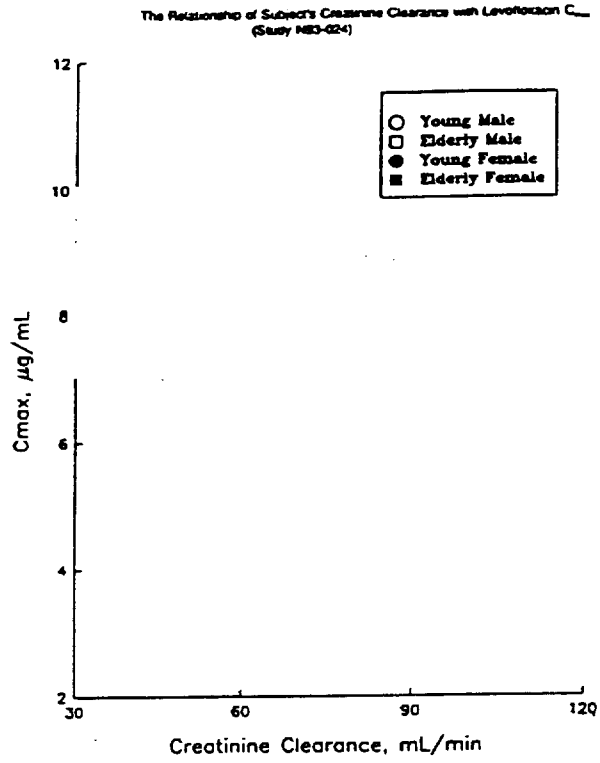


Figure 6

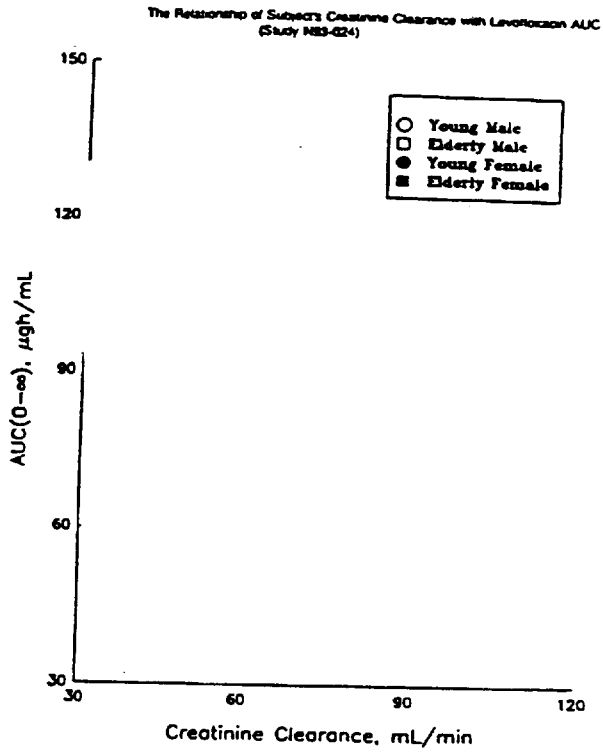


Figure 7

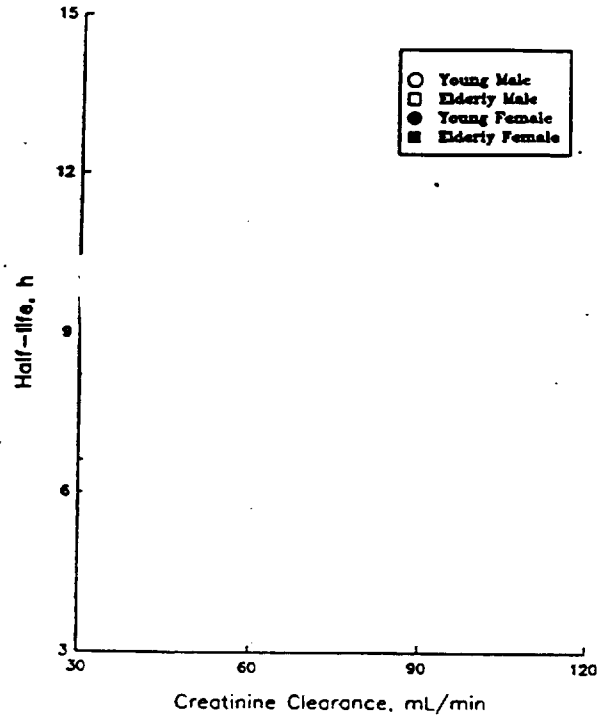


Figure 8

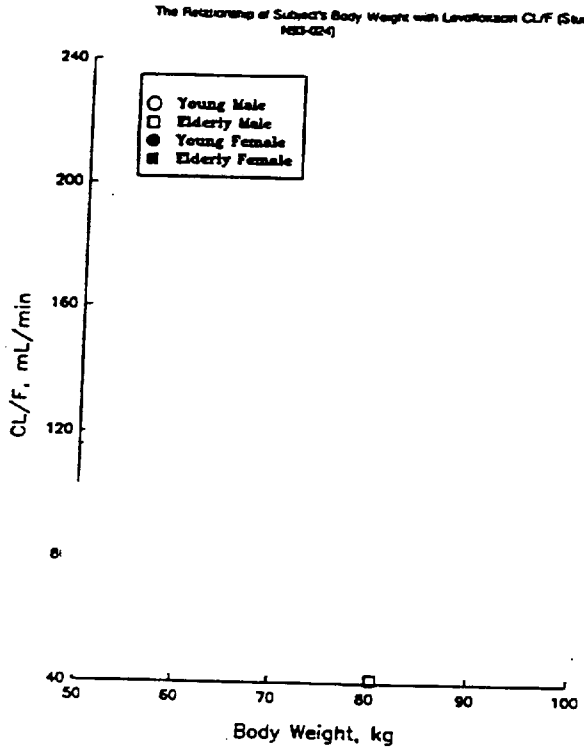


Figure 9

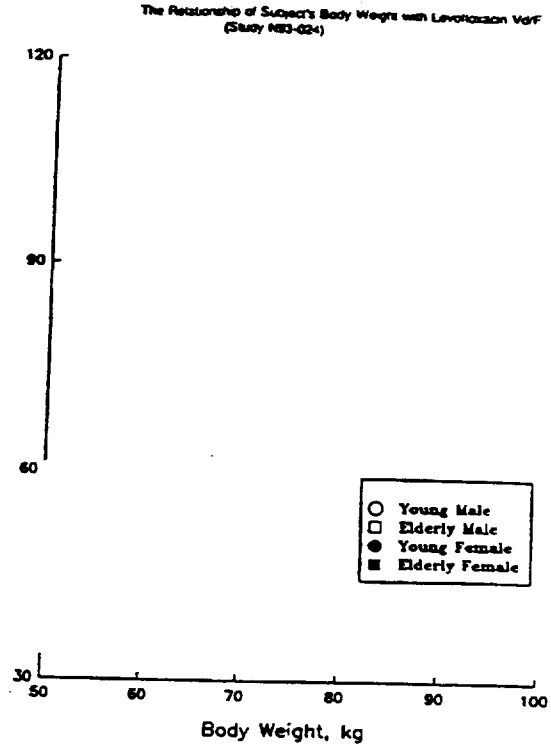


Figure 10

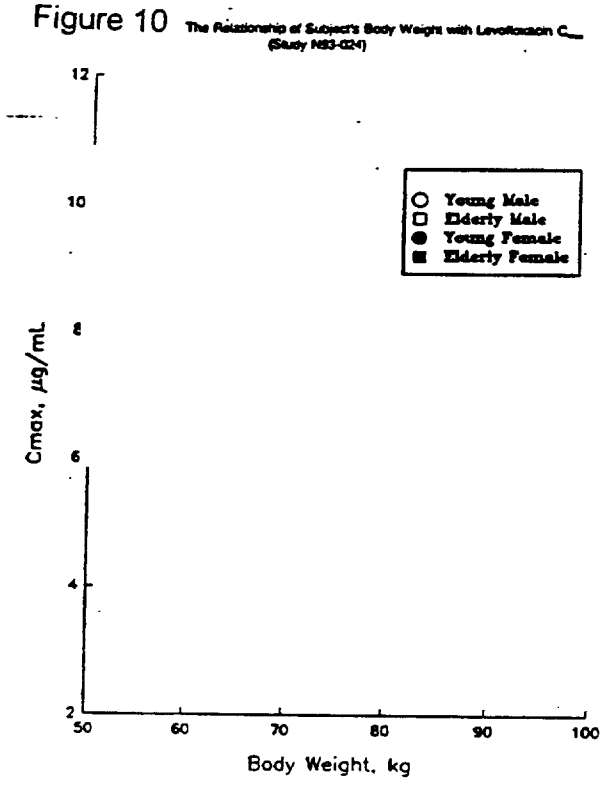
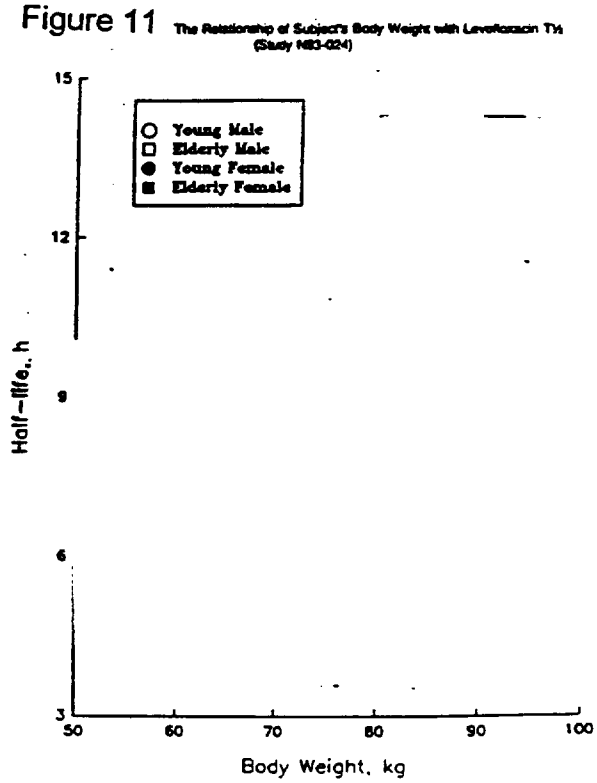


Figure 11



ATTACHMENT I: Baseline Demographics

Group	Subject	Age (yr)	Body Weight lb	Body Weight kg	Serum Creatinine (mg/dL)	Creatinine Clearance (mL/min)
Young Males		31	193	87.7	1.4	94.6
		36	190	86.4	1.3	95.5
		25	150	68.2	1.1	98.1
		22	134	60.9	1.1	90.1
		30	186	84.5	1.1	117.0
		33	165	75.0	1.1	100.6
Elderly Males		66	155	70.5	1.2	59.6
		66	191	86.8	1.1	80.0
		72	177	80.5	1.6	46.9
		66	177	80.5	1.3	63.3
		69	213	96.8	1.3	72.6
		75	205	93.2	1.2	69.8
Young Females		28	138	62.7	0.9	91.7
		26	180	81.8	1.3	84.1
		27	178	80.9	1.1	97.9
		29	170	77.3	0.9	112.0
		18	112	50.9	0.9	81.3
		24	155	70.5	1.0	95.9
Elderly Females		71	153	69.5	1.0	56.1
		66	155	70.5	1.0	61.0
		80	110	50.0	0.9	38.7
		66	115	52.3	0.9	50.1
		71	127	57.7	0.9	52.2
		74	132	60.0	1.0	46.6
Males: Subjects						
	Mean	50	178	80.9	1.2	82.4
	SD	21	23	10.6	0.2	20.4
	Max	75	213	96.8	1.6	117.0
	Min	23	134	60.9	1.1	46.9
Females: Subjects						
	Mean	49	144	65.3	1.0	72.3
	SD	24	25	11.4	0.1	24.2
	Max	81	180	81.8	1.3	112.0
	Min	18	110	50.0	0.9	38.7
Young: Subjects						
	Mean	28	163	74.0	1.1	97.0
	SD	5	25	11.0	0.2	10.0
	Max	37	193	88.0	1.6	117.0
	Min	18	112	51.0	0.9	81.0
Elderly Subjects						
	Mean	71	159	72.0	1.1	58.0
	SD	5	34	16.0	0.2	12.0
	Max	81	213	97.0	1.6	80.0
	Min	66	110	50.0	0.9	39.0

The following formula (based on age, body weight, and sex of the subject) is used to determine the creatinine clearance level:

$$\text{For male: } \frac{\text{Weight (kg)} \times (140 - \text{age in years})}{72 \times \text{serum creatinine (mg/dL)}}$$

For female: 0.85 x the above formula

ATTACHMENT 2 : Plasma Levofloxacin Concentration Data (N93-024)

	Plasma Concentration (µg/mL) at Sampling Time (h)												
Subj.	0	0.5	1	1.5	2	2.5	3	4	6	8	12	24	36
Males: Subjects [redacted]													
Mean	0.00	2.52	4.75	4.71	4.52	4.29	3.94	3.44	2.75	2.23	1.56	0.59	0.21
SD	0.00	1.93	1.58	1.19	0.70	0.57	0.60	0.64	0.66	0.60	0.59	0.36	0.22
Max	0.00	6.16	7.89	6.37	5.92	5.35	5.12	4.59	4.15	3.53	3.06	1.55	0.83
Min	0.00	0.62	1.77	1.73	3.36	3.38	3.13	2.57	1.87	1.59	0.92	0.26	0.00
Females: Subjects [redacted]													
Mean	0.00	2.47	5.78	6.28	6.13	6.22	5.70	4.95	4.13	3.30	1.97	0.54	0.14
SD	0.00	1.76	2.08	2.07	1.71	1.58	1.40	1.23	1.17	1.37	0.86	0.29	0.11
Max	0.00	5.94	8.11	9.14	8.95	9.93	8.66	7.52	6.48	6.97	4.13	1.20	0.38
Min	0.00	0.32	0.75	1.42	2.49	3.55	3.60	2.83	2.26	1.70	1.00	0.19	0.00
Young: Subjects [redacted]													
Mean	0.00	2.34	4.32	4.50	4.65	4.61	4.26	3.65	2.90	2.21	1.30	0.63	0.09
SD	0.00	1.91	1.84	1.59	1.19	0.95	0.82	0.84	0.84	0.60	0.30	0.12	0.06
Max	0.00	6.16	7.29	6.49	6.65	6.35	5.63	5.23	4.86	3.37	1.85	0.60	0.25
Min	0.00	0.32	0.75	1.42	2.49	3.38	3.13	2.57	1.87	1.59	0.92	0.19	0.00
Elderly: Subjects [redacted]													
Mean	0.00	2.64	6.21	6.49	6.01	5.90	5.38	4.73	3.98	3.32	2.22	0.77	0.27
SD	0.00	1.77	1.43	1.53	1.56	1.75	1.63	1.34	1.23	1.36	0.80	0.34	0.20
Max	0.00	5.94	8.11	9.14	8.95	9.93	8.66	7.52	6.48	6.97	4.13	1.55	0.83
Min	0.00	0.46	4.09	4.45	3.86	3.82	3.50	3.02	2.40	1.86	1.35	0.43	0.13

ATTACHMENT 3: Urine Levofloxacin Concentration Data (N93-024)

Subj.	Urine Concentrations (µg/mL) at Sampling Time[a]					
	predose	0-4 h	4-8 h	8-12 h	12-24 h	24-36 h
	0					
	0					
	0					
	0					
	0					
	0					
	0					
	0					
	0					
	0					
	0					
	0					
	0					
	0					
	0					
	0					
	0					
	0					
	0					
	0					
	0					
	0					
	0					
	0					

Limit of Quantification = 25.0 µg/mL
No sample received

ATTACHMENT 4: Urine Levofloxacin Amount (N93-024)

Subj.	Urine Amount (mg) Excreted During Sampling Time Intervals						Total (mg)
	predose	0-4 h	4-8 h	8-12 h	12-24 h	24-36 h	0-36 h
	0						
	0						
	0						
	0						
	0						
	0						
	0						
	0						
	0						
	0						
	0						
	0						
	0						
	0						
	0						
	0						
	0						
	0						
	0						
	0						
	0						
	0						
	0						
	0						

[a] No sample received

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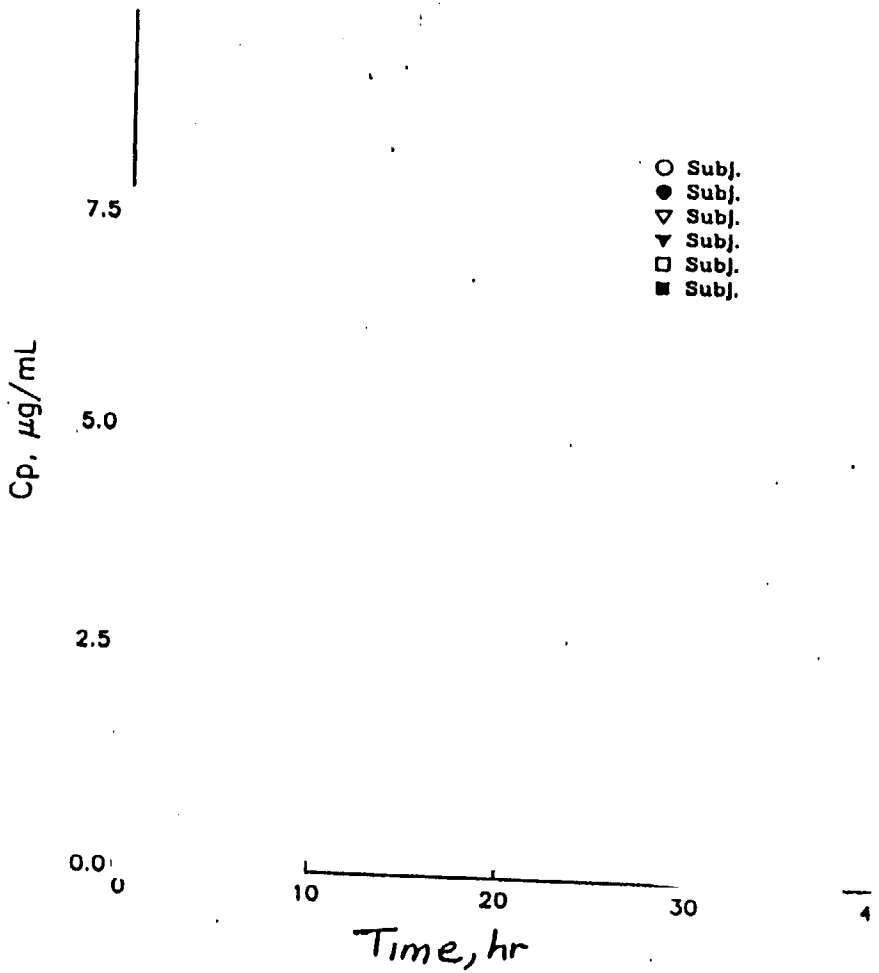
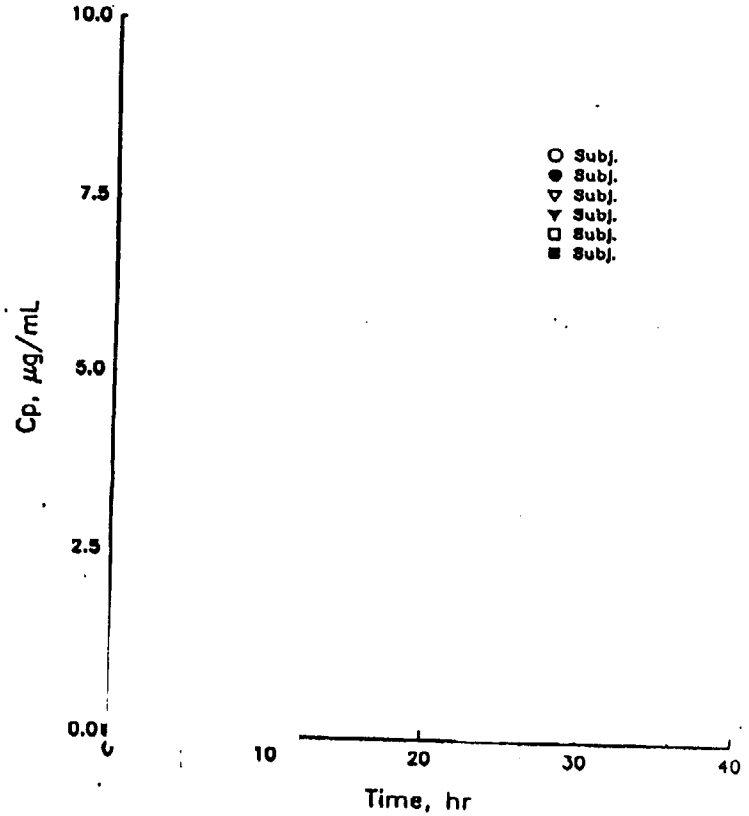
ATTACHMENT 5: Pharmacokinetic Parameters of Levofloxacin in 24 Healthy Subjects After a Single Oral 500 mg Dose of Levofloxacin (Study N93-024)

Group	Subject	C_{max} (µg/mL)	T_{max} (h)	AUC 0-36h	AUC 0-inf	$T_{\frac{1}{2}}$ (h)	MRT (h)	CL/F (mL/min)	Vd/F (L)	Vd/F (L/kg)	Au% 0-36h	CLr (mL/min)
Young Males												
Elderly Males												
Young Females												
Elderly Females												
Males: Subjects [redacted]												
	Mean	5.52	1.2	51.3	54.4	7.5	10.0	166	89	1.11	75	126
	SD	1.07	0.4	15.3	18.9	2.1	2.2	44	13	0.19	14	36
	Max	7.89	2.0	88.3	103.9	13.1	15.5	230	114	1.47	92	200
	Min	4.02	0.5	35.4	36.3	5.2	7.0	80	69	0.89	51	41
Female: Subjects [redacted]												
	Mean	6.96	1.7	66.1	67.7	6.1	8.6	136	62	0.94	77	106
	SD	1.57	0.5	23.5	24.2	0.8	1.0	44	16	0.14	7	40
	Max	9.93	2.5	122.4	126.4	7.2	10.0	220	90	1.16	85	182
	Min	4.17	1.0	35.6	37.8	4.4	6.2	66	35	0.69	64	46
Young: Subjects [redacted]												
	Mean	5.52	1.5	46.1	47.5	6.0	8.4	182	83	1.13	77	140
	SD	1.02	0.6	9.9	9.8	0.9	1.2	35	18	0.18	10	33
	Max	7.29	2.5	65.2	65.9	7.8	10.5	230	114	1.47	88	200
	Min	4.02	0.5	35.4	36.3	4.4	6.2	126	55	0.87	59	91
Elderly: Subjects [redacted]												
	Mean	6.96	1.4	71.3	74.7	7.6	10.2	121	67	0.92	75	91
	SD	1.60	0.5	21.5	23.3	2.0	2.0	33	19	0.12	11	29
	Max	9.93	2.5	122.4	126.4	13.1	15.5	176	95	1.07	92	134
	Min	4.52	1.0	46.0	47.4	5.8	8.4	66	35	0.69	51	41

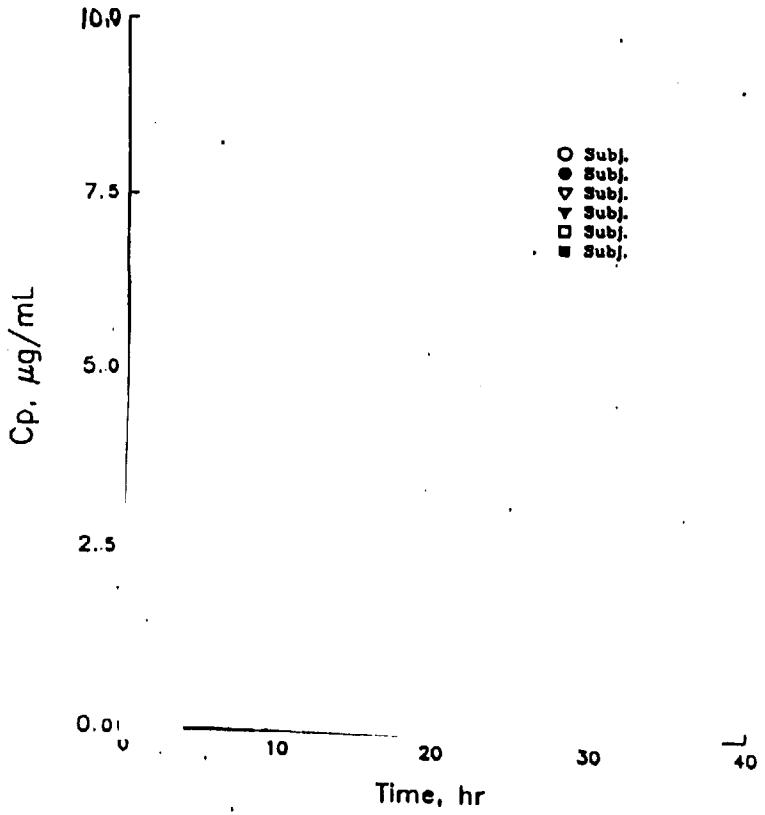
ATTACHMENT 6: Levofloxacin Plasma Concentration-Time Profiles: Six Young Female Subjects (Study N93-024)



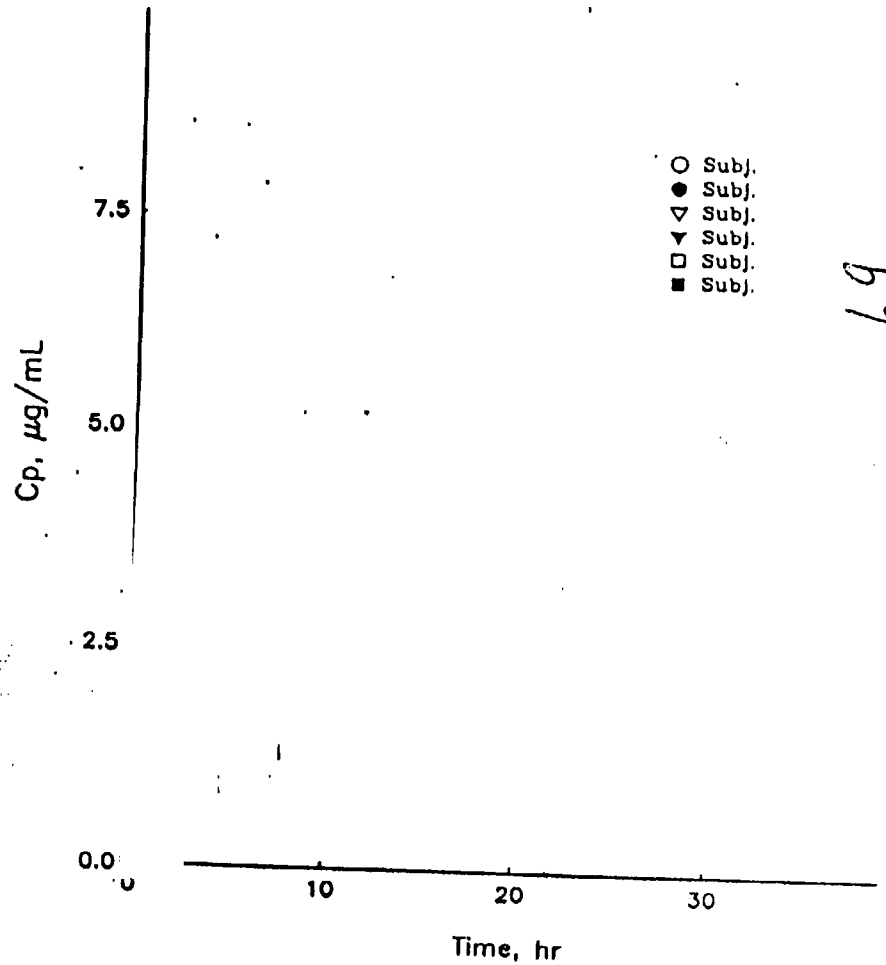
ATTACHMENT 7: Levofloxacin Plasma Concentration-Time Profiles: Six Elderly Female Subjects (Study N93-024)



ATTACHMENT 8: Levofloxacin Plasma Concentration-Time Profiles: Six Young Male Subjects (Study N93-024)



ATTACHMENT 9: Levofloxacin Plasma Concentration-Time Profiles: Six Elderly Male Subjects (Study N93-024)



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TITLE OF STUDY: SINGLE-DOSE PHARMACOKINETICS OF LEVOFLOXACIN IN RENALLY COMPROMISED SUBJECTS(STUDY M92-046). **Volumes 1.75 - 1.76.**

INVESTIGATOR and LOCATION:

OBJECTIVE: The objective of this study was to determine the pharmacokinetics and safety of a single oral 500 mg dose of levofloxacin in subjects with varying degrees of renal impairment ranging from mild impairment to severe impairment requiring dialysis treatment.

DEMOGRAPHICS: Thirty-eight subjects (17 males, 21 females) were entered into the study (Table 1).

STUDY DESIGN: This was a Phase I, unblinded, single dose study in which subjects were grouped according to the degree of renal impairment. The groups included subjects not treated with dialysis having creatinine clearances in the ranges of less than 20, 20-49, and 50-80 mL/min; subjects treated with regularly scheduled hemodialysis; and subjects treated with continuous ambulatory peritoneal dialysis (CAPD). Creatinine clearances in the nondialysis subjects were assessed by 24-hour urinary creatinine clearance determination. Stability of renal function was evaluated by two separate serum creatinine determinations performed within 3 weeks prior to admission.

DOSING: The subjects received a single 500 mg clinical tablet of levofloxacin (Formula No. FD-25213-097-G-22, Batch Nos. 5159 or 5324) as follows:

Nondialysis subjects: Each subject received a 500 mg oral dose of levofloxacin administered as one 500 mg clinical tablet with 120 mL of water following an 8-hour overnight fast.

Hemodialysis subjects: Each subject received a 500 mg oral dose of levofloxacin administered as one 500 mg clinical tablet with 120 mL of water following an 8-hour overnight fast. These subjects received a scheduled 4-hour hemodialysis treatment approximately 24 hours after dosing.

CAPD subjects: Each subject received a 500 mg oral dose of levofloxacin administered as one 500 mg clinical tablet with 120 mL of water following an 8-hour overnight fast. These subjects were dosed immediately following the completion of a CAPD fluid exchange and continued on their regularly scheduled CAPD.

SAMPLING: Blood samples were collected from nondialysis subjects at: 0 (predose), 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, 24, 48, 72, 96, 120, and 144 hours after levofloxacin administration. The 96, 120, and 144 hour samples were collected only for subjects with creatinine clearances less than 50 mL/min. Hemodialysis subjects had blood samples collected at: 0 (predose), 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, 24, 36, 48, 72, 96, 120, and 144 hours after dosing. In addition, paired arterial/venous blood samples were collected during the first hemodialysis session following dosing at: 0 (prior to dialysis), hourly during dialysis, and immediately following dialysis. CAPD subjects had blood samples collected at: 0 (predose), 0.5, 1, 1.5, 2, 3, 4, 5, 6, 8, 10, 14, 24, 48, 72, and 96 hours after dosing.

Urine was collected quantitatively from nondialysis subjects for the following intervals: 0 (predose), 0-6, 6-12, 12-24, 24-36, 36-48, and 48-72 hours postdosing in the 50-80 mL/min creatinine clearance group. For subjects with creatinine clearances less than 50 mL/min an additional sample at 72-96 hours postdosing was collected.

ANALYTICAL METHOD: Plasma, dialysate fluid, and urine samples were assayed for levofloxacin according to validated HPLC procedures at

DATA ANALYSIS: The following levofloxacin pharmacokinetic parameters were determined: C_{max}, T_{max}, AUC (0-*), AUC (0-∞), CL/F, k_e, $t_{1/2}$, A_e (% Dose), Cl_R, A_e, and CL_D. Vd_{ss}/F was not determined because of the assumptions inherent in its calculation. Statistical comparisons were performed with SAS software.

RESULTS: The mean levofloxacin pharmacokinetic parameters determined for the five groups of subjects are summarized in Table 2. The results show that the pharmacokinetics of levofloxacin were altered by renal impairment with CL/F, CL_R, k_e, decreasing with increasing renal impairment, and AUC and $t_{½}$ increasing with increasing renal impairment.

Statistical comparison of pharmacokinetic parameters by ANOVA showed significant differences in AUC, CL_R, CL/F, k_e and $t_{½}$ between the three groups of nondialysis subjects, and significant differences in k_e and $t_{½}$ between each of the dialysis groups and the three groups of nondialysis subjects. There were no significant differences between groups in C_{max} or T_{max} (Table 3).

CAPD was not effective at removing levofloxacin from the body, as indicated by an average of only 11.6% of the dose (58 mg) of levofloxacin being removed in an ongoing 4-day dialysis period. Clearance during hemodialysis averaged 219.42 mL/min, thus levofloxacin was readily dialyzable from plasma. However, hemodialysis did not appear to be effective at removing levofloxacin from the body as indicated by the data from an individual that shows 12.39% of the dose removed in a 4-hour dialysis treatment, and by the rebound in plasma concentrations following completion of the hemodialysis treatment. These results can be explained by the large distribution volume of levofloxacin (V_{ss} ~90 L), wherein the levofloxacin in plasma is readily removed by hemodialysis, but

because majority of the amount of levofloxacin in the body is being distributed into peripheral tissues, this large fraction is not available for hemodialysis removal.

CONCLUSION: The pharmacokinetics of levofloxacin were shown to be affected by renal impairment, with statistically significant decreased renal elimination and clearance and increased plasma elimination half-lives with decreasing renal function, as estimated by creatinine clearance. Renally impaired patients will accumulate levofloxacin to a greater extent than patients with normal renal function if dosed at the same rate. Therefore, levofloxacin dosage adjustments will be required in renally impaired patients in order to maintain plasma concentrations in the same range as patients with normal renal function.

Neither hemodialysis nor CAPD appear to be effective at removing levofloxacin from the body. The apparent ineffectiveness of the dialysis procedures is probably due the high volume of distribution (V_{ss}~90 L) of levofloxacin. Hence, supplemental doses of levofloxacin will not be required in order to replace levofloxacin losses following hemodialysis or CAPD.

Table 1: Demographic and Baseline Characteristics

(All Subjects Enrolled in Study M92-046)

	Dialysis* (N=16)	Nondialysis (N=22)	Total (N=38)
Sex			
Men	10	7	17
Women	6	15	21
Race			
Caucasian	1	3	4
Black	13	19	32
Hispanic	2	0	2
Age (years)			
Mean ± S.D.	47.1±14.2	53.0±12.6	50.5±13.4
Range			
Weight (lb)			
Mean ± S.D.	187.8±54.8	152.8±39.5	167.5±49.1
Range			
Height (in)			
Mean ± S.D.	67.1±4.3	65.0±3.6	65.9±4.0
Range			

* Dialysis group includes subjects on hemodialysis and CAPD.

Table 2: Summary of Levofloxacin Pharmacokinetic Parameters (Mean ±SD)

(Study M92-046)

Parameter	Nondialysis CL_{CR} <20 (mL/min) N=6	Nondialysis CL_{CR} 20-49 (mL/min) N=8	Nondialysis CL_{CR} 50-80 (mL/min) N=3	Hemodialysis N=4	CAPD N=4
C_{max}	8.18	7.10	7.52	5.71	6.93
(µg/mL)	(2.56)	(3.09)	(1.75)	(0.99)	(2.31)
T_{max}	1.08	2.13	1.50	2.75	1.38
(h)	(1.02)	(1.30)	(0.50)	(2.18)	(1.11)
AUC (0-*)	251.74	173.44	93.20		
(µg•h/mL)	(75.68)	(57.28)	(12.29)	NA	NA
AUC (0-∞)	263.49	182.09	95.62		
(µg•h/mL)	(72.48)	(62.61)	(11.83)	NA	NA
CL/F	33.34	51.44	87.99		
(mL/min)	(7.60)	(19.41)	(10.16)	NA	NA
k_e	0.0203	0.031	0.077	0.011[a]	0.016[a]
(h^{-1})	(0.00315)	(0.015)	(0.007)	(0.0047)	(0.0074)
$t_{1/2}$	34.83	26.57	9.09	76.05[a]	50.68[a]
(h)	(5.49)	(10.22)	(0.89)	(41.54)	(23.82)
A_e	16.01	34.65	60.53		
(% dose)	(7.63)	(11.65)	(11.60)	NA	NA
CL_R	12.72	26.43	56.59		
(mL/min)	(3.05)	(12.89)	(7.69)	NA	NA
A_d				12.39	11.60
(% dose)	NA	NA	NA	(N=1)[b]	(N=2)[b]
				219.42	5.03
CL_D				(24.90)	(0.94)
(mL/min)	NA	NA	NA	(N=4)	(N=4)

[a] Note: Values for k_e and $t_{1/2}$ were estimated from the levofloxacin plasma concentration profiles, including the times when these subjects were receiving their dialysis treatments, thus, these parameters represent elimination by a combination of both endogenous and exogenous processes.

[b] Four subjects received dialysis treatment, however, not all dialysis fluid samples were available for summation of the amount removed by dialysis.

NA = Not applicable

AUC (0-*) Area under the plasma concentration-time curve from time zero to the time of the last measurable plasma concentration

A_e (%Dose) The amount of unchanged levofloxacin recovered in the urine expressed as a percentage of the dose administered

A_d The amount of unchanged levofloxacin recovered in dialysate fluid from a 4-hour hemodialysis treatment or from 4 days of CAPD treatment

Table 3: Results of ANOVA Statistical Comparisons of Pharmacokinetic Parameters Between Subject Groups (Study M92-046)

Parameter	ANOVA Results
C_{max}[a]	NS
T_{max}[b]	NS
AUC (0-*)[a,c]	SIG
AUC (0-∞)[a]	SIG
CL/F	SIG
k_e	SIG
$t_{½}$	SIG
CL_R	SIG

[a] C_{max} and AUCs log-transformed for statistical comparison.

[b] T_{max} was ranked for comparison.

[c] AUC (0-*) AUC from time zero to the time of the last measurable plasma concentration.

NS = Difference between means is not statistically significant ($p>0.05$).

SIG = Difference between means is statistically significant ($p \leq 0.05$).

TABLE 4 SINGLE-DOSE PHARMACOKINETICS OF LEVOFLOXACIN IN THE PRESENCE OF RENAL DYSFUNCTION

PROTOCOL:M92-046

OBS	GROUP	SUBJECT	CMAX	TMAX	AUC	AUC 0-∞	k_e	T_HALF	CL/F	CL_R
1	CLCR < 20		5.79	0.5	177.48	199.99	0.016	43.11	41.67	15.72
2	CLCR < 20		7.93	0.5	223.44	228.35	0.025	28.12	36.49	12.44
3	CLCR < 20		12.90	0.5	386.49	393.70	0.021	33.54	21.17	7.66
4	CLCR < 20		7.89	0.5	203.96	214.75	0.018	37.96	38.81	16.01
5	CLCR < 20		8.48	1.5	289.22	299.69	0.023	29.99	27.81	12.78
6	CLCR < 20		6.07	3.0	229.88	244.48	0.019	36.27	34.09	11.70
7	CLCR 20-49		7.48	3.0	152.20	155.36	0.054	12.74	53.64	27.48
8	CLCR 20-49		3.84	3.0	96.37	97.93	0.053	13.18	85.09	37.43
9	CLCR 20-49		13.60	0.5	214.13	232.55	0.026	26.33	35.83	18.97
10	CLCR 20-49		8.66	1.5	253.61	262.42	0.023	30.08	31.76	11.47
11	CLCR 20-49		4.53	2.0	129.92	132.58	0.033	21.20	62.86	34.41
12	CLCR 20-49		7.37	0.5	227.46	241.62	0.019	35.94	34.49	15.77
13	CLCR 20-49		5.09	3.0	117.34	121.28	0.021	32.47	68.71	48.76
14	CLCR 20-49		6.22	4.0	196.47	213.00	0.017	40.62	39.12	17.14
15	CLCR 50-80		6.06	2.0	85.26	88.59	0.069	10.08	94.07	50.16
16	CLCR 50-80		7.04	1.5	86.98	88.99	0.078	8.87	93.65	65.11
17	CLCR 50-80		9.46	1.0	107.36	109.28	0.083	8.33	76.26	54.49
18	HEMODIALYSIS		5.04	2.0	204.82	336.82	0.005	134.95	24.74	.
19	HEMODIALYSIS		6.48	1.5	269.58	350.60	0.009	75.48	23.77	.
20	HEMODIALYSIS		4.69	1.5	210.59	236.13	0.014	48.50	35.29	.
21	HEMODIALYSIS		6.64	6.0	310.93	343.70	0.015	45.26	34.25	.
22	CAPD		8.06	1.0	323.65	578.33	0.008	82.88	14.41	.
23	CAPD		9.63	0.5	221.11	271.27	0.017	41.10	30.72	.
24	CAPD		5.18	3.0	223.62	241.85	0.026	26.77	34.46	.
25	CAPD		4.84	1.0	213.62	284.78	0.013	51.97	29.26	.

Figure 1: Mean Levofloxacin Plasma Concentration-Time Profiles in Subjects with Different Degrees of Renal Impairment (Study M92-046)

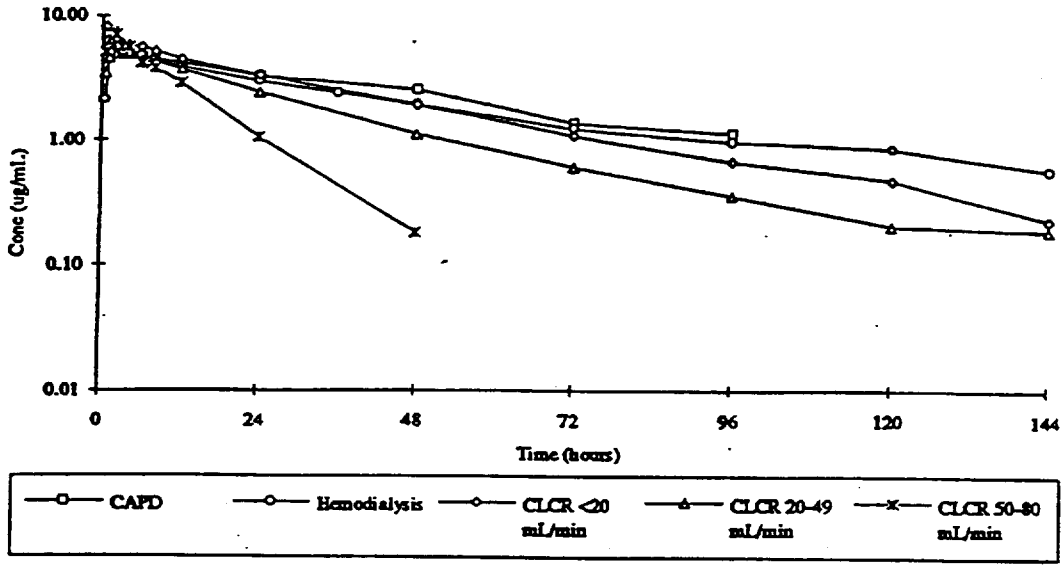


Figure 2: Mean Plasma Concentration-Time Curve for Four Subjects Prior To, During, and Following A Single 4-Hour Hemodialysis Treatment (Study M92-046)

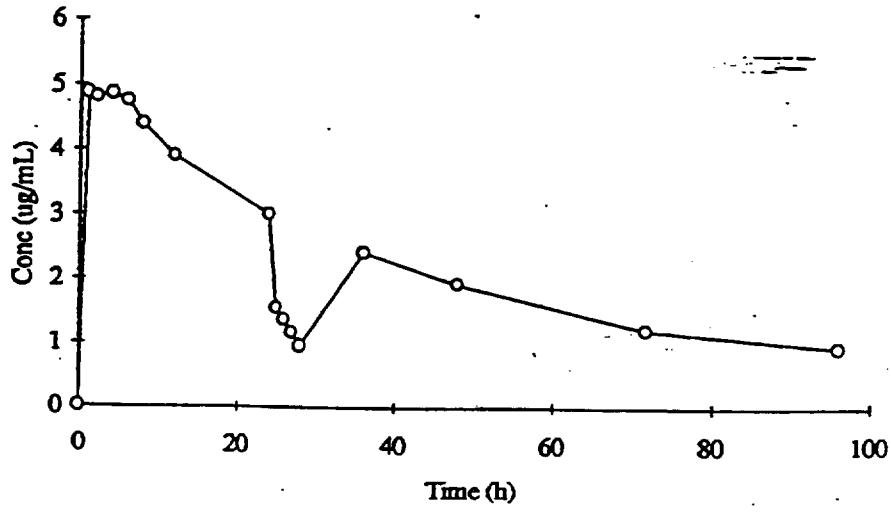


Figure 3 : Levofloxacin CL_R In Renally Impaired Subjects As A Function of CL_{CR} Following A 500 mg Single Oral Dose To Nondialysis Subjects (Study M92-046)

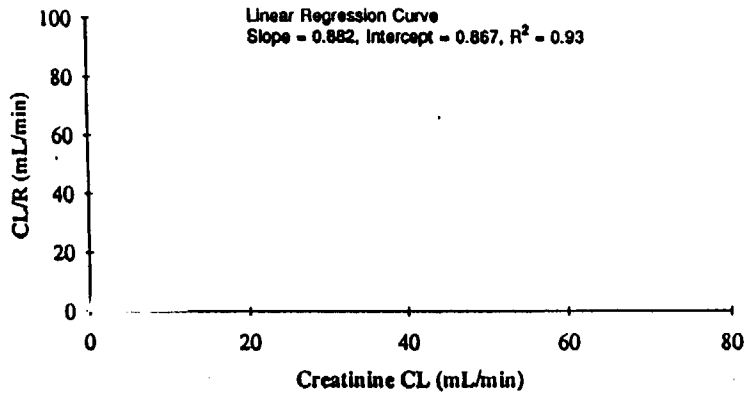


Figure 4 : Levofloxacin CL/F In Renally Impaired Subjects As A Function of CL_{CR} Following A 500 mg Single Oral Dose To Nondialysis Subjects (Study M92-046)

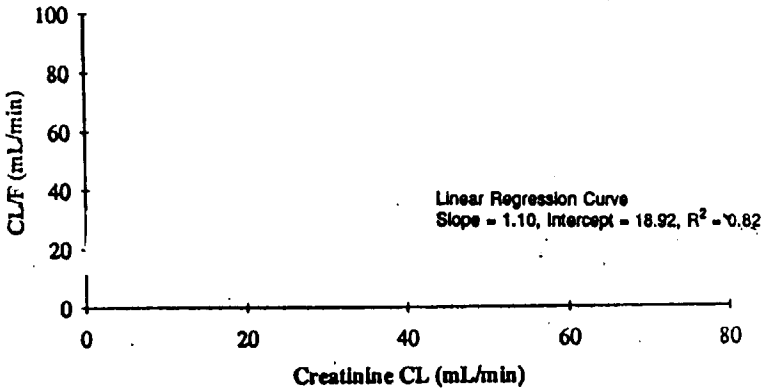


Figure 5 : Levofloxacin CL/F In Renally Impaired Subjects As A Function of CL_R Following A 500 mg Single Oral Dose To Nondialysis Subjects (Study M92-046)

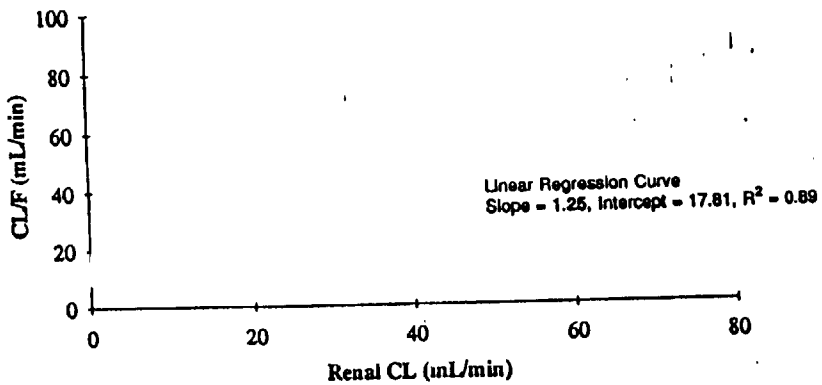


Table 5: Levofloxacin Pharmacokinetic Parameters In Subjects With Normal Renal Function and In Subjects With Impaired Renal Function (DM95331)

Parameter[a]	Normal Renal Function, CL_{cr} >80 mL/min N=23[b]	Slightly Impaired Renal Function CL_{cr} 50-80 mL/min N=3[c]	Moderate To Severely Impaired Renal Function CL_{cr} 20-49 mL/min N=8[c]	Severely Impaired Renal Function CL_{cr} <20 mL/min N=6[c]	Hemodialysis Patients N=4[c]	CAPD[d] Patients N=4[c]
CL/F (mL/min)	177.7 (27.8)	96.0 (10.2)	51.4 (19.4)	33.3 (7.6)	--	--
CL_R (mL/min)	103.4 (29.5)	56.8 (7.7)	26.4 (12.9)	12.7 (3.1)	--	--
Half-life (h)	6.3 (0.8)	9.1 (0.9)	26.8 (10.2)	34.8 (5.5)	76.1 (41.5)	50.7 (23.8)

a Data are the mean (± SD)
b Data for subjects with normal renal function from Study LOFBO-PHI0-097
c Data for subjects with impaired renal function from Study M92046
d Continuous Ambulatory Peritoneal Dialysis

Figure 6: Mean Levofloxacin Plasma Concentration-Time Profiles Following Single Oral 500 mg Doses To Subjects With Various Levels of Renal Function (DM95331)

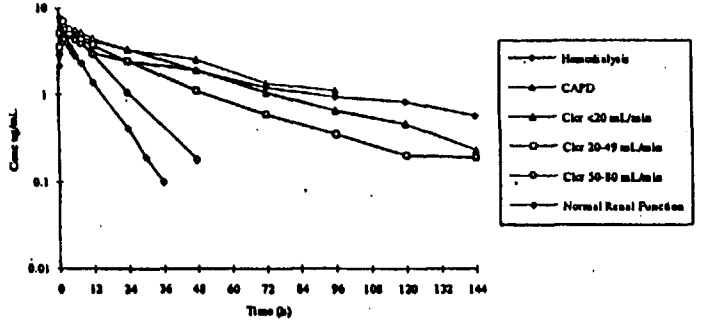


Figure 7: Simulated Levofloxacin Plasma Concentration:Time Profiles To Steady-State Conditions For Subjects With Normal Renal Function (CL_{CR} >80 mL/min) (500 mg Orally q24h and 500 mg q12h) (DM95331)

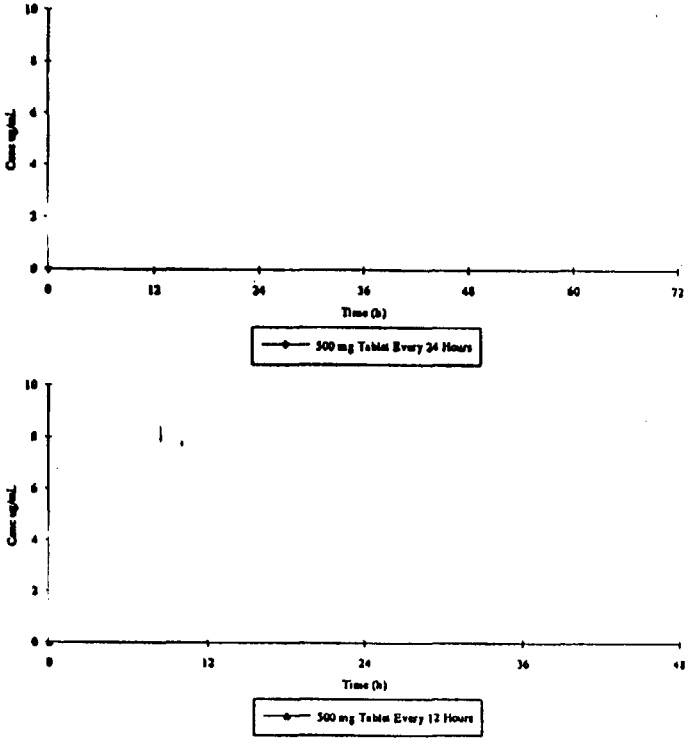


Figure 8 Simulated Levofloxacin Plasma Concentration:Time Profiles To Steady-State Conditions For Subjects With Slightly Impaired Renal Function (CL_{cr} 50-80 mL/min) (500 mg Orally q24h) (DM85331)

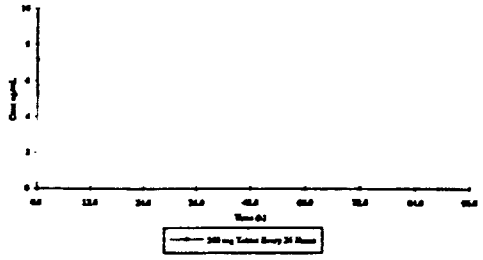


Figure 9 Simulated Levofloxacin Plasma Concentration:Time Profiles To Steady-State Conditions For Subjects With Moderate To Severely Impaired Renal Function (CL_{cr} 20-49 mL/min) (500 mg Oral Dose Initially, Followed by 250 mg Orally q24h) (DM85331)

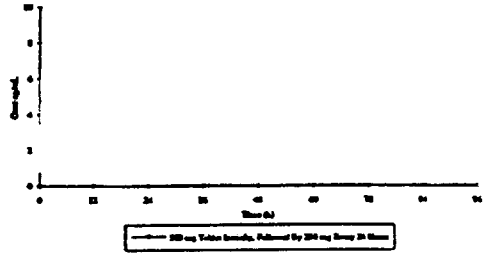


Figure 10 Simulated Levofloxacin Plasma Concentration:Time Profiles To Steady-State Conditions For Subjects With Severely Impaired Renal Function (CL_{cr} 10-19 mL/min) (500 mg Oral Dose Initially Followed by 250 mg Orally q48h) (DM85331)

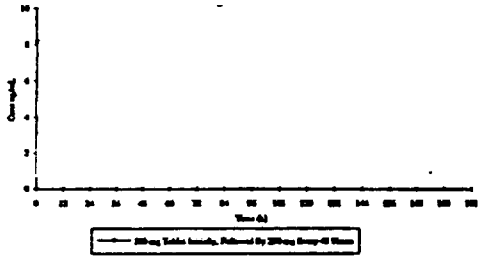


Figure 11 Simulated Levofloxacin Plasma Concentration:Time Profiles To Steady-State Conditions For Subjects Receiving Hemodialysis (500 mg Oral Dose Initially, Followed by 250 mg Orally q48h) (DM85331)

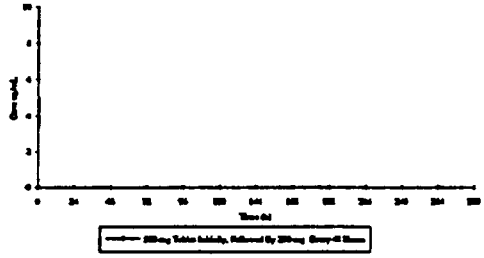
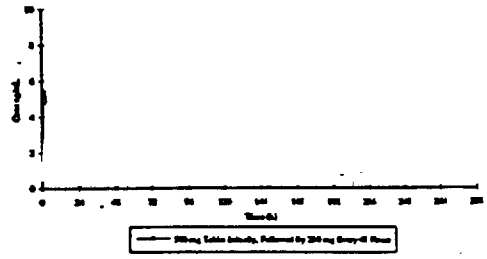


Figure 12 Simulated Levofloxacin Plasma Concentration:Time Profiles To Steady-State Conditions For Subjects Receiving CAPD (500 mg Oral Dose Initially Followed by 250 mg Orally q48h) (DM85331)



ATTACHMENT 1: Levofloxacin Plasma Concentration-Time Data Following a 500 mg Single Oral Dose Given to Subjects With Creatinine Clearances Less Than 20 mL/min (Study M92-046)

LEVOFLOXACIN PLASMA DATA - CLcr <20

SUBJECT	CONCENTRATION (µg/mL) AT TIME (hours)																		
	0.00	0.50	1.00	1.50	2.00	3.00	4.00	5.00	6.00	8.00	10.00	12.00	14.00	24.00	36.00	48.00	72.00	96.00	120.00	144.00
MEAN	0.00	8.18	7.45	6.89	6.50	5.89	5.76	A	5.62	5.20	A	4.47	A	3.32	A	1.90	1.05	0.65	0.46	0.23
S DEV	0.00	2.80	2.22	1.97	1.91	2.08	1.64	A	2.06	1.61	A	1.20	A	0.97	A	0.72	0.42	0.28	0.15	0.09
CV %	0.00	34.22	29.76	28.59	29.39	35.24	28.54	A	36.71	31.03	A	26.73	A	29.28	A	38.12	40.07	42.98	31.80	39.43
MEDIAN	0.00	7.89	7.39	7.10	6.41	6.12	5.70	A	5.36	4.88	A	4.32	A	3.10	A	1.61	0.92	0.63	0.44	0.22
GEOMETRIC MEAN	0.00	7.85	7.19	6.63	6.24	5.57	5.57	A	5.32	4.99	A	4.34	A	3.20	A	1.81	0.98	0.60	0.44	0.21

A NO SAMPLE COLLECTED

ATTACHMENT 2: Levofloxacin Plasma Concentration-Time Data Following a 500 mg Single Oral Dose Given to Subjects With Clearances 20-49 mL/min (Study M92-046)

LEVOFLOXACIN PLASMA DATA - CLcr 20-49

SUBJECT	CONCENTRATION (ug/mL) AT TIME (hours)																	
	0.00	0.50	1.00	1.50	2.00	3.00	4.00	5.00	6.00	8.00	10.00	12.00	16.00	24.00	36.00	48.00	72.00	96.00	120.
MEAN	0.00	3.45	4.56	5.01	4.92	5.23	5.09	A	4.30	4.25	A	3.71	A	2.43	A	1.11	0.59	0.35	0.
S DEV	0.00	4.72	2.37	2.35	1.60	1.13	1.18	A	0.85	0.79	A	0.85	A	0.73	A	0.54	0.39	0.27	0.
CV %	0.00	136.68	51.88	47.00	32.52	21.67	23.25	A	19.80	18.67	A	22.81	A	30.19	A	48.81	65.88	76.29	83.
MEDIAN	0.00	1.27	4.73	5.23	4.87	5.01	4.67	A	4.45	4.15	A	3.87	A	2.33	A	1.13	0.55	0.34	0.
GEOMETRIC MEAN	0.00	1.54	3.89	4.47	4.67	5.13	4.97	A	4.22	4.19	A	3.62	A	2.34	A	0.98	0.46	0.32	0.

A NO SAMPLE COLLECTED
D BELOW LOWER QUANTIFICATION LIMIT

ATTACHMENT 3: Levofloxacin Plasma Concentration-Time Data Following a 500 mg Single Oral Dose Given to Subjects With Creatinine Clearances 50-80 mL/min
(Study M92-046)

LEVOFLOXACIN PLASMA DATA - CLcr 50to80

SUBJECT	CONCENTRATION (ug/mL) AT TIME (hours)																		
	0.00	0.50	1.00	1.50	2.00	3.00	4.00	5.00	6.00	8.00	10.00	12.00	14.00	24.00	36.00	48.00	72.00	96.00	120.00	144.00
MEAN	0.00	5.07	7.14	7.28	7.04	5.62	5.62	A	4.15	3.81	A	2.69	A	1.06	A	0.18	0.00	0.00	0.00	0.00
S DEV	0.00	3.14	2.06	1.60	1.20	1.27	1.06	A	0.77	0.19	A	0.29	A	0.09	A	0.04	0.00	0.00	0.00	0.00
CV %	0.00	61.96	28.84	21.95	17.09	22.52	18.87	A	18.45	5.10	A	10.08	A	8.43	A	22.38	0.00	0.00	0.00	0.00
MEDIAN	0.00	5.17	6.43	7.04	6.67	5.21	5.50	A	3.71	3.71	A	2.82	A	1.04	A	0.16	0.00	0.00	0.00	0.00
GEOMETRIC MEAN	0.00	4.30	6.95	7.17	6.97	5.53	5.55	A	4.10	3.80	A	2.68	A	1.06	A	0.18	0.00	0.00	0.00	0.00

A NO SAMPLE COLLECTED
D BELOW LOWER QUANTIFICATION LIMIT

ATTACHMENT 4: Levofloxacin Plasma Concentration-Time Data Following A 500 mg Single Oral Dose Given to Subjects On Hem (Study M92-046).

LEVOFLOXACIN PLASMA DATA - HEMODIALYSIS

SUBJECT	CONCENTRATION (µg/mL) AT TIME (hours)																	
	0.00	0.50	1.00	1.50	2.00	3.00	4.00	5.00	6.00	8.00	10.00	12.00	14.00	24.00	36.00	48.00	72.00	96.00	120.00
MEAN	0.00	2.09	4.88	4.88	4.81	4.75	4.86	A	4.74	4.38	A	3.89	A	2.98	2.39	1.91	1.20	0.93	0.82
S DEV	0.00	1.29	1.10	1.56	0.60	1.03	1.13	A	1.28	1.02	A	1.13	A	1.12	0.28	0.42	0.40	0.14	0.13
CV %	0.00	61.47	22.65	31.98	12.52	21.72	23.32	A	26.98	23.19	A	29.04	A	37.78	11.53	21.92	33.34	14.89	16.28
MEDIAN	0.00	2.62	4.56	5.11	4.83	4.51	4.57	A	4.21	4.14	A	3.25	A	2.85	2.47	1.85	1.26	0.97	0.77
GEOMETRIC MEAN	0.00	1.38	4.79	4.66	4.78	4.67	4.76	A	4.63	4.30	A	3.79	A	2.82	2.38	1.88	1.15	0.92	0.81

A NO SAMPLE COLLECTED

ATTACHMENT 5: Levofloxacin Plasma Concentration-Time Data Following A 500 mg Single Oral Dose Given to Subjects On CAPD (Study M92-046)

LEVOFLOXACIN PLASMA DATA - CAPD

SUBJECT	CONCENTRATION (µg/mL) AT TIME (hours)																		
	0.00	0.50	1.00	1.50	2.00	3.00	4.00	5.00	6.00	8.00	10.00	12.00	14.00	24.00	36.00	48.00	72.00	96.00	120.00	144.00
MEAN	0.00	4.99	5.41	5.10	5.13	5.20	4.80	A	4.66	4.52	A	A	A	3.28	A	2.53	1.33	1.10	A	A
S DEV	0.00	3.40	1.78	1.49	1.32	1.22	0.82	A	1.04	0.89	A	A	A	0.39	A	0.80	0.52	0.72	A	A
CV %	0.00	68.16	32.87	29.30	25.62	23.56	17.19	A	22.25	19.74	A	A	A	11.80	A	31.78	38.92	65.23	A	A
MEDIAN	0.00	4.10	4.64	4.44	4.81	4.85	4.61	A	4.52	4.54	A	A	A	3.29	A	2.34	1.25	0.90	A	A
GEOMETRIC MEAN	0.00	4.19	5.23	4.96	5.02	5.10	4.74	A	4.57	4.45	A	A	A	3.26	A	2.44	1.26	0.95	A	A

A NO SAMPLE COLLECTED

ATTACHMENT 6 : Levofloxacin Hemodialysis Clearance Values Following A 500 mg Single Oral Dose Given to Hemodialysis Subjects
(Study M92-046)

1. Subject [redacted] CL_D = [redacted] mL/min

Dialysis Time (h)	Dialysis Flow (mL/min)	Concentration In Dialysate (µg/mL)	Amount In Dialysate (mg)	Plasma Conc. (µg/mL)	Plasma AUC (mL)
		SUMS	61.94		AUC (1-4 h)= 3.1030

2. Subject [redacted] CL_D = [redacted] mL/min

Dialysis Time (h)	Dialysis Flow (mL/min)	Concentration In Dialysate (µg/mL)	Amount In Dialysate (mg)	Plasma Conc. (µg/mL)	Plasma AUC (mL)
		SUMS	Incomplete		AUC (1-3 h)= 2.8456

ATTACHMENT 6 : Levofloxacin Hemodialysis Clearance Values Following A 500 mg Single Oral Dose Given to Hemodialysis Subjects
(Study M92-046) (Continued)

3. Subject [redacted] CL_D = [redacted] mL/min

Dialysis Time (h)	Dialysis Flow (mL/min)	Concentration In Dialysate (µg/mL)	Amount In Dialysate (mg)	Plasma Conc. (µg/mL)	Plasma AUC (mL)
		SUMS	Incomplete		AUC (1-3 h)= 2.4876

4. Subject [redacted] CL_D = [redacted] mL/min

Dialysis Time (h)	Dialysis Flow (mL/min)	Concentration In Dialysate (µg/mL)	Amount In Dialysate (mg)	Plasma Conc. (µg/mL)	Plasma AUC (mL)
		SUMS	Incomplete		AUC (1-2 h)= 1.9679

ATTACHMENT 7: Levofloxacin CAPD Clearance Values Following A 500 mg Single Oral Dose Given to CAPD Subjects
(Study M92-046)

1. Subject No. [redacted]

Day	Bag No.	Volume (mL)	Concentration in Dialysate (µg/mL)	Amount in Dialysate (mg)	Plasma AUC (1.5-14 h) µg-h/mL	CL_D (mL/min)
1	1					
	2					
	3					
	4					
	5					
2	1					
	2					
	3					
	4					
3	1					
	2					
	3					
	4					
4	1					
	2					
	3					
	4					

mg

ATTACHMENT 8: Levofloxacin CAPD Clearance Values Following A 500 mg Single Oral Dose Given to CAPD Subjects
(Study M92-046) (Continued)

2. Subject No. [redacted]

Day	Bag No.	Volume (mL)	Concentration In Dialysate (µg/mL)	Amount In Dialysate (mg)	Plasma AUC (1.5-14 h) µg•h/mL	CL_D (mL/min)
1	1					
	2					
	3					
	4					
	5					
2	1					
	2					
	3					
	4					
3	1					
	2					
	3					
	4					
4	1					
	2					
	3					
	4					

ATTACHMENT 9 : Levofloxacin CAPD Clearance Values Following A 500 mg Single Oral Dose Given to CAPD Subjects
(Study M92-046) (Continued)

3. Subject No. [redacted]

Day	Bag No.	Volume (mL)	Concentration In Dialysate (µg/mL)	Amount In Dialysate (mg)	Plasma AUC (1.5-14 h) µg•h/mL	CL_D (mL/min)
1	1					
	2					
	3					
	4					
	5					
2	1					
	2					
	3					
	4					
3	1					
	2					
	3					
	4					
	5					
4	1					
	2					
	3					
	4					
	5					

TITLE OF STUDY: EVALUATION OF THE PHARMACOKINETICS AND SAFETY OF SINGLE AND MULTIPLE HIGH-DOSE REGIMENS OF LEVOFLOXACIN (RWJ-25213-000) IN HIV SEROPOSITIVE SUBJECTS.(PROTOCOL N93-032). **VOLUME 1.77.**

INVESTIGATOR AND LOCATION:

OBJECTIVES: The objective of this study was to evaluate the pharmacokinetics and safety of levofloxacin in HIV seropositive subjects after single and multiple 750-mg once-daily oral doses of levofloxacin for 2 weeks followed by intermittent 750-mg or 1-g doses of levofloxacin thrice-weekly for 2 weeks.

STUDY DESIGN: This was a sequential, two-part, randomized, double-blind, placebo-controlled study in 26 adult male and female volunteers with HIV infection. Subjects were group into two parallel panels based on their CD4 cell counts: Panel 1 (N = 13) with CD4 cell counts <250; Panel 2 (N = 13) with CD4 cell counts ≥250. Subjects were randomly assigned to three treatment groups (A, B, and C of 5, 5, and 3 subjects, respectively, in each panel) receiving levofloxacin or placebo doses according to the following schedule:

Period	Duration	Regimen	Group A	Group B	Group C
Part One	Days 1-14	once-daily	750 mg	750 mg	placebo
Part Two	Days 15-28	thrice-weekly	750 mg	1 g	placebo

The 750-mg dose consisted of one 500-mg (Formula No. FD 25213-097-G-22, Batch No. 5324), two 125-mg (Formula No. FD 25213-097-H-22, Batch No. R5520) levofloxacin tablets and two placebo tablets. The 1-g dose consisted of one 500-mg and four 125-mg levofloxacin tablets. Serial venous blood samples and quantitative urine collections were obtained following dose administration on Days 1, 14, 15, and 26 from the subjects for levofloxacin pharmacokinetic evaluation. Sparse samples were also obtained on Days 5, 13, and 24 for drug levels monitoring purpose.

DEMOGRAPHICS: Although the protocol specified that 26 subjects would be enrolled, four additional subjects were enrolled to replace four subjects who discontinued prematurely (Table 1).

SAMPLE COLLECTION AND HANDLING: Serial venous (5 mL) blood samples for the determination of plasma levofloxacin concentrations were collected into heparinized tubes from each subject starting on Study Day 1 and continuing through Study Day 29 at the following times:

Study Day	Postdose Blood Sampling
1	0,* 0.5, 1, 1.5, 2, 3, 4, 8, 12, 16, and 24* h
5	0,* 1, 2, 4, and 24* h
13	0* and 2 h
14	0,* 0.5, 1, 1.5, 2, 3, 4, 8, 12, and 16 h
15	0,* 0.5, 1, 1.5, 2, 3, 4, 8, 12, 16, and 24 h
24	0* and 2 h
26	0,* 0.5, 1, 1.5, 2, 3, 4, 8, 12, 16, 24, 48, and 72 h

* Sample taken immediately prior to dosing.

Urine samples for the assessment of levofloxacin concentrations were collected at the following time intervals:

Study Day	Postdose Urine Sample Collection
1	0,* 0-2, 2-4, 4-8, 8-12, and 12-24 h
5	0-4 h
14	0-2, 2-4, 4-8, 8-12, and 12-24 h
15	0-2, 2-4, 4-8, 8-12, and 12-24 h
26	0-2, 2-4, 4-8, 8-12, 12-24, 24-48, and 48-72 h

* Predose urine sample.

ANALYTICAL METHOD: Plasma and urine samples were assayed for levofloxacin concentrations according to a validated reversed-phase high pressure liquid chromatography (HPLC) procedure at

DATA ANALYSIS: The peak plasma concentration (C_{max}), time of C_{max} (T_{max}), area under the plasma concentration versus time curve (AUC), plasma elimination half-life for terminal elimination phase ($t_{½}$), peak urine concentration (Cu_{max}), amount of drug excreted unchanged in urine (Ae), apparent total body clearance (CL/F), and renal clearance (CL_R) were determined from the data.

RESULTS: The levofloxacin pharmacokinetic parameter estimates are summarized in Table 2. Levofloxacin was rapidly absorbed after oral administration to the HIV seropositive subjects. Peak plasma concentrations were reached in approximately 1.5 hours in most cases. The interday (C.V.) variation in T_{max}, $t_{½}$, and CL/F for the subjects (Days 1, 14, 15, and 26), on average, were 28, 20, and 13%, respectively; indicating the absorption and disposition processes of levofloxacin remained linear and unchanged for the subjects throughout the course of the study. Following multiple 750 mg q.d. doses of levofloxacin, the ratio of AUC on Days 14 to 1 (mean ± SD) was 1.29 ± 0.33, indicating a moderate degree of accumulation upon multiple dosing. As expected, only modest degree of accumulation was observed following the thrice-weekly regimen. The degree of

accumulation (mean ± SD) following the 750-mg and 1-g doses was 1.11 ± 0.26 and 1.05 ± 0.19, respectively.

Subjects with CD4 cell counts <250 (Panel 1), on average, appeared to have longer terminal plasma elimination half-lives ($t_{\frac{1}{2}}$) and lower clearances of levofloxacin (CL/F and CL_R) than the subjects with CD4 cell counts ≥250 (Panel 2). As levofloxacin is eliminated primarily through the kidney, these apparent differences in levofloxacin elimination, among other factors, were probably related to the differences in renal function between the two panels of subjects. Renal function as estimated from the prestudy creatinine clearance values (CL_{CR}) of the subjects, was on average, 23% lower in the subjects with CD4 cell counts <250 (CL_{CR} ranged from 50 to 140 mL/min, mean = 83 mL/min) than the subjects with CD4 cell counts ≥250 (CL_{CR} ranged from 81 to 182 mL/min, mean =108 mL/min) in this study. As shown in Table 2, the variability in parameter values was quite low even after combining all the subjects' data. Overall, the levofloxacin pharmacokinetics in this HIV seropositive population, were comparable to those in healthy subjects.

CONCLUSION: The results of this study indicate that the pharmacokinetics of levofloxacin in the HIV seropositive subjects are linear and unchanged following the 750-mg (q.d. and t.i.w.) and 1-g (t.i.w.) oral doses of levofloxacin. Levofloxacin pharmacokinetics in this HIV seropositive population were comparable to those in healthy subjects.

TABLE 1: Demographic and Baseline Characteristics
(All Subjects Enrolled in Study N93-032)

	Levofloxacin 750 mg q.d./ 750 mg t.i.w. (N = 11)	Levofloxacin 750 mg q.d./ 1000 mg t.i.w. (N = 12)*	Placebo q.d./ Placebo t.i.w. (N = 7)	Total (N = 30)*
Sex				
Men	11	10	7	28
Women	0	2	0	2
Race				
Caucasian	9	9	5	23
Black	1	2	1	4
Hispanic	1	1	1	3
Age (yr)				
Mean ± SD	31.5 ± 4.3	40.8 ± 7.4	32.9 ± 4.3	35.5 ± 7.1
Range				
Weight (kg)				
Mean ± SD	72.9 ± 9.7	82.1 ± 23.2	79.3 ± 14.0	78.1 ± 17.1
Range				
Height (cm)				
Mean ± SD	178.2 ± 6.2	169.2 ± 17.4	181.0 ± 3.1	175.5 ± 12.3
Range				

* Data for height was missing for one of the 12 subjects.

TABLE 2: Summary of Levofloxacin Pharmacokinetic Parameter Estimates (mean ± SD)

	750 mg				1 g	
Parameter	Day 1	Day 14	Day 15	Day 26	Day 15	Day 26
Subjects with CD4 cell count <250:						
C_{max}, µg/mL	8.89 ± 2.64	11.4 ± 2.4	10.4 ± 3.3	8.94 ± 1.29	15.7 ± 4.5	12.1 ± 1.8
T_{max}, h	1.5 ± 0.7	1.4 ± 0.4	1.9 ± 1.2	1.6 ± 0.9	1.2 ± 0.3	1.4 ± 0.5
AUC, µg·h/mL[a]	71.1 ± 17.3	97.7 ± 26.6	91.4 ± 28.9	73.9 ± 14.0	122 ± 28	101 ± 28
CL/F, mL/min	151 ± 22	139 ± 45	153 ± 64	142 ± 33	133 ± 28	151 ± 49
$t_{½}$, h	7.91 ± 1.50	9.22 ± 2.06	9.41 ± 1.94	9.98 ± 4.32	10.5 ± 1.9	10.2 ± 4.2
Cu_{max}, µg/mL	563± 288	718 ± 444	825 ± 422	856 ± 241	1156 ± 601	826 ± 666
Ae, % dose[b]	60.8 ± 22.2	74.0 ± 29.0	79.3 ± 27.3	86.0 ± 32.4	61.9 ± 9.7	69.2 ± 8.4
CL_R, mL/min	115 ± 52	103 ± 59	120 ± 54	139 ± 65	89 ± 23	103 ± 40
Subjects with CD4 cell count ≥ 250:						
C_{max}, µg/mL	8.70 ± 2.37	9.88 ± 2.38	11.2 ± 3.5	10.1 ± 1.4	10.6 ± 1.9	9.61 ± 1.55
T_{max}, h	1.4 ± 0.6	1.5 ± 0.4	1.3 ± 0.3	1.4 ± 0.4	1.4 ± 0.4	2.2 ± 0.8
AUC, µg·h/mL[a]	56.3 ± 8.0	60.7 ± 8.5	68.5 ± 8.7	55.8 ± 8.6	74.6 ± 19.9	76.7 ± 17.2
CL/F, mL/min	208 ± 31	210 ± 35	185 ± 23	207 ± 43	224 ± 73	194 ± 51
$t_{½}$, h	6.63 ± 1.17	6.69 ± 0.68	6.10 ± 0.88	7.47 ± 1.86	7.30 ± 2.36	8.30 ± 1.08
Cu_{max}, µg/mL	393 ± 259	684 ± 405	725 ± 209	517 ± 201	902 ± 416	839 ± 486
Ae, % dose[b]	60.6 ± 17.2	72.9 ± 23.4	69.9 ± 22.6	72.5 ± 24.1	60.9 ± 35.5	66.0 ± 11.9
CL_R, mL/min	135 ± 39	150 ± 59	124 ± 32	162 ± 77	144 ± 110	135 ± 42
All Subjects:						
C_{max}, µg/mL	8.79 ± 2.45	10.7 ± 2.4	10.8 ± 3.2	9.50 ± 1.41	13.1 ± 4.2	10.9 ± 2.1
T_{max}, h	1.4 ± 0.6	1.4 ± 0.4	1.6 ± 0.9	1.5 ± 0.7	1.3 ± 0.4	1.8 ± 0.8
AUC, µg·h/mL[a]	63.7 ± 15.2	79.2 ± 28.0	80.0 ± 23.4	64.8 ± 14.5	98.1 ± 33.7	88.9 ± 25.5
CL/F, mL/min	184 ± 39	175 ± 53	169 ± 49	178 ± 50	174 ± 68	170 ± 51
$t_{½}$, h	7.17 ± 1.43	8.10 ± 2.03	7.94 ± 2.28	8.59 ± 3.24	9.06 ± 2.57	9.37 ± 3.21
Cu_{max}, µg/mL	475 ± 280	701 ± 414	775 ± 318	686 ± 275	1029 ± 505	833 ± 550
Ae, % dose[b]	60.7 ± 19.4	73.4 ± 25.1	75.1 ± 24.3	77.6 ± 26.1	61.5 ± 22.8	67.6 ± 9.9
CL_R, mL/min	125 ± 46	130 ± 62	122 ± 43	152 ± 68	113 ± 75	119 ± 42

[a] AUC calculated from-0 to 24 h.

[b] Ae on Days 1, 14, and 15 based on 24-h urine recovery values, on Day 26 based on 72-h urine recovery values.

FIGURE 1: Mean Plasma Concentration vs. Time Profiles of Levofloxacin in HIV Seropositive Subjects Following Single and Multiple 750-mg Oral Doses of Levofloxacin.

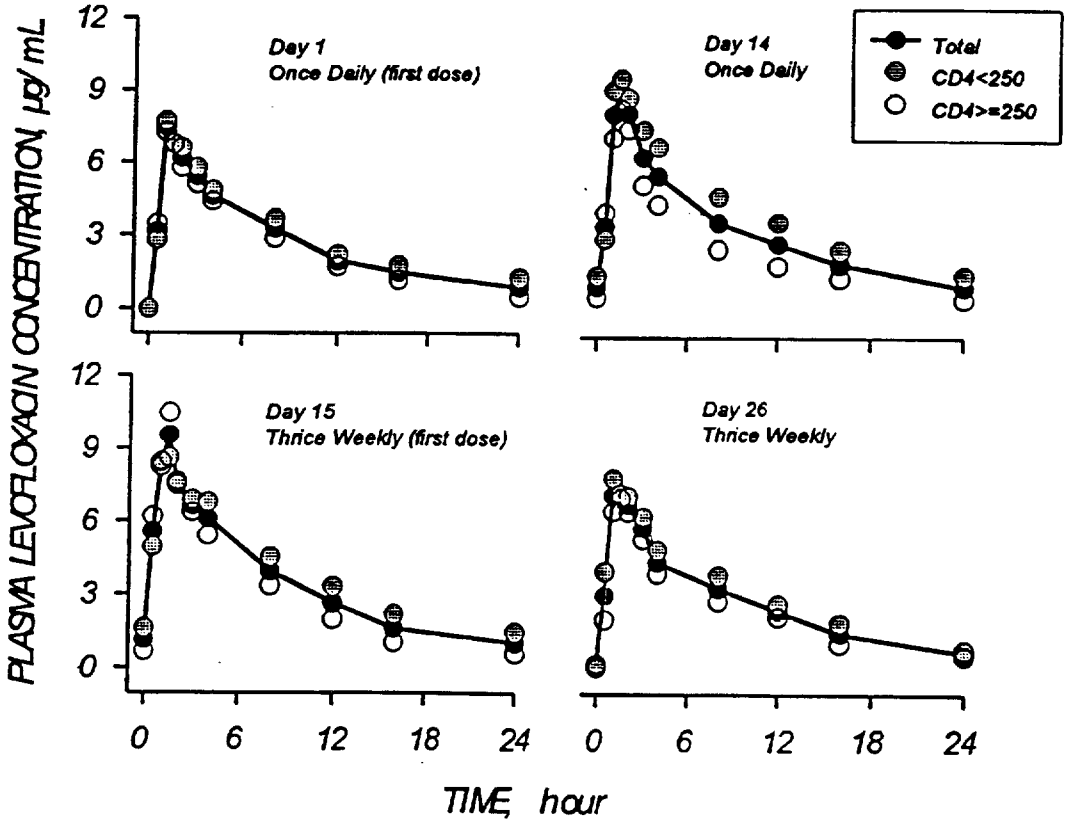
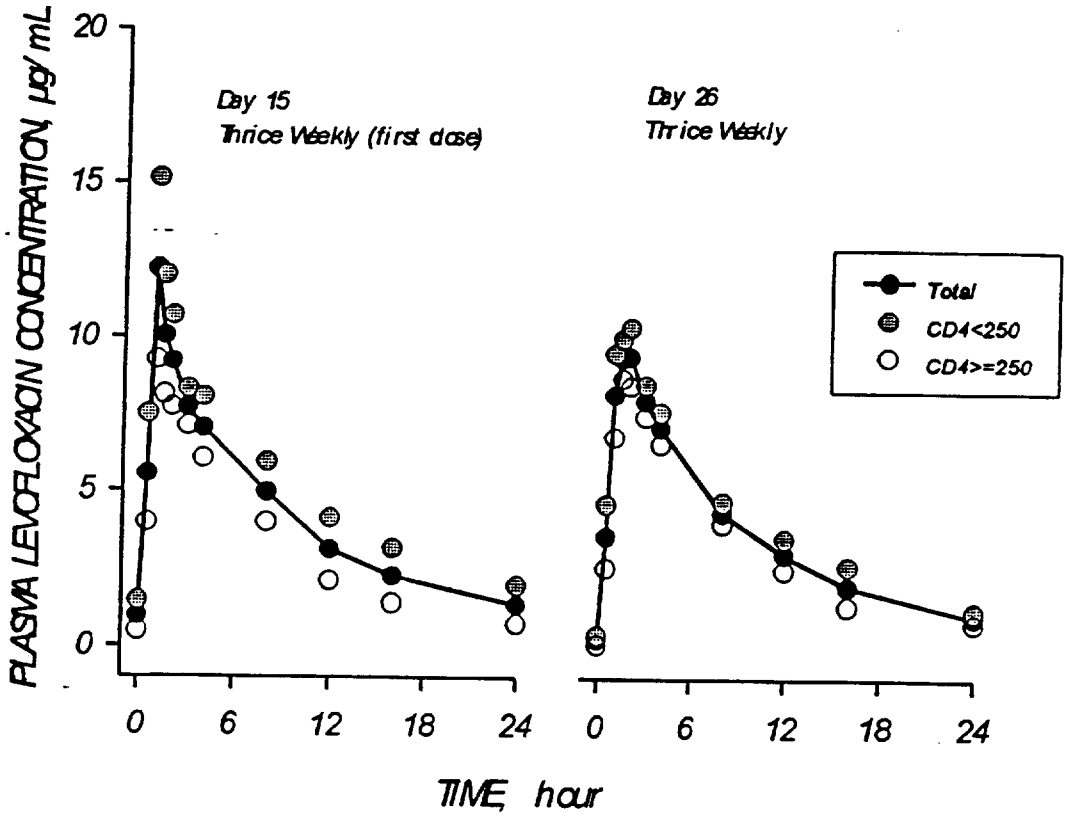


FIGURE 2: Mean Plasma Concentration vs. Time Profiles of Levofloxacin in HIV Seropositive Subjects Following Dose Increment from 750 mg to 1 g on Day 15 and Multiple Thrice-Weekly 1-g Doses of Levofloxacin Administered Orally.



TITLE OF STUDY: A DOUBLE-BLIND STUDY TO EVALUATE THE SAFETY AND PHARMACOKINETICS OF LEVOFLOXACIN (RWJ 25213) IN SUBJECTS WITH HIV INFECTION. Study # K90-024. VOLUME 1.80.

PRINCIPAL INVESTIGATOR:

OBJECTIVE: To evaluate the safety and pharmacokinetics of levofloxacin in male, HIV-infected subjects without opportunistic infections or neoplasms.

STUDY DESIGN: This was a Phase I, randomized, double-blind, placebo-controlled study conducted at one U.S. study center. It was designed to evaluate the pharmacokinetics and safety of oral levofloxacin in 10 subjects with HIV infection. Following screening, subjects were assigned randomly to receive levofloxacin or placebo. Levofloxacin was administered as three 100-mg and one 50-mg levofloxacin hemihydrate tablets containing 97.6 mg and 48.8 mg anhydrous levofloxacin, respectively. On Day 1, subjects received a single dose of study medication. Day 2 was a washout period and no study medication was administered. On Days 3 through 9, subjects received study medication three times a day. Plasma and urine samples were obtained at specified intervals during the study for pharmacokinetic analysis.

DEMOGRAPHICS: All 10 subjects enrolled in this study were males (Table 1).

FORMULATION AND DOSING INFORMATION: On the morning of Day 1, subjects received a single 341.6 mg oral dose of levofloxacin (or placebo). Each dose of study medication was administered as three 97.6-mg tablets and one 48.8-mg tablet. Day 2 was a washout period and no study medication was dispensed. On Days 3 through 9, subjects received 341.6 mg of levofloxacin (or placebo) every eight hours. On the morning of Day 10, subjects received a single dose of 341.6 mg of levofloxacin (or placebo). Subjects were instructed to fast eight hours before and two hours after receipt of study medication on Days 1 and 10.

SAMPLING: Plasma samples were obtained immediately before dosing and at 0.5, 1, 2, 3, 4, 8, 12, 24, and 36 hours after the first dose on Day 1 and immediately before the morning dose on Days 3, 4, 6, 7, 8, and 9. On Day 10, plasma samples were obtained immediately before dosing and at 0.5, 1, 2, 3, 4, 8, 12, 24, 36, 48, 60, and 72 hours

postdose. Urine samples were collected beginning eight hours before the first dose on Day 1 and up to 48 hours postdose. Additional samples were collected at the time of the last dose on Day 10 up to 48 hours postdose. In addition, fecal samples were to be collected from all subjects following the initial dose of study medication and continuing until the morning dose on Day 3. These samples were only to be assayed if the plasma and urine data were inconsistent with the dose administered.

ANALYTICAL METHOD: Plasma, dialysate fluid, and urine samples were assayed for levofloxacin according to validated HPLC procedures at the R.W. Johnson research lab.

RESULTS: In this study, levofloxacin was rapidly absorbed, appeared to be extensively distributed in the body and unaffected by the subjects' disease state. Mean AUC_{0-8} values on Days 1 and 10 were 17.2 and 31.2 µg*h/mL, respectively. In addition, the mean AUC_{0-} (Day 1) and AUC_{0-} (Day 10) values were 29.0 and 56.8 µg*h/mL. The mean trough (8 hour) plasma concentration (C_{min}) after administration of a single 341.6-mg dose of levofloxacin on Day 1 was 1.16 µg/mL, while the range of the morning predose mean plasma concentrations (C_{min}) from Days 4 to 9 was 1.80 to 2.48 µg/mL. These values indicate modest accumulation of levofloxacin upon multiple dosing versus single-dose administration. It was apparent that steady-state conditions had been achieved within three days after initiation of the multiple-dose regimen, as no trend was observed towards further increment in the C_{min} values. Levofloxacin appeared to be extensively distributed in the body, with a mean volume of distribution at steady-state of 104 L. The mean effective half-life at steady-state was 6.5 hours. This half-life further suggests that steady-state had been achieved within three days of dosing. These results indicate that the pharmacokinetics of levofloxacin in asymptomatic HIV-infected subjects, like that in normal, healthy volunteers, are linear and predictable.

Following administration of single (Day 1) and multiple thrice daily (Day 10) doses of levofloxacin 341.6 mg, mean (± SD) peak urinary concentrations were 535 ± 271 and 990 ± 167 µg/mL, respectively. Corresponding mean urinary recoveries of intact levofloxacin on Day 1 (0-48 hours postdose) and on Day 10 (0-8 hours postdose) were 64 ± 26% and 77 ± 15%, respectively. Day 1 and Day 10 renal clearance values were 8.3 ± 4.5 L/h and 8.6 ± 2.9 L/h, respectively. Renal clearance accounted for approximately 70% of total clearance.

CONCLUSIONS: Steady-state plasma levels were achieved within three days and there was a modest accumulation of levofloxacin upon multiple dosing versus single-dose

administration. The mean effective half-life at steady-state was 6.5 hours. Renal clearance accounted for approximately 70% of the total clearance. The pharmacokinetics of levofloxacin in asymptomatic HIV-infected subjects, like that in normal, healthy volunteers, are linear and stable.

Based on the results of this Phase I study no dosage adjustments for levofloxacin appear to be necessary in asymptomatic HIV-infected subjects.

Table 1: Baseline Demographic Characteristics: All Subjects. (Study K90-024)

Parameter	Levofloxacin (N = 5)	Placebo (N = 5)
Sex		
Male	5	5
Race		
Caucasian	4	4
Black	1	1
Age (years)		
Mean	36.8	32.0
SD	13.6	4.9
Minimum	24	26
Maximum	57	38
Weight (lbs)		
Mean	165.9	176.3
SD	9.6	12.3
Minimum	150.0	163.0
Maximum	175.5	190.5

Table 2: Lot Numbers of Levofloxacin and Placebo

(Study K90-024)

Study Medication	Dosage	FD Number	Lot Number
Levofloxacin	97.6 mg	FD 25213-B-22	4943
Levofloxacin	48.8 mg	FD 25213-A-22	4945
Placebo	0 mg [100 mg]	FD-25213-BX-22	4944
Placebo	0 mg [50 mg]	FD 25213-AX-22	4946

Table 3: Pharmacokinetic Profile of Levofloxacin in HIV-Infected Subjects. (Study K90-024)

Parameter (Units)	Single Dose - Day 1 (Mean±SD) N=5	Steady-State - Day 10 (Mean±SD) N=5
Plasma		
C_{max} (µg/mL)	4.79 ±1.00	6.92 ±1.56
T_{max} (h)	1.00 ±0.61	0.90 ±0.22
AUC[a] (µg*h/mL)	29.0 ±6.7	31.2 ±5.6
Cl/F (L/h)	12.3 ±2.8	11.2 ±1.8
Vd/F (L)	98.6 ±15.4	104.0 ±12.6
$t_{½}$ (h)	5.7 ±0.7	6.5 ±0.5
Urine		
AU%	64 ±26	77 ±15
C_{max} (µg/mL)	535 ±271	990 ±167
CL_r (L/h)	8.3 ±4.5	8.6 ±2.9

[a] AUC_{0-} for single dose and AUC_{0-8} for multiple dose at steady-state.

FIGURE 1

Mean plasma levofloxacin concentrations following single (Day 1) and multiple (Day10) 350 mg doses of levofloxacin hemihydrate to HIV patients

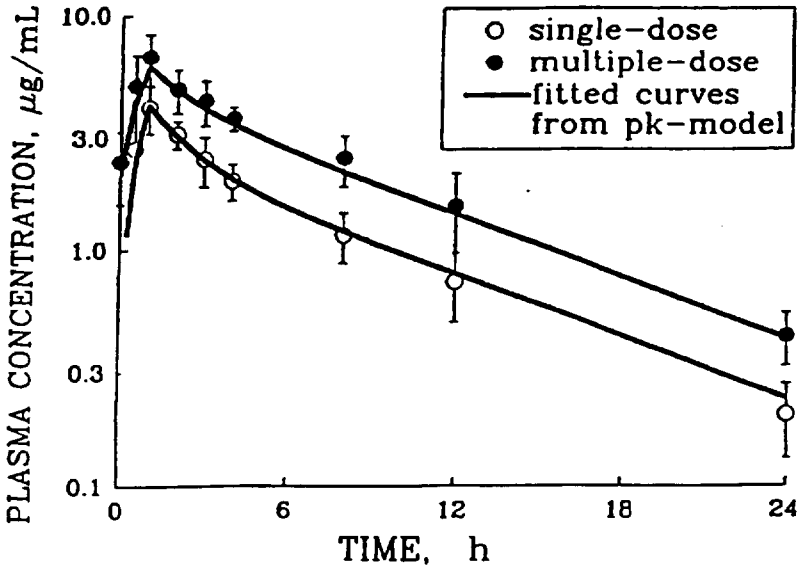
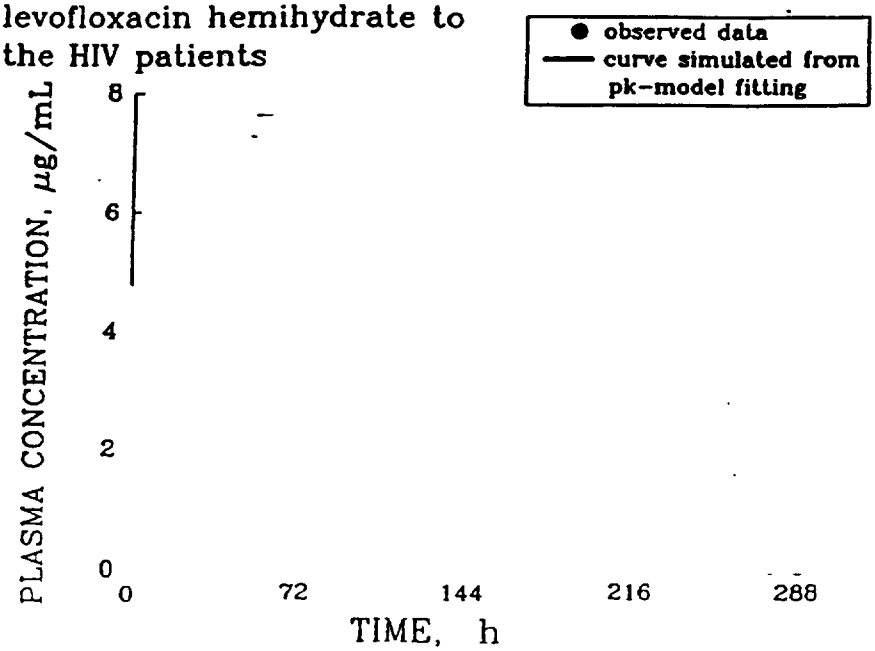


FIGURE 2

The observed and predicted plasma concentrations of levofloxacin after multiple 350 mg Q8H doses of levofloxacin hemihydrate to the HIV patients



TITLE OF STUDY: A DOUBLE-BLIND STUDY TO EVALUATE THE SAFETY AND PHARMACOKINETICS OF LEVOFLOXACIN (RWJ 25213-097)IN SUBJECTS WITH HIV INFECTION. **VOLUME 1.81**

INVESTIGATOR AND LOCATION:

OBJECTIVE: To evaluate the safety and pharmacokinetics of levofloxacin in HIV-infected male subjects without opportunistic infections or neoplasms who were receiving treatment with zidovudine (AZT).

STUDY DESIGN: This was a Phase I, randomized, double-blind, placebo-controlled study conducted at one U.S. study center. It was designed to evaluate the pharmacokinetics and safety of levofloxacin in 16 subjects with HIV infection who were being treated with AZT. Following screening, subjects were assigned randomly to receive levofloxacin or placebo.

FORMULATION AND DOSING INFORMATION: Levofloxacin was administered as three 100-mg (FD 25213-B-22, Lot No. 4943) and one 50-mg (FD 25213-A-22, Lot No. 4945) levofloxacin hemihydrate tablets containing 97.6 and 48.8 mg anhydrous levofloxacin, respectively. On Days 1 and 10, subjects received a single dose of study medication while on Days 3 to 9, subjects received study medication every eight hours. Subjects were instructed to fast eight hours before and two hours after receipt of study drug on Days 1 and 10.

AZT dosing was scheduled so that the first and the last doses of study drug were given simultaneously with a dose of AZT (100-mg tablet five times a day at various dosing intervals for a maximum daily dose of 500 mg per day). In between, ~~AZT~~ was administered according to the regimen used by the subject prior to entering the study and although not specified in the protocol, subjects were to receive a maximum of 500 mg per day with individualized dosing intervals.

DEMOGRAPHIC AND BASELINE CHARACTERISTICS: All 16 subjects enrolled in this study were male (Table 2).

SAMPLING: On Day 0, plasma samples were obtained for baseline AZT levels before AZT dosing and at 0.5, 1, 1.5, 2, 4, and 6 hours postdose. Additional plasma samples were obtained immediately prior to dosing on Days 1, 3, 4, 6, 7, 8, 9, and 10 and at 0.5,

1, 2, 3, 4, 8, 12, 24, and 36 hours after dosing on Days 1 and 10, at 12 hours after dosing on Day 3, and 48, 60 and 72 hours after dosing on Day 10.

ANALYTICAL METHOD: Plasma samples were assayed for levofloxacin and AZT according to a validated procedure that involves a 1-step liquid-liquid extraction with reversed-phase HPLC on C_{18} column at The LOQs are 80 ng/mL for levofloxacin and 50 ng/mL for AZT.

RESULTS: The pharmacokinetic analysis was restricted to six of the eight subjects receiving levofloxacin who completed the study. On Day 10, all six subjects had reached steady state. Mean C_{max} values of levofloxacin after the first dose (Day 1) and at steady state (Day 10) following the multiple q8h dose regimen were 3.82 and 7.06 µg/mL, respectively. The corresponding times to reach C_{max} (T_{max}), were 1.0 h and 1.1 h, respectively. Mean AUC values following a single dose (Day 1, AUC_{0-}) and at steady state (Day 10, AUC_{0-8}) were 30.1 and 37.4 µg*h/mL, respectively. Mean elimination half-life values following a single dose and at steady state were 6.2 and 7.2 hours, respectively. Corresponding values for volume of distribution were 98 and 109 L, respectively. Mean total body clearance values following a single dose and at steady state were 11.4 and 9.4 L/h, respectively. The pharmacokinetic profiles of levofloxacin were similar between single-dose and multiple q8h dosing with a moderate accumulation in C_{max} (observed 185% versus expected 169%) and in AUC (observed 124% versus expected 169%). The pharmacokinetic study results were similar to those observed previously in HIV-positive subjects not receiving AZT (Study K90-024) and in normal healthy volunteers (Studies K90-077 and K90-014).

AZT concentrations were measured but pharmacokinetic analysis was not performed since subjects were on a variety of AZT regimens. No apparent difference was observed in the mean AZT concentration time profile with or without levofloxacin.

CONCLUSIONS: Based on these results, the pharmacokinetic profile of levofloxacin in these subjects does not appear to be affected by concomitant administration of AZT. Thus, no dosage adjustments for levofloxacin appear to be necessary in asymptomatic HIV-infected subjects receiving AZT therapy.

Table 1: Lot Numbers of Levofloxacin and Placebo Tablets (Study K90-086)

Study Medication	Dosage	FD Number	Lot Number
Levofloxacin	97.6 mg	FD 25213-B-22	4943
Levofloxacin	48.8 mg	FD 25213-A-22	4945
Placebo	0 mg [100 mg]	FD 25213-BX-22	4944
Placebo	0 mg [50 mg]	FD 25213-AX-22	4946

Table 2: Baseline Demographic Characteristics: All Subjects. (Study K90-086)

Parameter	Levofloxacin N = 8	Placebo N = 8
Sex		
Men	8	8
Race		
White	4	6
Black	3	0
Hispanic	1	2
Age (years)		
Mean±SD	30.5±4.47	32.9±5.67
Min-Max	26-40	27-41
Weight (lbs)		
Mean±SD	172.6±21.45	167.0±20.34
Min-Max	150-205	142-200

Table 3: Pharmacokinetic Profile of Levofloxacin in HIV-Infected Subjects (Study K90-086).

	Levofloxacin 341.6 mg, N=6		
	T_{max} (h)	C_{max} (µg/mL)	AUC[a] (µg•h/mL)
Day 1[b]	1.0±0.5	3.82±0.78	30.1±1.8
Day 10[c]	1.1±0.5	7.06±1.90	37.4±6.2
	Terminal $T_{½}$ (h)	CL/F (L/h)	Vd/F (L)
Day 1	6.2±0.9	11.4±0.7	98±18
Day 10	7.2±1.4	9.4±1.5	109±23

[a] $AUC_{0-\infty}$ (Day 1) versus AUC_{0-8} (Day 10).
[b] Single-dose.
[c] Multiple q8h dose (steady state).

Table 4: Pharmacokinetic Parameters of Levofloxacin After a Single Dose

Study	T_{max} (h)	C_{max} (µg/mL)	Mean C_{max}* (Per 100 mg dose)	$AUC_{0-\infty}$ (µg*h/mL)	Mean $AUC^*_{0-\infty}$ (Per 100 mg dose)	T½[b] (h)	CL/F (L/h)	Vd/F (L)
K90-086[a]	1.0±0.5	3.82±0.78	1.09	30.1±1.8	8.60	6.2±0.9	11.4±0.7	98±18
K90-024[c]	1.0±0.6	4.79±1.00	1.37	29.0±6.7	8.29	5.7±0.7	12.3±2.8	99±15
K90-077[d]	1.3±0.5	5.19±1.21	1.04	47.7±7.59	9.54	e	10.5±1.8	97±12
K90-014[f]	1.2±0.6	5.21±0.91	1.04	49.6±8.80	9.92	g	10.2±1.9	94±14

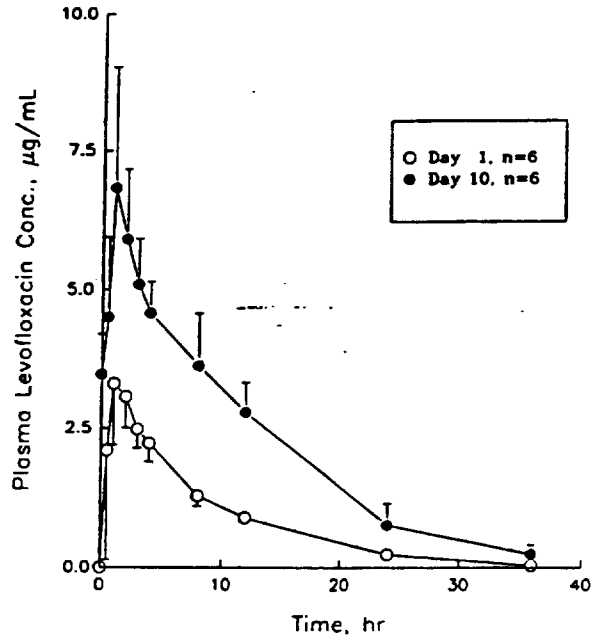
Data are mean±sd.
[a] 350 mg levofloxacin hemihydrate tablet q8h, HIV-infected subjects, with concomitant AZT (n=6): current study.
[b] Terminal half-life.
[c] 350 mg levofloxacin hemihydrate tablet q8h, HIV-infected subjects, without concomitant AZT (n=5).
[d] 500 mg levofloxacin hemihydrate tablet qd, healthy subjects (n=10).
[e] The terminal half-life was not determined in this study; however, the effective half-life was calculated to be 6.5±0.7h.
[f] 500 mg levofloxacin hemihydrate tablet bid, healthy subjects (n=10).
[g] The terminal half-life was not determined in this study; however, the effective half-life was calculated to be 6.5±1.0h.

Table 5: Pharmacokinetic Parameters of Levofloxacin at Steady State

Study	T_{max} (h)	C_{max} (µg/mL)	Mean C_{max}* (Per 100 mg dose)	$AUC_{0-\tau}$* (µg•h/mL)	Mean $AUC^*_{0-\tau}$ (Per 100 mg dose)	T½[c] (h)	CL/F (L/h)	Vd/F (L)
K90-086[b]	1.1±0.5	7.06±1.90	2.01	37.4±6.2	10.70	7.2±1.4	9.4±1.5	109±23
K90-024[d]	0.9±0.2	6.92±1.56	1.98	31.2±5.6	8.91	6.5±0.5	11.2±1.8	104±13
K90-077[e]	1.1±0.4	5.72±1.40	1.14	47.5±6.7	9.50	f	10.5±1.5	102±22
K90-014[g]	1.3±0.6	7.80±1.07	1.56	59.0±11.8	11.80	h	8.6±1.8	102±16

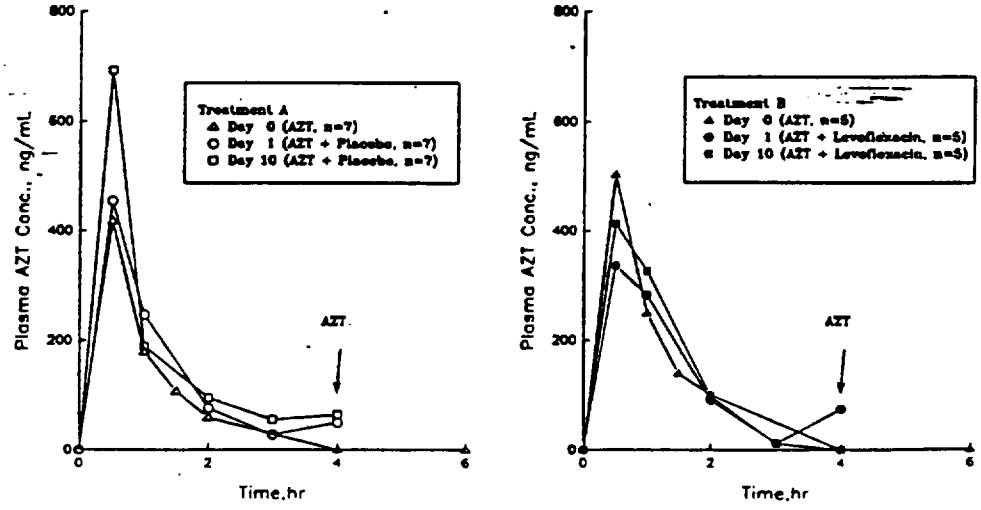
Data are mean±sd.
[a] τ=dosing interval.
[b] 350 mg levofloxacin hemihydrate tablet q8h, HIV-infected subjects, with concomitant AZT (n=6): current study.
[c] Terminal half-life.
[d] 350 mg levofloxacin hemihydrate tablet q8h, HIV-infected subjects, without concomitant AZT (n=5).
[e] 500 mg levofloxacin hemihydrate tablet qd, healthy subjects (n=10).
[f] The terminal half-life was not determined in this study; however, the effective half-life was calculated to be 6.8±1.3h.
[g] 500 mg levofloxacin hemihydrate tablet bid, healthy subjects (n=10).
[h] The terminal half-life was not determined in this study; however, the effective half-life was calculated to be 8.4±1.3h.

FIG 1 Mean (SD) Plasma Levofloxacin Concentration Versus Time Data Following Single (Day 1) and Multiple (Day 10) 341.6 mg q8h Doses of Levofloxacin* to Six HIV-Infected Subjects (Study K90-086)



* 350 mg levofloxacin hemihydrate (equivalent to 341.6 mg levofloxacin) was given as a single dose on Days 1 and 10, and as the multiple q8h doses from Days 3 to 9.

FIGURE 2 Mean Plasma AZT Concentration Versus Time Data in HIV-Infected Subjects Under AZT Treatment (100 mg Tablet Five Times per Day) With or Without Levofloxacin* (Study K90-086)



* 350 mg levofloxacin hemihydrate (equivalent to 341.6 mg levofloxacin) was given as a single dose on Days 1 and 10, and as the multiple q8h doses from Days 3 to 9.

TITLE OF STUDY: ASSESSMENT OF THE EFFECT OF ORALLY ADMINISTERED LEVOFLOXACIN AT STEADY-STATE CONDITIONS ON THE PHARMACOKINETICS OF THEOPHYLLINE FOLLOWING SINGLE-DOSE INTRAVENOUS ADMINISTRATION IN HEALTHY MALE SUBJECTS. PROTOCOL LOFBO-PHI-101. **VOLUME 1.82-1.83**

INVESTIGATOR AND LOCATION:

OBJECTIVES: The primary objective of this study was to determine whether orally administered levofloxacin at steady-state conditions had any effect on the pharmacokinetics of theophylline following single-dose intravenous administration. Secondary objectives of the study included assessing the ophthalmological safety of levofloxacin at steady-state conditions when administered as a multiple dose regimen of 500 mg q12h, and determining whether levofloxacin crystals could be found by microscopic examination of urine collected at steady-state conditions.

STUDY DESIGN: This was a Phase I, randomized, complete, two-way crossover study. The study was double-blind with respect to levofloxacin and placebo, and was open-label with respect to theophylline. Sixteen healthy male subjects were enrolled in the study. The subjects received each of the following two treatments which were separated by a 1-week washout period. Eight subjects were randomized to receive Treatment A first, and eight subjects were randomized to receive Treatment B first.

Treatment A: Each subject received 500 mg oral doses of levofloxacin administered as one 500 mg clinical tablet (Formula No. FD-25213-097-G-22, Batch No. R5826) given orally q12h for nine doses. Immediately after administration of the sixth levofloxacin dose, the subjects were given theophylline intravenous solution in D5W (Formula No. FD-02962-000-A-45, Batch No. R5915), 4.5 mg/kg, administered as a 30 minute, constant rate intravenous infusion.

Treatment B: Each subject received oral doses of placebo tablets matching the levofloxacin 500 mg clinical tablet (Formula No. FD-25213-097-LX-22, Batch No. 5314) given q12h for nine doses. Immediately after administration of the sixth placebo dose, the subjects were given theophylline intravenous solution in D5W (Formula No. FD-02962-000-A-45, Batch No. R5915), 4.5 mg/kg, administered as a 30 minute, constant rate intravenous infusion.

DEMOGRAPHICS: Sixteen healthy male subjects were recruited but fourteen subjects completed the study (Table 1).

SAMPLING: Serial venous blood samples (5 mL) were drawn from each subject at: -24, -12, 0 (predose), 0.25, 0.5, 0.75, 1, 1.5, 2, 3, 4, 6, 8, 12, 18, 24, 36, and 48 hours from the start of the theophylline infusion. Urine was collected quantitatively during the interval from 0-2 hours postdose following administration of the fifth levofloxacin dose. The subjects were instructed not to void from the beginning until the end of the collection interval, at which time an aliquot of the freshly voided urine was removed from the collection and kept at 37 °C during the process of being examined microscopically for levofloxacin crystals.

ANALYTICAL METHODS: Plasma samples were assayed for theophylline according to a validated HPLC procedure at Plasma samples were also assayed for levofloxacin according to a validated HPLC procedure at

the same laboratory. Urine samples were assayed for levofloxacin according to a validated HPLC procedure at RWJPRI, Spring House, PA.

DATA ANALYSIS: The following pharmacokinetic parameters were determined for theophylline: C_{max}, T_{max}, AUC (0-*), AUC (0-∞), CL, k_e, $t_{½}$ and V_{ss} The following pharmacokinetic parameters were determined for levofloxacin: C_{max}, T_{max}, AUC (0-τ), C_{min}, and CL/F.

Analysis of variance models were fitted to the data with the pharmacokinetic parameter (C_{max}, AUC (0-*), AUC (0-∞), T_{max}, V_{ss}, CL/F, k_e, and $t_{½}$) as the dependent variable and treatment sequence group, subjects nested within treatment sequence group, treatment and period as predictors and the main effects were tested. For C_{max} and AUCs, 90% confidence intervals for the ratio of the means from the two treatments were constructed using the intra-subject variability from the analysis of variance models. C_{max} and AUCs were log-transformed prior to analysis. Analysis of T_{max} was done using ranked values. All other parameters were analyzed in the original units.

RESULTS: The mean pharmacokinetic parameters for theophylline together with the results of statistical comparisons between the two treatments are summarized in Table 2. The results showed no statistically significant differences in C_{max} or in AUCs for the two treatments. The 90% confidence intervals for the ratio of the means for C_{max} and AUCs, calculated based on log-transformed data analysis fell within the range of 80 to 125%, indicating that there were no clinically significant differences in these parameters between the two treatments. In addition, there were no statistically significant differences in CL, V_{ss}, k_e, or $t_{½}$ by ANOVA comparisons between the treatments for theophylline, showing that at steady-state conditions, levofloxacin 500 mg q12h had no significant effect on either the distribution or elimination pharmacokinetics of theophylline from intravenous administration.

The mean steady-state pharmacokinetic parameters for levofloxacin are summarized in Table 3. These mean steady-state levofloxacin pharmacokinetic parameters are consistent with those observed in other multiple dose studies with the 500 mg q12h dosing regimen, indicating that a single 4.5 mg/kg intravenous infusion dose of theophylline has no effect on the steady-state pharmacokinetics of orally administered levofloxacin.

CONCLUSION: The pharmacokinetics of theophylline, from a single-dose intravenous infusion of 4.5 mg/kg, were not significantly affected by levofloxacin under steady-state conditions of 500 mg given orally q12h. The interaction was evaluated at steady-state conditions of levofloxacin with high levofloxacin plasma concentrations from multiple dose administration (C_{min} ~ 3.8 µg/mL, and C_{av} ~ 6 µg/mL), and at plasma theophylline concentrations (C_{max} ~ 10-11 µg/mL) calculated to provide a margin of safety, yet be at or near the therapeutic concentration range.

The steady-state pharmacokinetics of levofloxacin were comparable to other studies in which multiple oral doses of levofloxacin were given, indicating that there was no effect of theophylline on the pharmacokinetics of levofloxacin.

These results indicate that when required, levofloxacin and theophylline can be administered concurrently without concern that the pharmacokinetics of either drug would be altered.

At a high dosing rate of levofloxacin (500 mg q12h), there were no levofloxacin crystals found in any urine sample collected at steady-state conditions. These results provide evidence that there is no likelihood of occurrence of levofloxacin crystalluria during multiple dose administration at high doses.

Table 1: Demographic and Baseline Characteristics
(All Subjects Enrolled in Study LOFBO-PHI-101)

	Levofloxacin/Placebo (N=8)	Placebo/Levofloxacin (N=8)	Total (N=16)
Race			
Caucasian	4	8	12
Black	2	0	2
Hispanic	2	0	2
Age (years)			
Mean ± SD	24.5±5.0	27.3±5.5	25.9±5.3
Range			
Weight (lbs)			
Mean ± SD	172.1±19.0	161.4±19.8	166.8±19.5
Range			
Height (in)			
Mean ± SD	70.4±2.8	71.9±3.2	71.2±3.0
Range			

Note: This study enrolled only men.

Table 2: Summary of Theophylline Pharmacokinetic Parameters [a]
(Study LOFBO-PHI-101).

Theophylline Parameter	Treatment A With Levofloxacin	Treatment B With Placebo	% Difference[b]	ANOVA Results[c]	90% Confidence Interval Test Results[d]
C_{max} (µg/mL)	11.35 (1.78)	10.68 (1.32)	+6.27	NS	EQ
T_{max} (h)	0.77 (0.27)	0.64 (0.19)	+ 20.3	NS	—
AUC (0-*)[e] (µg·h/mL)	118.53 (31.11)	120.58 (28.99)	-1.7	NS	EQ
AUC (0-∞) (µg·h/mL)	124.01 (32.27)	126.06 (30.28)	-1.6	NS	EQ
CL (mL/min)	48.64 (11.6)	47.40 (10.25)	+2.6	NS	—
k_e (h^{-1})	0.090 (0.022)	0.089 (0.021)	+1.1	NS	—
$t_{½}$ (h)	8.10 (1.86)	8.18 (1.84)	-0.98	NS	—
V_{ss} (L)	31.65 (3.46)	32.01 (3.86)	-1.1	NS	—

[a] Data are the mean (±SD) for 14 subjects.
[b] With reference to Treatment B, [A-B]/B x 100%.
[c] ANOVA - SIG = difference between means is statistically significant ($p \leq 0.05$), NS = difference between means is not statistically significant ($p > 0.05$).
[d] ANOVA 90% Confidence Interval Test for C_{max}, AUC (0-*), AUC (0-∞) - EQ=90% confidence interval limits for the log-transformed data are within 80-125% of the reference mean. NEQ=90% confidence interval limits for the log-transformed data are outside of 80-125% of the reference mean.
[e] AUC (0-*), AUC calculated from time zero to the time of the last measurable plasma concentration.

Table 3: Summary of Steady-State Levofloxacin Pharmacokinetic Parameters [a]
(Study LOFBO-PHI-101)

Parameter	Mean (±SD)
C_{max} (µg/mL)	9.18 (0.89)
T_{max} (h)	1.68 (0.60)
AUC (0-τ)[b] (µg·h/mL)	72.69 (9.79)
C_{min} (µg/mL)	3.78 (0.74)
CL/F (mL/min)	116.67 (16.38)

[a] Data are the mean (±SD) for 14 subjects.
[b] AUC (0-τ) is AUC calculated from time zero, immediately prior to dosing, until the end of the 12 hour dosing interval at steady-state.

Table 4

						90% Confidence Intervals	
Parameter	Root MSE	df	Geometric Mean for Reference	Geometric Mean for Test	Ratio (%)	Lower (%)	Upper (%)
AUC (0-48)	0.08	12	115.2	113.6	98.6	93.1	104.3
AUC (0-∞)	0.08	12	120.5	118.8	98.5	93.6	103.7
C_{max}	0.10	12	10.6	11.2	105.1	98.0	112.8

Figure 1: Mean Theophylline Plasma Concentration-Time Profiles For 14 Healthy Male Subjects (Study LOFBO-PHI-101)

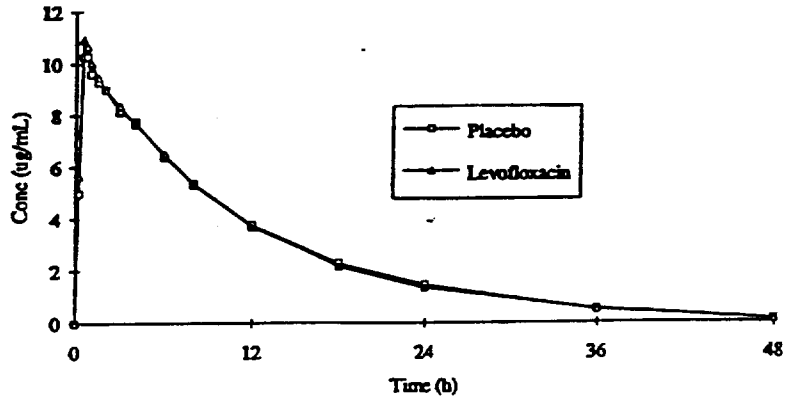
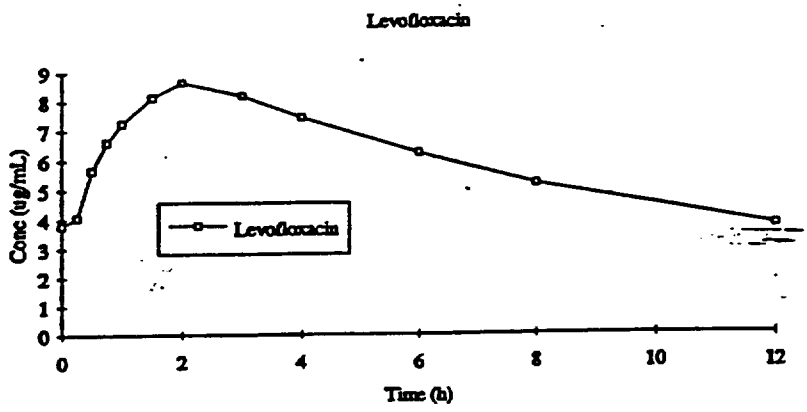


Figure 2: Mean Levofloxacin Plasma Concentration-Time Profile From 14 Healthy Male Subjects (Study LOFBO-PHI-101)



TITLE OF STUDY: BLINDED, RANDOMIZED, TWO-WAY CROSSOVER EVALUATION OF THE EFFECT OF LEVOFLOXACIN ON WARFARIN DISPOSITION AND ANTICOAGULATION. LOFBO-PHI0-098. VOLUME 1.84-1.85

PRINCIPAL INVESTIGATOR:

OBJECTIVES: The objective of this study was to evaluate the potential effect of levofloxacin on plasma warfarin concentrations and prothrombin time following oral administration of a single dose of warfarin during concomitant oral administration of multiple doses of levofloxacin. Secondary objectives of the study included assessing the ophthalmological safety of levofloxacin and determining whether levofloxacin crystals could be found by microscopic examination of urine collected at steady-state condition of levofloxacin when administered as a multiple dose regimen of 500 mg q12h.

DEMOGRAPHICS: Sixteen healthy male subjects were enrolled in the study (Table 1).

STUDY DESIGN: This was a placebo-controlled, randomized, blinded, two-way crossover Phase I study. Each subject received a 500 mg dose of levofloxacin (Formula No. FD-25213-097-G-22, Batch No. R5826) or placebo tablet orally q12h on Days 1-9. A single 30 mg oral dose of racemic warfarin sodium was administered with 240 mL of water after a 10-hour overnight fast on Day 4, presumably at steady-state condition of levofloxacin plasma concentrations. A 21-day washout period was allowed between the warfarin doses for the two crossover treatments.

SAMPLING: Blood samples (10 mL) were drawn from each subject at 0 (predose), 1, 2, 4, 8, 12, 24, 36, 48, 60, 72, 84, 96, 120, and 144 hours after warfarin dosing. Urine samples were collected during the following time periods: predose (-2 to 0 hour), 0-12, 12-24, 24-48, 48-72, 72-96, 96-120, and 120-144 hours after warfarin dosing. Two mL of blood for prothrombin time (PT) measurements were drawn at 0 (predose), 12, 24, 36, 48, 72, 96, 120, and 144 hours after warfarin dosing.

ANALYTICAL METHODS: Plasma samples from this study were analyzed by validated HPLC methods by
Prothrombin time was measured on Days 0, 4, 5, 6, 7, 8, 9, 10, 21, 25, 26, 27, 28, 29, 30, and 31. Activated partial thromboplastin time was measured on Days 0, 10, 21, and 31.

DATA ANALYSIS: The following pharmacodynamic parameters for baseline corrected prothrombin time (PT) were determined: Peak prothrombin time (PT_{max}), Time to peak PT, ($T_{max, PT}$) and Area under the PT vs. time curve as measured by the trapezoidal method from time zero to the last time point, AUC $(0\text{-}t)_{PT}$.
The following pharmacokinetic parameters were analyzed statistically for the S- and R-warfarin: C_{max}, T_{max}, AUC (0-∞), AUC (0-t), CL/F, k_e, and $t_{½}$. For baseline corrected prothrombin time, AUC $(0\text{-}t)_{PT}$, $T_{max, PT}$, and PT_{max} were analyzed.
The analysis was carried out on log-transformed bioavailability parameters for AUC (0-∞), AUC (0-t) and C_{max}. T_{max} was analyzed using ranked values and Clearance, k_e, and $t_{½}$ were analyzed in the original units.
Analysis of variance models were fit to the data with one of the pharmacokinetic parameters of interest: AUC (0-∞), AUC (0-t), C_{max}, Clearance, Ranked T_{max} (RT_{max}), k_e, and $t_{½}$ as the dependent variable and the effects due to treatment sequence group, subjects nested within the treatment sequence groups, treatment and period as predictors. In addition, similar analysis of variance models were fitted to the pharmacodynamic

Analysis of variance models were fit to the data with one of the pharmacokinetic parameters of interest: AUC (0-∞), AUC (0-t), C_{max}, Clearance, Ranked T_{max} (RT_{max}), k_e, and $t_{½}$ as the dependent variable and the effects due to treatment sequence group, subjects nested within the treatment sequence groups, treatment and period as predictors. In addition, similar analysis of variance models were fitted to the pharmacodynamic parameters, and the main effects were tested. The 90% CI for AUC $(0\text{-}t)_{PT}$ and PT_{max} were constructed.

RESULTS: The mean (SD) pharmacokinetic parameters of R- and S-warfarin for the two treatments and the results from the statistical analysis are summarized in Table 2.

R-Warfarin: Peak R-warfarin plasma concentrations were reached in approximately 1.5 hours. Mean (±SD) R-warfarin plasma C_{max} were 1.64 ± 0.28 µg/mL with concomitant placebo treatment and 1.59 ± 0.23 µg/mL with concomitant levofloxacin treatment. Mean oral clearance of R-warfarin was 2.93 ± 0.92 mL/min for placebo and 2.89 ± 0.88 mL/min for levofloxacin. The mean plasma elimination half-life of R-warfarin was about 46 hours with both placebo and levofloxacin treatments. There was no statistically significant difference for any pharmacokinetic parameter of R-warfarin between the two treatments. The 90% confidence intervals for C_{max}, AUC (0-t), and AUC (0-∞) mean values for R-warfarin with levofloxacin treatment were within the 80 to 125% limits of the mean values with placebo treatment.

S-Warfarin: Peak S-warfarin plasma concentrations were reached in approximately 1.3 hours. Mean (±SD) S-warfarin plasma C_{max} were 1.70 ± 0.25 µg/mL with concomitant placebo treatment and 1.64 ± 0.21 µg/mL with concomitant levofloxacin treatment. Mean oral clearance of S-warfarin was 4.72 ± 1.23 mL/min for placebo and 4.58 ± 1.17 mL/min for levofloxacin. The mean plasma elimination half-life of S-warfarin was about 32 hours with both placebo and levofloxacin treatments. There was no statistically significant difference for any pharmacokinetic parameter of S-warfarin between the two treatments. The 90% confidence interval for C_{max}, AUC (0-t), and AUC (0-∞) mean values for S-warfarin with levofloxacin treatment were within the 80 to 125% limits of the mean values with placebo treatment. Concomitant oral administration of levofloxacin has no effect on warfarin disposition.

Prothrombin Time. The mean (SD) prothrombin time (PT) pharmacodynamic parameters and the results of the statistical analysis for the two treatments are summarized in Table 3. Following warfarin administration, PT increased to reach peak PT of approximately 15 seconds by 36 hours in most cases. There was no statistically significant difference between baseline-corrected PT_{max}, $T_{max,\ PT}$, and AUC $(0\text{-}t)_{PT}$ values for the two treatments. The 90% confidence intervals for PT_{max}, and AUC $(0\text{-}t)_{PT}$ for levofloxacin were within the 80 to 125% limits of the mean values for placebo. Thus, concomitant oral administration of levofloxacin had no effect on the anticoagulation effect of warfarin as measured by prothrombin time.

CONCLUSION: Concomitant oral administration of levofloxacin had no effect on warfarin disposition and its anticoagulation effect. Therefore, a significant interaction due to concomitant administration of levofloxacin is not likely to occur in patients being treated with warfarin.

Table 1: Demographic and Baseline Characteristics
(All Subjects Enrolled in Study LOFBO-PHI0-098)

	Levofloxacin/Placebo (N = 8)	Placebo/Levofloxacin (N = 8)	Total (N = 16)
Race			
Caucasian	2	3	5
Black	3	5	8
Hispanic	3	0	3
Age (years)			
Mean (SD)	33.5 (4.7)	31.5 (4.9)	32.5 (4.8)
Range			
Weight (lb)			
Mean (SD)	175.9 (12.9)	170.4 (13.7)	173.2 (13.2)
Range			
Height (in)			
Mean (SD)	69.3 (2.4)	71.4 (2.8)	70.3 (2.7)
Range			

Note: This study enrolled only men.

Table 2: Summary of Pharmacokinetic Parameters of R- and S-Warfarin
(Study LOFBO-PHI0-098)

Parameter	Levofloxacin (Treatment A)	Placebo (Treatment B)	% Difference[a]	ANOVA[b]	90% CI[c]
R-Warfarin:					
C_{max} (µg/mL)	1.59 (0.23)	1.64 (0.28)	-3.0	NS	EQ
T_{max} (h)	1.33 (0.49)	1.47 (0.83)	-9.5	NS[d]	–
AUC (0-t) (µg·h/mL)	75.9 (17.0)	75.0 (17.4)	+1.2	NS	EQ
AUC (0-∞) (µg·h/mL)	87.0 (24.1)	86.1 (23.9)	+1.0	NS	EQ
CL/F (mL/min)	2.89 (0.88)	2.93 (0.92)	-1.4	NS	–
k_e (h^{-1})	0.0160 (0.0041)	0.0157 (0.0038)	+1.9	NS	–
$t_{\frac{1}{2}}$ (h)	46.0 (11.2)	46.3 (10.0)	-0.6	NS	–
S-Warfarin:					
C_{max} (µg/mL)	1.64 (0.21)	1.70 (0.25)	-3.5	NS	EQ
T_{max} (h)	1.27 (0.46)	1.33 (0.49)	-4.5	NS[d]	–
AUC (0-t) (µg·h/mL)	51.1 (11.9)	49.3 (10.1)	+3.7	NS	EQ
AUC (0-∞) (µg·h/mL)	54.2 (14.8)	52.1 (11.8)	+4.0	NS	EQ
CL/F (mL/min)	4.58 (1.17)	4.72 (1.23)	-3.0	NS	–
k_e (h^{-1})	0.0224 (0.0041)	0.0225 (0.0039)	-0.4	NS	–
$t_{\frac{1}{2}}$ (h)	31.9 (7.5)	31.7 (6.4)	+0.6	NS	–

[a] Reference to placebo Treatment B, (A-B)/B x 100.
[b] ANOVA results on log-transformed parameters; NS = difference between means is not statistically significant, $p>0.05$.
[c] 90% confidence interval results on log-transformed C_{max}, AUC (0-t), and AUC (0-∞). EQ = 90% confidence interval is within the 80 to 125% limits of the reference mean.
[d] Ranked T_{max} was used in comparison.

Table 3: Summary of Pharmacodynamic Parameters of Prothrombin Time (Study LOFBO-PHI0-098)

Parameter[a]	Levofloxacin (Treatment A)	Placebo (Treatment B)	% Difference[b]	ANOVA[c]	90% CI[d]
PT_{max} (sec)	3.5 (1.5)	3.7 (2.1)	-5.4	NS	EQ
$T_{max, PT}$ (h)	43.2 (21.7)	35.2 (7.1)	+22.7	NS[e]	–
AUC $(0\text{-}t)_{PT}$ (sec· h)	186 (84)	209 (102)	-11.0	NS	EQ

[a] Baseline Corrected prothrombin time.
[b] Reference to placebo Treatment B, (A-B)/B x 100.
[c] ANOVA results on log-transformed parameters; NS = difference between means is not statistically significant, $p>0.05$.
[d] 90% confidence interval results on log-transformed PT_{max} an AUC (0-t), EQ = 90% confidence interval is within the 80 to 125% limits of the reference mean.
[e] Ranked $T_{max, PT}$ was used in ANOVA.

Table 4: ANOVA Results for R-Warfarin (Study LOFBO-PHI0-098)

	Group Sequence Effect			Period Effect			Treatment Effect		
Parameter	F	df	p-value	F	df	p-value	F	df	p-value
C_{max}	2.15	1,13	0.167	0.76	1,13	0.400	1.18	1,13	0.297
RT_{max}[a]	1.23	1,13	0.288	1.25	1,13	0.284	0.01	1,13	0.929
AUC (0-∞)	0.41	1,13	0.535	1.05	1,13	0.325	0.54	1,13	0.475
AUC (0-t)	0.42	1,13	0.526	1.28	1,13	0.279	1.14	1,13	0.304
CL/F	0.57	1,13	0.466	0.92	1,13	0.356	0.53	1,13	0.478
k_e	0.60	1,13	0.453	0.98	1,13	0.341	1.25	1,13	0.283
$t_{½}$	0.28	1,13	0.608	0.92	1,13	0.356	0.14	1,13	0.710

[a] RT_{max} = Ranked T_{max} used in ANOVA

Table 5: 90% Confidence Interval for R-Warfarin (Study LOFBO-PHI0-098)

			Geometric Mean			90% CI	
Parameter	RMSE (log scale)	df	Levofloxacin (Treatment A)	Placebo (Treatment B)	Ratio[a] (%)	Lower Limit	Upper Limit
C_{max} (µg/mL)	0.079	1,13	1.58	1.63	96.90	92.04	102.00
AUC (0-∞) (h· µg/mL)	0.039	1,13	84.00	83.12	101.05	98.54	103.63
AUC (0-t) (h· µg/mL)	0.036	1,13	74.24	73.19	101.43	99.07	103.85

[a] Reference to placebo Treatment B

Table 6: ANOVA Results for S-Warfarin

(Study LOFBO-PHI0-098)

	Group Sequence Effect			Period Effect			Treatment Effect		
Parameter	F	df	p-value	F	df	p-value	F	df	p-value
C_{max}	1.44	1,13	0.252	0.29	1,13	0.598	1.04	1,13	0.323
RT_{max}[a]	0.70	1,13	0.420	1.72	1,13	0.213	0.13	1,13	0.726
AUC (0-∞)	1.17	1,13	0.299	9.85	1,13	0.008	1.45	1,13	0.251
AUC (0-t)	0.96	1,13	0.346	10.10	1,13	0.007	1.52	1,13	0.239
CL/F	0.82	1,13	0.382	8.68	1,13	0.011	1.20	1,13	0.293
k_e	1.45	1,13	0.250	0.16	1,13	0.692	0.00	1,13	0.969
$t_{½}$	1.75	1,13	0.209	0.43	1,13	0.523	0.14	1,13	0.717

[a] RT_{max} = Ranked T_{max} used in ANOVA

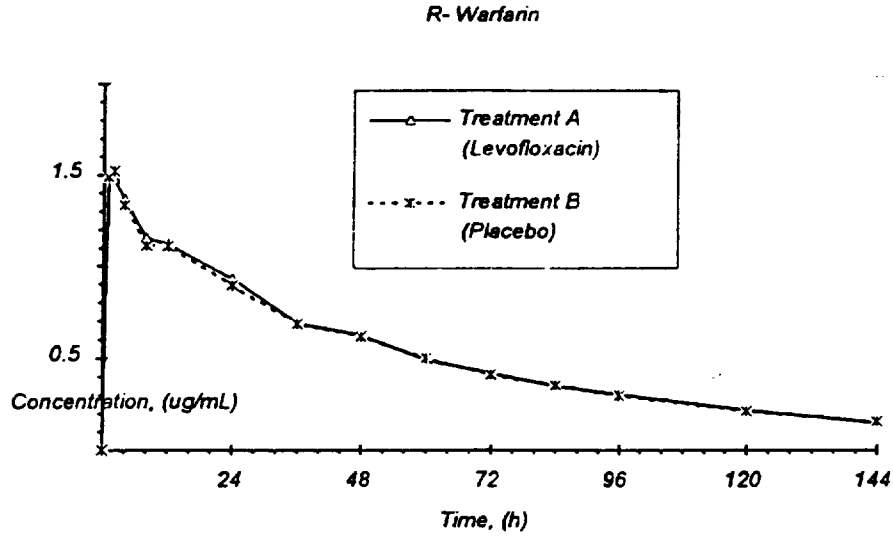
Table 7: 90% Confidence Interval for S-Warfarin

(Study LOFBO-PHI0-098)

			Geometric Mean			90% CI	
Parameter	RMSE (log scale)	df	Levofloxacin (Treatment A)	Placebo (Treatment B)	Ratio[a] (%)	Lower Limit	Upper Limit
C_{max} (µg/mL)	0.082	1,13	1.63	1.69	96.97	91.93	102.29
AUC (0-∞) (h· µg/mL)	0.063	1,13	52.01	50.59	102.80	98.70	107.01
AUC (0-t) (h· µg/mL)	0.059	1,13	49.51	48.21	102.71	98.84	106.73

[a] Reference to placebo Treatment B

Figure 1: Mean R- and S-Warfarin Plasma Concentration Profiles
Warfarin/Levofloxacin Interaction Study (LOFBO-PHI0-098)



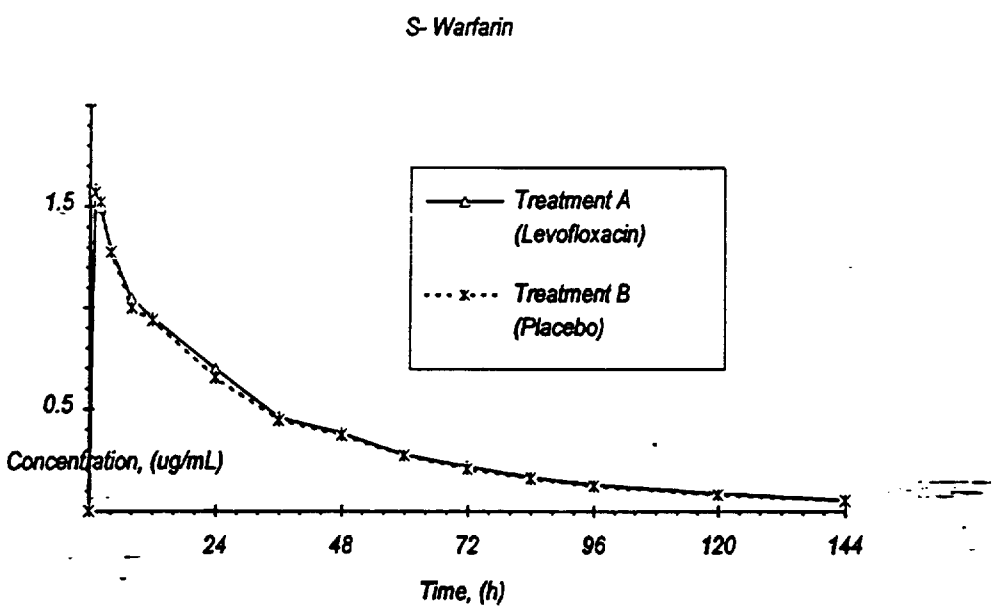


Figure 2: Mean Prothrombin Time Profiles for Levofloxacin and Placebo Treatments (Study LOFBO-PHI0-098)

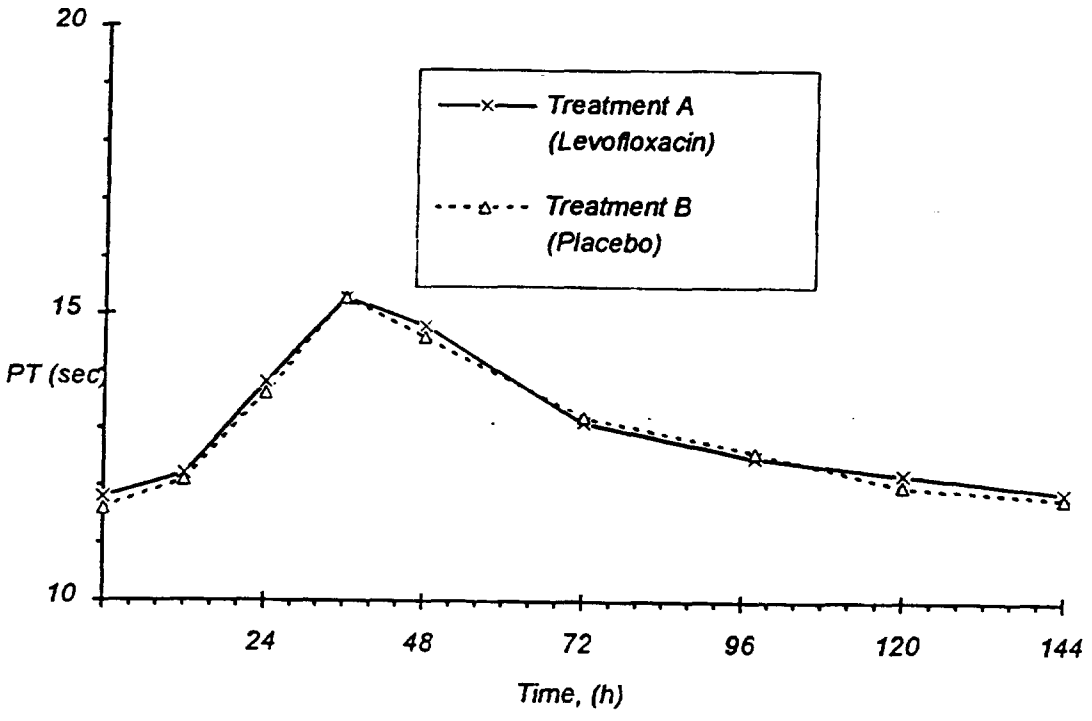


Table 8: ANOVA Results for Baseline Corrected PT

(Study LOFBO-PHI0-098)

	Group Sequence Effect			Period Effect			Treatment Effect		
Parameter	F	df	p-value	F	df	p-value	F	df	p-value
AUC (0-t) $_{PT}$	1.66	1,13	0.221	0.24	1,13	0.630	1.32	1,13	0.272
PT_{max}	1.05	1,13	0.325	42.64	1,13	<0.001	0.36	1,13	0.558
$RT_{max,PT}$*	7.08	1,13	0.020	0.20	1,13	0.663	1.74	1,13	0.210

* RT_{max} = Ranked T_{max} used in ANOVA

Table 9: 90% Confidence Interval for Baseline Corrected PT

(Study LOFBO-PHI0-098)

			Geometric Mean			90% CI	
Parameter	RMSE (log scale)	df	Levofloxacin (Treatment A)	Placebo (Treatmment B)	Ratio* (%)	Lower Limit	Upper Limit
AUC (0-t)$_{PT}$ (h· sec)	0.210	1,13	167.77	183.21	91.57	79.93	104.90
PT_{max} (sec)	0.148	1,13	3.29	3.18	103.31	93.87	113.71

* Reference to placebo Treatment B

TITLE OF STUDY: A COMPARATIVE STUDY TO EVALUATE THE EFFECT OF LEVOFLOXACIN (RWJ-25213-097) ON THE PHARMACOKINETICS OF CYCLOSPORINE (SANDIMMUNE®) IN NORMAL HEALTHY SUBJECTS (PROTOCOL N93-059). **VOLUME 1.86**

PRINCIPAL INVESTIGATOR:

OBJECTIVES: The objective of this study was to evaluate the effect of levofloxacin on the pharmacokinetics of cyclosporine in 12 healthy male and female subjects.

DEMOGRAPHICS: Fourteen healthy men and women were enrolled in the study. Two of the female subjects discontinued the study prior to the levofloxacin dosing period and were replaced (Table 1).

STUDY DESIGN: This was a placebo-controlled, randomized, double-blind, cross-over study conducted at one U.S. center. Twelve of the 14 enrolled subjects completed the study as outlined in the protocol. Two of the female subjects discontinued the study early and were replaced. Of these 12 subjects, six subjects, 3 of each gender, were randomly assigned to one of two treatment sequences according to a computer-generated randomization schedule. Each treatment group had three male and three female subjects. During Period 1, subjects assigned to Group A received 500 mg q12h levofloxacin (FD No. 25213-097-G-22, Batch No. 5324) for 6 days and those in Group B received placebo (FD No. 25213-097-LX-22, Batch No. 5314) q12h for 6 days. On Study Day 5, after an overnight 8-hour fast, all subjects received a single 10 mg/kg oral dose of cyclosporine in the form of Sandimmune® (FD No. 17779-000-A-41, Batch No. R5716) administered concomitantly with levofloxacin or placebo. Following a washout period of at least 6 days, subjects were crossed-over to receive the alternate treatment and cyclosporine in a manner identical to Period 1.

SAMPLING: Blood samples were collected for 48 hours following administration of the morning dose of Sandimmune® on Study Days 5 and 17. Subject No. 209 had a 10-day wash out period and had blood samples collected on Study Days 5-7 and 21-23. Blood samples were collected at the following times following administration of the cyclosporine dose: 0 (predose), 0.5, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 12, 16, 24, 36, and 48 hours postdosing.

ANALYTICAL METHODS: Blood samples were analyzed for cyclosporine concentrations according to a validated radioimmunoassay method at

The quantification range was 28.2-1218 ng/mL. The assay utilized a commercially available radioimmunoassay kit supplied by

Plasma samples were analyzed for levofloxacin concentrations according to a validated HPLC method at . The quantification range was µg/mL. The method for quantifying levofloxacin concentration in plasma utilized reverse-phase liquid chromatography with UV detection.

DATA ANALYSIS: The following pharmacokinetic parameters were determined for cyclosporine and levofloxacin: C_{max}, T_{max}, AUC (0-t), k_e (levofloxacin only), $t_{½}$, and CL/F. Comparison of cyclosporine pharmacokinetic parameters with and without concomitant levofloxacin was made using analysis of variance models which were fitted to raw data and to the log-transformed data (natural logarithm) for each parameter, except T_{max}, for which the ranked raw data were analyzed. For C_{max}, AUC (0-*), and AUC (0-∞) the estimate of intra-subject variability from the analysis of variance model (without the treatment by gender interaction) was used to construct 90% confidence intervals for the difference in means for the log-transformed data.

RESULTS: Mean (±SD) cyclosporine single dose blood pharmacokinetic parameters when administered concomitantly with levofloxacin or placebo are summarized in Table 2. Mean (±SD) levofloxacin plasma pharmacokinetic parameters are summarized in Table 3. Mean single dose cyclosporine C_{max}, AUC (0-*), AUC (0-∞), and CL/F values with concomitant levofloxacin administration were within 9% of the corresponding values with concomitant placebo administration. The 90% confidence interval bounds for the ratio of the means based on log-transformed C_{max}, AUC (0-*), and AUC (0-∞) parameters fell within the bioequivalence criteria of 80 to 125%.

CONCLUSION: The results demonstrate that levofloxacin, administered 500 mg twice-daily for 5 days, had no effect on single dose cyclosporine pharmacokinetics. There was no pharmacokinetic interaction between levofloxacin and cyclosporine.

Table 1: Demographic and Baseline Characteristics

(All Subjects Enrolled in Study N93-059)

	Levofloxacin/Placebo (N=6)	Placebo/Levofloxacin[a] (N=8)	Total (N=14)
Sex			
Men	3	3	6
Women	3	5	8
Race			
Caucasian	3	4	7
Black	1	4	5
Hispanic	2	0	2
Age (years)			
Mean ± SD	28.0 ± 4.7	28.3 ± 7.2	28.1 ± 6.0
Range			
Weight (kg)			
Mean ± SD	72.7 ± 12.4	76.2 ± 8.4	74.7 ± 10.0
Range			
Height (in)			
Mean ± SD	66.9 ± 3.8	67.4 ± 3.5	67.2 ± 3.5
Range			

[a] Two subjects (Nos. 202 and 206) discontinued and received placebo only.

Table 2: Single Dose Blood Cyclosporine Pharmacokinetic Parameters[a] and Comparative Statistics With Concomitant Administration of Levofloxacin or Placebo (Study N93-059)

Cyclosporine Parameters	Placebo	Levofloxacin	Percent[c] Difference	ANOVA[b]	90% Confidence Interval Test Results[d]
C_{max} (ng/mL)	1058.3 (348.1)	1080.4 (313.7)	2.1	NS	EQ
T_{max} (h)	1.8 (0.7)	2.4 (1.1)	32.6	NS[e]	–
AUC (0-*) (ng·h/mL)	6897.3 (2333.6)	7189.3 (2274.4)	4.2	NS	EQ
AUC (0-∞) (ng·h/mL)	7243.0 (2444.5)	7822.0 (2585.6)	8.0	NS	EQ
$t_{½}$ (h)	6.44 (3.52)	8.84 (7.71)	37.3	NS	–
CL/F (mL/min)	25.9 (9.8)	23.6 (7.9)	-8.9	NS	–

[a] AUC calculated to the Last Measured Concentration.

[b] Data are the mean (±SD), N = 12 for each treatment.

[b] From ANOVA. NS = Not statistically significantly different ($p>0.05$).

[e] Ranked raw data values were used for comparative statistical analysis.

[d] 90% confidence intervals for the ratio of means. EQ = 90% confidence interval bounds are within the bioequivalence criteria range of 80-125% of the reference treatment mean.

[c] With reference to placebo.

Table 3: Levofloxacin Plasma Pharmacokinetic Parameters[a] (Study N93-059)

C_{max} (µg/mL)	6.01
	(1.20)
T_{max} (h)	2.9
	(1.1)
AUC (0-12 h) (µg·h/mL)	54.73
	(13.15)
k_e (1/h)	0.0778
	(0.0204)
$t_{½}$ (h)	9.49
	(2.50)
CL/F (mL/min)	160.4
	(37.8)

[a] Data are the mean (±SD), N = 12.

TABLE 4:

(90% Confidence Intervals Based on Log-Transformed Parameters)

CROSSOVER EVALUATION OF THE EFFECT OF LEVOFLOXACIN ON THE PHARMACOKINETICS OF CYCLOSPORINE

PROTOCOL N93-059

90% CONFIDENCE INTERVALS FOR SCHUIRMANN'S TEST

ANALYSIS ON LOG TRANSFORMED DATA

PARAMETER	GEOMETRIC MEAN FOR PLACEBO	GEOMETRIC MEAN FOR LEVOFLOXACIN	SE_POOL	DF	RATIO (%)	LOWER LIMIT (%)	UPPER LIMIT (%)
AUC_LST	6523.69	6866.75	0.062446	10	105.259	93.9950	117.872
AUC_INF	6848.62	7437.00	0.066782	10	108.591	96.2116	122.564
C_MAX	1005.69	1042.63	0.066712	10	103.674	91.8664	116.999

Figure 1: Mean Cyclosporine Blood Concentration vs. Time Profiles from Six Healthy Male and Six Healthy Female Subjects Following a Single Oral 10mg/kg Dose of Cyclosporine Administered Concomitantly with Levofloxacin or Placebo (Study N93-059).

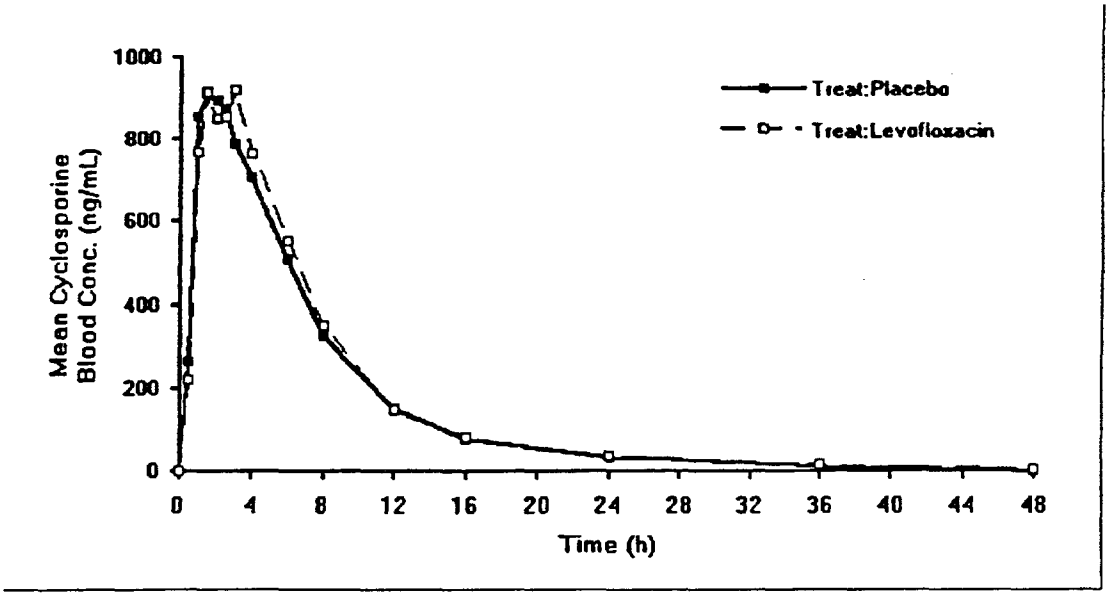
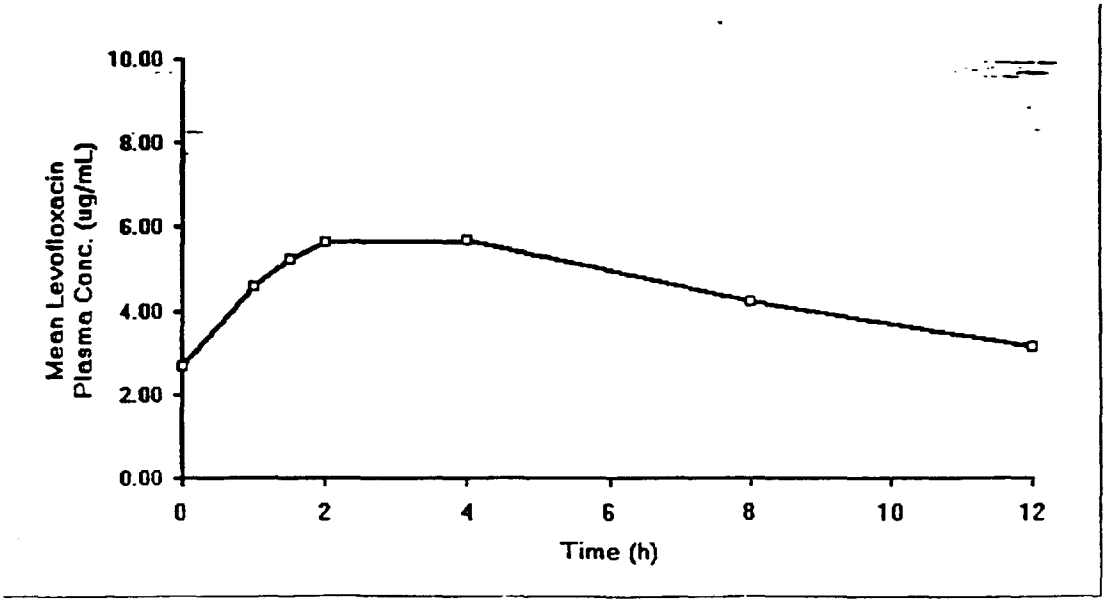
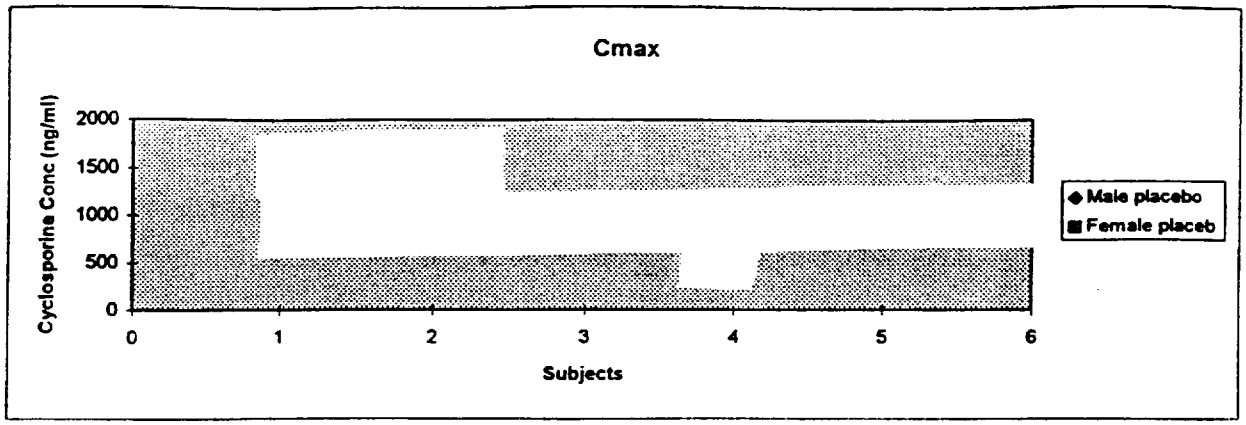
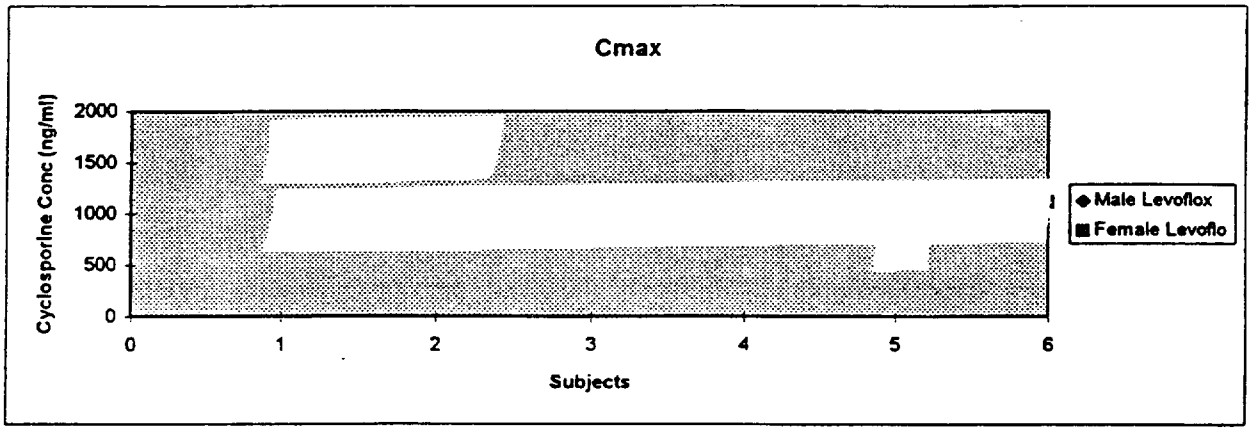
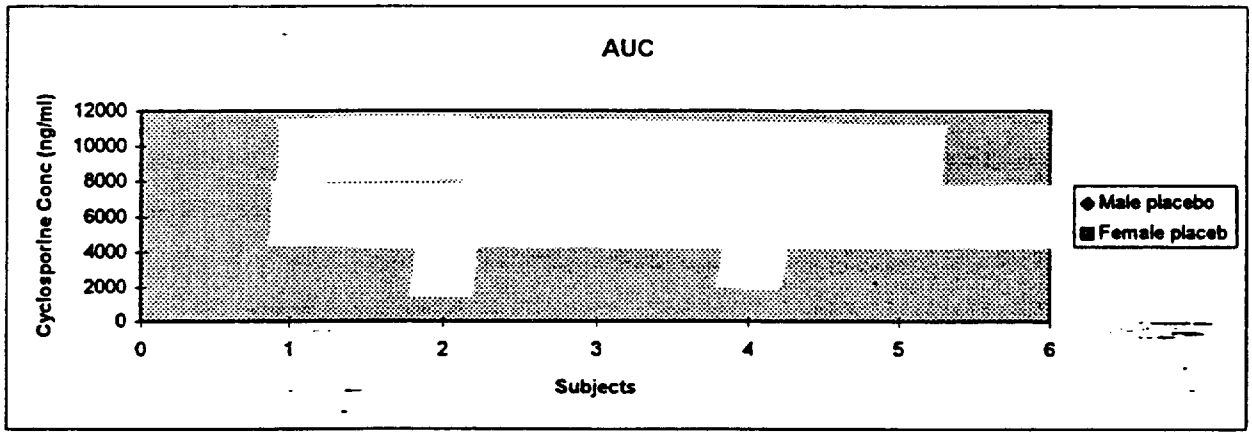


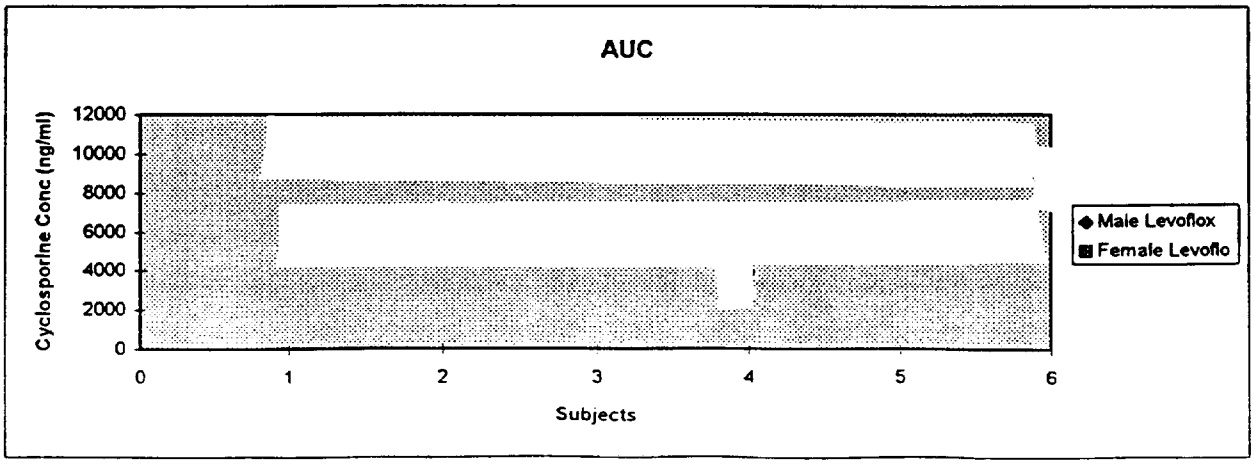
Figure 2: Mean Steady-State Levofloxacin Plasma Concentration vs. Time Profile from Six Healthy Male and Six Healthy Female Subjects Receiving Levofloxacin 500 mg q12h Regimen with Concomitant Single Oral 10 mg/kg Dose of Cyclosporine (Study N93-059).




Cmax
Cyclosporine Conc (ng/ml)
2000
1500
1000
500
0
0
1
2
3
4
5
6
Subjects
Male placebo
Female placeb


Cmax
Cyclosporine Conc (ng/ml)
2000
1500
1000
500
0
0
1
2
3
4
5
6
Subjects
Male Levoflox
Female Levoflo


AUC
Cyclosporine Conc (ng/ml)
12000
10000
8000
6000
4000
2000
0
0
1
2
3
4
5
6
Subjects
Male placebo
Female placeb


AUC
Cyclosporine Conc (ng/ml)
12000
10000
8000
6000
4000
2000
0
0
1
2
3
4
5
6
Subjects
Male Levoflox
Female Levoflo

TITLE OF STUDY: DOUBLE-BLIND, RANDOMIZED, CROSSOVER EVALUATION OF THE EFFECT OF LEVOFLOXACIN (RWJ-25213-097) ON THE PHARMACOKINETICS OF DIGOXIN IN HEALTHY SUBJECTS (PROTOCOL LOFBO-PHI0-094). **VOLUME 1.87**

PRINCIPAL INVESTIGATOR:

OBJECTIVES: To investigate whether levofloxacin alters the pharmacokinetics of digoxin in healthy adult volunteers.

DEMOGRAPHICS: Twelve healthy men and women were enrolled in and completed the study (Table 1).

STUDY DESIGN: Twelve healthy adult subjects (six males and six females) were enrolled in and completed this sequence placebo-controlled, randomized, double-blind, two-way crossover Phase I study. Subjects were randomly assigned to one of the two treatment sequence groups (three males and three females per sequence group) according to a computer-generated randomization schedule. During Period 1, subjects assigned to Group 1 received 500 mg q12h levofloxacin (FD 25213-097-G-22, Batch No. R5601) for 6 days and those in Group 2 received placebo (FD 25213-097-LX-22, Batch No. 5314) q12h for 6 days. On Study Day 5, after an overnight 8-hour fast, all subjects received a single 0.4-mg oral dose of digoxin (as two 0.2-mg Lanoxicap® capsules, FD 50766-000-A-31, Batch No. R5818) administered concomitantly with the morning dose of levofloxacin or placebo. Following a 6-day washout period, subjects were crossed-over to receive the alternate treatment.

SAMPLING: On Study Days 4 and 5 of each treatment period, 5 ml blood samples were drawn to assess plasma levofloxacin concentrations at the following times: 0 hour (predose) and 1, 1.5, 2, 4, 8, and 12 hours following the morning dose; quantitative urine samples for assessment of urine levofloxacin concentrations were collected predose (-8 to 0 hour) and 0-12 hours after the administration of study medications.

On Study Days 5 through 9 of each treatment period, 5 ml blood samples were drawn from each subject to assess serum concentrations of digoxin at the following times: 0 hour (pre-digoxin dose) and at the following time post-digoxin dose: 0.5, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 12, 24, 36, 48, 72, and 96 hours; quantitative urine samples for assessment of urine

digoxin concentrations were collected predose (-8 to 0 hour) and at the following time intervals postdigoxin dose: 0-12, 12-24, 24-48, 48-72, and 72-96 hours.

ANALYTICAL METHODS: Plasma and urine samples were assayed for levofloxacin according to a validated HPLC procedure at Blood and urine samples were analyzed for digoxin by a validated and specific radioimmunoassay method at Levofloxacin was not measured for samples collected from subjects receiving placebo tablets.

DATA ANALYSIS: The following pharmacokinetic parameters were determined for both levofloxacin and digoxin: C_{max}, T_{max}, AUC, CL/F, Ae, CL_R, and $t_{½}$.
Comparison of digoxin pharmacokinetic parameters with and without concomitant levofloxacin was made using analysis of variance models. The analysis of $AUC_{0-\infty}$ and C_{max} was carried out on log-transformed data (natural logarithms). The analysis of T_{max} was carried out on ranked values. The remaining parameters were analyzed in their original units. Analysis of variance models were fitted to the data with treatment sequence group, sex, treatment sequence group by sex interaction, subjects nested within treatment sequence group by sex interaction, treatment, period, and sex by treatment interaction. The 90% confidence intervals for the ratio of means of $AUC_{0-\infty}$ and C_{max} with and without levofloxacin were constructed using the estimated intrasubject variability from the model.

RESULTS:
Digoxin: The sex by treatment interaction was not significant for any of the digoxin pharmacokinetic parameters. Hence further analysis was done with data from both males and females pooled together. The mean (±SD) digoxin pharmacokinetic parameter values in 12 subjects receiving a single oral dose of 0.4 mg digoxin concomitantly with 500 mg of levofloxacin or placebo are summarized in Table 2.
The C_{max}, AUC, CL/F, Ae, CL_R, and $t_{½}$ values of a single oral dose of 0.4 mg digoxin administered concomitantly with levofloxacin were within 8% of the corresponding values for digoxin administered with placebo. There was a 14% difference in T_{max} (0.8 h vs. 0.7 h). The digoxin pharmacokinetic parameter estimates in this study are comparable to the literature data where digoxin was administered alone.

Levofloxacin: The mean (±SD) levofloxacin pharmacokinetic parameter estimates in 12 subjects receiving multiple b.i.d. oral doses of 500 mg levofloxacin with or without the concomitant administration of digoxin are summarized in Table 3. Levofloxacin

pharmacokinetic parameters were comparable in subjects receiving levofloxacin with or without the concomitant administration of digoxin. A single 0.4-mg oral dose of digoxin does not appear to have any effect on levofloxacin pharmacokinetics.

CONCLUSION: The study results demonstrate that levofloxacin, administered 500 mg twice-daily, had no statistically significant effect on the pharmacokinetics of a single 0.4-mg oral dose of digoxin. The pharmacokinetics of levofloxacin appeared similar with or without digoxin administration. Multiple oral dosing (500 mg q12h for 6 days) with levofloxacin was found to be safe

TABLE 1: Demographic and Baseline Characteristics

(All Subjects Enrolled in Study LOFBO-PHI0-094)

	Levofloxacin/Placebo (N=6)	Placebo/Levofloxacin (N=6)	Total (N=12)
Sex			
Men	3	3	6
Women	3	3	6
Race			
Caucasian	5	5	10
Black	1	1	2
Age (yr)			
Mean ± SD	30.7 ± 13.1	35.2 ± 14.5	32.9 ± 13.4
Range			
Weight (lb)			
Mean ± SD	159.0 ± 14.5	176.8 ± 31.5	167.9 ± 25.2
Range			
Height (in.)			
Mean ± SD	67.0 ± 3.1	68.2 ± 2.8	67.6 ± 2.9
Range			

TABLE 2: Summary of Digoxin Pharmacokinetic Parameter Estimates[a] and the Comparative Statistics for the Concomitant Administration of Digoxin with Levofloxacin or Placebo. (Study LOFBO-PHI0-094)

	Digoxin with Levofloxacin	Digoxin with Placebo	% Difference[b]	ANOVA[c]	90% Confidence Interval
C_{max}, ng/mL	3.04 ± 0.68	3.31 ± 1.02	-8	NS	77-115
T_{max}, h	0.8 ± 0.3	0.7 ± 0.3	+14	NS	NE[d]
AUC[e], ng·h/mL	36.6 ± 8.48	37.0 ± 6.76	-1	NS	86-111
CL/F, mL/min	195 ± 66.9	186 ± 35.2	+5	NS	NE
Ae[f], % dose	55 ± 12	54 ± 17	+2	NS	NE
CL_R, mL/min	103 ± 19.1	99.2 ± 27.2	+4	NS	NE
$t_{½}$, h	43.8 ± 6.8	43.0 ± 7.7	+2	NS	NE

[a] Data are presented as mean ± SD (N=12).

[b] With reference to placebo.

[c] ANOVA comparison on log-transformed data (C_{max}, AUC), rank value (T_{max}), and untransformed data (CL/F, Ae, CL_R, and $t_{½}$): S = statistically significant, NS = not statistically significant (at 5% level).

[d] Not estimated

[e] AUC = 0-∞

[f] Ae = 0-96 h

TABLE 3: Summary of Levofloxacin Pharmacokinetic Parameter Estimates[a]. (Study LOFBO-PHI0-094)

	Day 4 (Levofloxacin Without Digoxin)	Day 5 (Levofloxacin With Digoxin)
C_{max}, µg/mL	8.03 ± 2.77	8.29 ± 1.54
T_{max}, h	1.4 ± 0.4	1.3 ± 0.4
$AUC_{0-12\,h}$, µg·h/mL	59.6 ± 19.9	62.5 ± 12.2
CL/F, mL/min	181 ± 156	138 ± 27
$Ae_{0-12\,h}$, % dose	74 ± 34	97 ± 26
CL_R, mL/min	186 ± 64	194 ± 61
$t_{½}$, h	8.3 ± 6.1	6.9 ± 0.9

[a] Data are presented as mean ± SD (N=12).

FIGURE 1: Mean (±SD) Serum Digoxin Concentration - Time Profiles in 12 Healthy Subjects Receiving a Single Oral Dose of 0.4 mg Digoxin With Concomitant Administration of 500 mg Levofloxacin or Placebo
(Study LOFBO-PHI0-094)

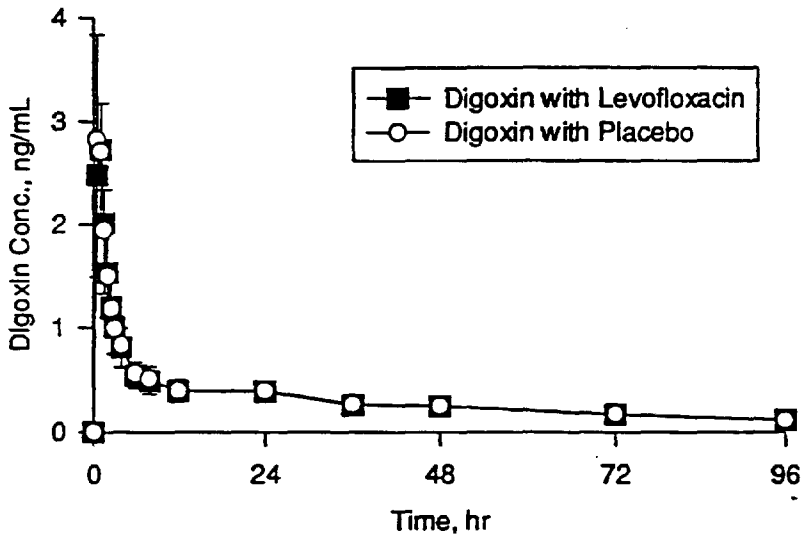
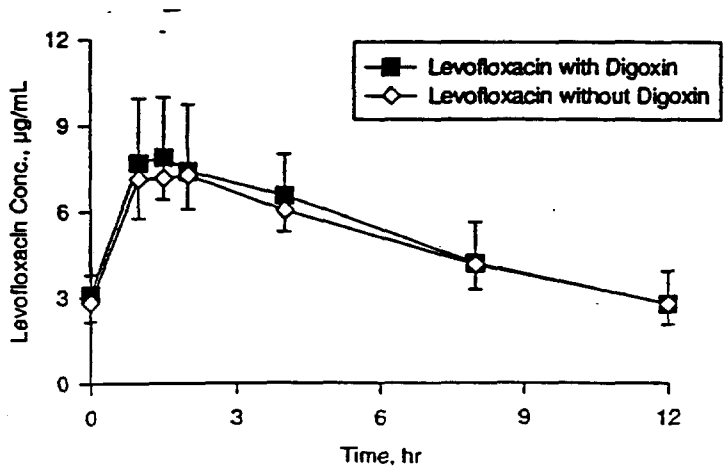


FIGURE 2: Mean (±SD) Plasma Levofloxacin Concentration - Time Profiles in 12 Healthy Subjects Receiving Multiple Twice-daily Doses of 500 mg Levofloxacin Orally with or Without the Concomitant Administration of 0.4 mg Digoxin
(Study LOFBO-PHI0-094)



TITLE	Investigation into the effects of cimetidine and probenecid on the pharmacokinetics of oral HR 355 in healthy volunteers.
VOLUME	1.88
INVESTIGATOR	
ANALYTICAL SITES	
STUDY OBJECTIVES	To investigate the pharmacokinetics of HR 355 (levofloxacin) when administered alone and in combination with probenecid and cimetidine
STUDY MEDICATION AND DOSAGE	500 mg HR 355 tablets (Batch 14) single dose 400 mg cimetidine tablets (Batch 1130) twice daily for 7 days 500 mg probenecid tablets (Batch 885931W) four times daily for 7 days.
STUDY DESIGN	Open, randomised, three-way crossover study with 12 subjects. There were 3 study periods, each of 7 days. On days 1 to 7 of each period, subjects received either probenecid, cimetidine or nothing. A single dose of levofloxacin was also administered on each day 4, with a washout period between doses of levofloxacin of at least 14 days.
STUDY POPULATION	12 healthy males; age 18-60; body weight -15% - +10% Broca – normal weight.
DATA ANALYSIS	Pharmacokinetics:- Analysis of the following parameters : *Levofloxacin (HR 355):* C_{max}, t_{max}, AUC_{0-72}, $AUC_{0-\infty}$, Ae_{0-72}, Ae_{0-72}(% dose), $t_{½,\beta}$, MRT, Cl/F, Cl_r, Cl_{NR}/F Statistics: - Analysis of variance, 90% and 95% confidence intervals, non-parametric confidence intervals, descriptive statistics.

DEMOGRAPHICS

Subjects enrolled:13; subject [redacted] dropped out.

12 of the 13 subjects were fully evaluated after receiving cimetidine, probenecid and levofloxacin in random order as planned.

Age range: years (mean 34.3 years)

Weight range: kg (mean 76.7 kg).

RESULTS

Pharmacokinetic parameters of HR 355 (levofloxacin); mean values ± S.D. and (ranges); (n = 12) are presented in the following Tables.

CONCLUSIONS:

- The absorption of levofloxacin was unaffected by co-administration of cimetidine or probenecid, indicated by the lack of statistically significant alterations in either C_{max} or t_{max} of HR355.

- Mean serum half-lives for levofloxacin were statistically significantly increased by approximately 30% with co-administration of probenecid or cimetidine.

- Mean AUC_{0-72} values for levofloxacin were statistically significantly increased by approximately 27% (cimetidine co-administration), 38% (probenecid co-administration).

- The total amounts of levofloxacin excreted in the urine over 72 hours (Ae_{0-72}) appear similar for all treatment phases. The renal clearance (Cl_r) was statistically significantly reduced by co-administration of either cimetidine or probenecid. The Ae_{0-72} for levofloxacin alone, cimetidine co-administered and probenecid co-administered were 74.4%, 71.70%, 66.04% (expressed as mean percentage eliminations of the oral dose). The corresponding Cl_r were 119 ml/min, 91 ml/min and 77 ml/min respectively.

- The reductions in apparent total clearance (Cl/F) of levofloxacin can be accounted for by the reductions in renal clearance seen with cimetidine or probenecid co-administration.

- The observed statistically significant kinetic differences may not be of clinical significance, except in the presence of concurrent renal impairment.

Parameter	Treatment		
	Levofloxacin alone	Levofloxacin + cimetidine	Levofloxacin + probenecid
C_{max} (ng/ml)	7265.1 ± 1779.8 (4607.8 - 10696.0)	6911.8 ± 1562.8 (4058.9 - 9148.5)	7103.2 ± 2144.0 (5089.8 - 11286.0)
t_{max} (h)	1.10 ± 0.49 (0.5 -2.00)	1.08 ± 0.50 (0.5 - 2.00)	1.04 ± 0.46 (0.5 - 2.00)
AUC_{0-72} (ngh/ml)	52785.0 ± 6053.7 (42422.0- 60007.1)	66984.0 ± 7551.0 (51010.9 - 78104.9)	72635.0 ± 6969.2 (61353.8 - 81864.9)
$AUC_{0-\infty}$ (ngh/ml)	53222.0 ± 5997.8 (42832.5 - 60269.6)	67611.0 ± 7581.6 (51559.9 - 78565.6)	73449.0 ± 7030.1 (62386.3 - 83129.5)
Ae_{0-72} (mg)	372.01 ± 43.71 (285.14 - 424.95)	358.48 ± 51.54 (236.61 - 409.38)	330.19 ± 29.89 (275.57 - 367.22)
Ae_{0-72} (% dose)	74.40	71.70	66.04
$t_{½,\beta}$ (h)	8.32 ± 0.87 (6.84 - 9.61)	10.85 ± 1.16 (9.25 - 13.54)	10.96 ± 0.64 (9.63 - 11.96)
MRT (h)	12.18 ± 1.33 (10.10 - 15.38)	14.79 ± 1.41 (12.50 - 18.49)	15.90 ± 1.12 (14.19 - 18.15)
Cl_r (ml/min)	119.16 ± 21.44 (82.44 - 162.10)	90.59 ± 17.80 (55.44 - 111.34)	76.78 ± 12.78 (57.43 - 98.39)
Cl/F (ml/min)	158.54 ± 18.98 138.27 - 194.56	124.84 ± 15.54 106.07 - 161.62	114.45 ± 11.34 100.24 - 133.58
Cl_r/F (ml/min)	39.38 ± 13.59 22.21 - 60.50	34.25 ± 13.59 22.27 - 60.62	37.67 ± 5.56 27.89 - 45.70

Parameter	Treatment (n=12, mean + SD)		
	Levofloxacin	Cimetidine	Probenecid
C_{max} (ng/ml)	7265.1 ± 1779.8	6911.8 ± 1562.8	7103.2 ± 2144.0
t_{max} (h)	1.10 ± 0.49	1.08 ± 0.50	1.04 ± 0.46

Cmax	Comparison		
	Cimetidine/ Levofloxacin	Probenecid/ Levofloxacin	Probenecid/ Cimetidine
Point Estimate (%) 90%	95.3	96.9	101.6
Confidence Interval 95%	83.7 - 108.6	85.1 - 110.4	89.2 - 115.8
Confidence Interval	81.4 - 111.6	82.8 - 113.4	86.8 - 119.0

Parameter	Treatment (n=12, mean + SD)		
	Levofloxacin	Cimetidine	Probenecid
AUC_{0-72} (ngh/ml)	52785.0 ± 6053.7	66984.0 ± 7551.0	72635.0 ± 6969.2
$AUC_{0-\infty}$ (ngh/ml)	53222.0 ± 5997.8	67611.0 ± 7581.6	73449.0 ± 7030.1

AUC_{0-72}	Comparison		
	Cimetidine/ Levofloxacin	Probenecid/ Levofloxacin	Probenecid/ Cimetidine
Point Estimate (%) 90%	127.0	138.2	108.8
Confidence Interval 95%	123.0 - 131.2	133.8 - 142.8	105.3 - 112.4
Confidence Interval	122.1 - 132.1	132.9 - 143.8	104.6 - 113.2

AUC_{0-}	Comparison		
	Cimetidine/ Levofloxacin	Probenecid/ Levofloxacin	Probenecid/ Cimetidine
Point Estimate (%) 90%	126.9	137.9	108.6
Confidence Interval 95%	122.7 - 131.2	133.3 - 142.6	105.1 - 112.3
Confidence Interval	121.9 - 132.2	132.4 - 143.6	104.3 - 113.1

AUC_{0-72} and AUC_{0-} of levofloxacin showed a statistically significant difference between levofloxacin alone and levofloxacin administered with the other compounds. The area was significantly larger when dosing with either probenecid or cimetidine had occurred. There is also a statistically significant difference between probenecid and cimetidine although this is less pronounced.

Parameter	Treatment (n=12, mean + SD)		
	Levofloxacin	Cimetidine	Probenecid
$t_{1/2,\beta}$ (h)	8.32 ± 0.87	10.85 ± 1.16	10.96 ± 0.64

$t_{½,\beta}$	Comparison		
	Cimetidine/ Levofloxacin	Probenecid/ Levofloxacin	Probenecid/ Cimetidine
Point Estimate (%)	130.5	131.8	101.0
90% Confidence Interval	123.1 - 137.7	124.6 - 139.0	95.5 - 106.5
95% Confidence Interval	121.7 - 139.3	123.0 - 140.6	94.3 - 107.7

$t_{½,\beta}$ of levofloxacin showed a statistically significant difference between levofloxacin alone and levofloxacin administered with another compound. The half-life was significantly higher when dosing with either probenecid or cimetidine had occurred. There is no statistically significant difference between probenecid and cimetidine.

Parameter	Treatment (n=12, mean + SD)		
	Levofloxacin	Cimetidine	Probenecid
MRT (h)	12.18 ± 1.33	14.79 ± 1.41	15.90 ± 1.12

MRT	Comparison		
	Cimetidine/ Levofloxacin	Probenecid/ Levofloxacin	Probenecid/ Cimetidine
Point Estimate (%)	121.5	130.9	107.7
90% Confidence Interval	118.1 - 125.1	127.2 - 134.8	104.7 - 110.9
95% Confidence Interval	117.4 - 125.8	126.5 - 135.6	104.1 - 111.5

MRT of levofloxacin showed a statistically significant difference between levofloxacin alone and levofloxacin administered with both probenecid and cimetidine. The MRT was significantly prolonged when dosing with either probenecid or cimetidine, probenecid co-administration having the greatest effect.

Parameter	Treatment (n=12, mean + SD)		
	Levofloxacin	Cimetidine	Probenecid
Ae 0-72 (mg)	372.01 ± 43.71	358.48 ± 51.54	330.19 ± 29.89
Ae 0-72 (% dose)	74.40	71.70	66.04

Ae0-72	Comparison		
	Cimetidine/ Levofloxacin	Probenecid/ Levofloxacin	Probenecid/ Cimetidine
Point Estimate (%) 90%	96.4	88.8	92.1
Confidence Interval 95%	92.0 - 100.7	84.4 - 93.1	87.6 - 96.6
Confidence Interval	91.1 - 101.6	83.5- 94.0	86.6 - 97.6

Ae_{0-72} of levofloxacin showed a statistically significant difference between levofloxacin alone and levofloxacin administered with probenecid. The cumulative urinary excretion over 72 hours was statistically significantly reduced when dosing with probenecid had occurred.

Parameter	Treatment (n=12, mean + SD)		
	Levofloxacin	Cimetidine	Probenecid
Cl_r (ml/min)	119.16 ± 21.44	90.59 ± 17.80	76.78 ± 12.78

Cl_r	Comparison		
	Cimetidine/ Levofloxacin	Probenecid/ Levofloxacin	Probenecid/ Cimetidine
Point Estimate (%) 90%	76.0	64.4	84.8
Confidence Interval 95%	70.9 - 81.2	59.3 - 69.6	78.0 - 91.5
Confidence Interval	69.8 - 82.2	58.2 - 70.6	76.6 - 92.9

Cl_r of levofloxacin showed a statistically significant difference between levofloxacin alone and levofloxacin administered with cimetidine or probenecid. The renal clearance was significantly lower when dosing with either probenecid or cimetidine, probenecid giving the greatest reduction.

Parameter	Treatment		
	Levofloxacin	Cimetidine	Probenecid
Cl/F (ml/min)	158.54 ± 18.98	124.84 ± 15.54	114.45 ± 11.34
Cl_r/F (ml/min)	39.38 ± 13.59	34.25 ± 13.59	37.67 ± 5.56

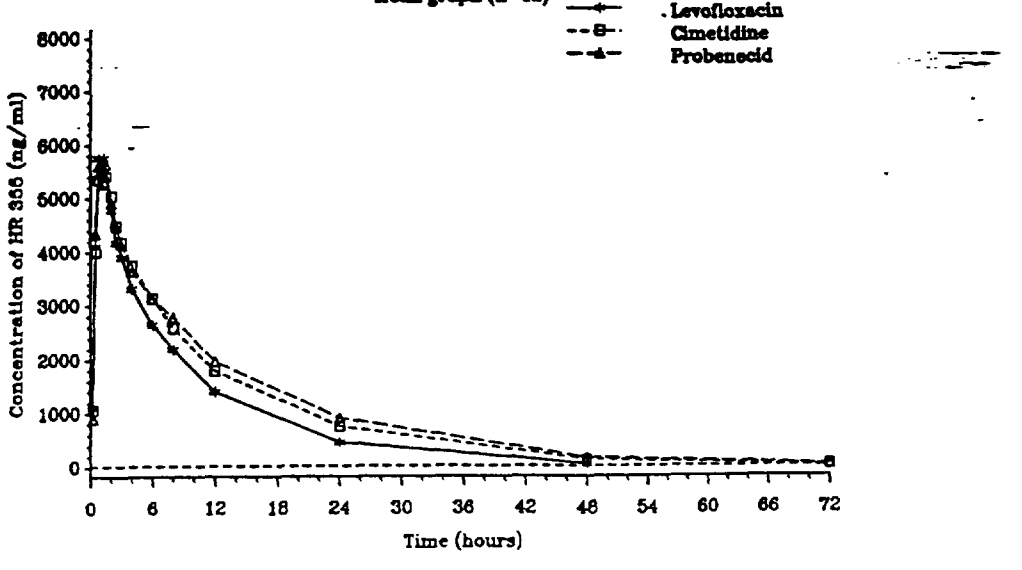
Cl/F	Comparison		
	Cimetidine/ Levofloxacin	Probenecid/ Levofloxacin	Probenecid/ Cimetidine
Point Estimate (%) 90%	78.7	72.2	91.7
Confidence Interval 95%	75.5 - 82.3	68.6 - 75.8	87.1 - 96.2
Confidence Interval	74.4 - 83.1	67.9 - 76.5	86.2 - 97.2

The apparent clearance of levofloxacin showed a statistically significant decrease between levofloxacin alone and levofloxacin administered with another compound. There is also a statistically significant difference between probenecid and cimetidine although this is less pronounced.

Cl_R/F	Comparison		
	Cimetidine/ Levofloxacin	Probenecid/ Levofloxacin	Probenecid/ Cimetidine
Point Estimate (%) 90%	87.0	95.7	110.0
Confidence Interval 95%	74.3 - 99.6	83.0 - 108.3	95.4 - 124.5
Confidence Interval	71.7 - 102.3	80.8 - 110.6	92.4- 127.6

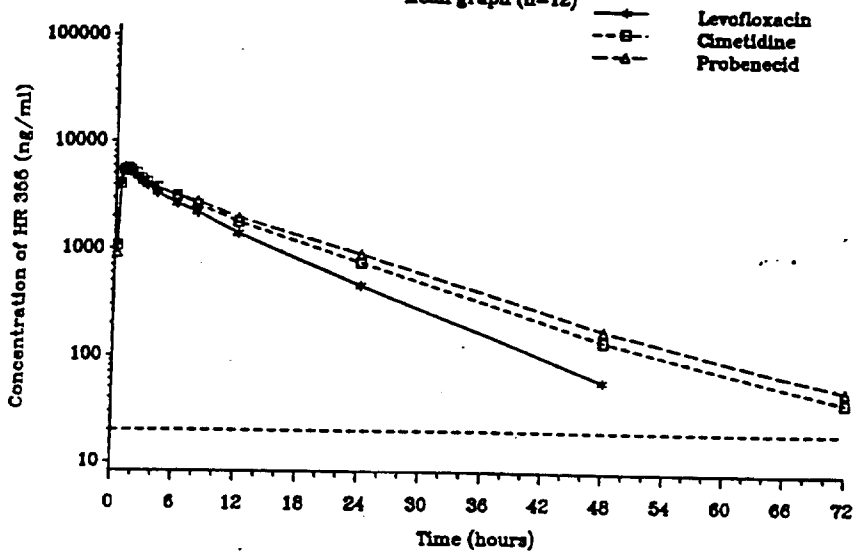
The 90 % confidence interval for 'cimetidine plus levofloxacin' versus 'levofloxacin alone' suggests a statistically significant difference in non-renal clearance. However, this is not supported by the 95 % confidence interval. No further statistically significant differences in the apparent non-renal clearance of levofloxacin were observed between the three treatments.

Figure 1
HR 355/1/GB/101/—
Serum concentrations of Levofloxacin after dosing with Levofloxacin alone, Levofloxacin and Cimetidine and Levofloxacin and Probenecid (Linear Scale)
Mean graph (n=12)



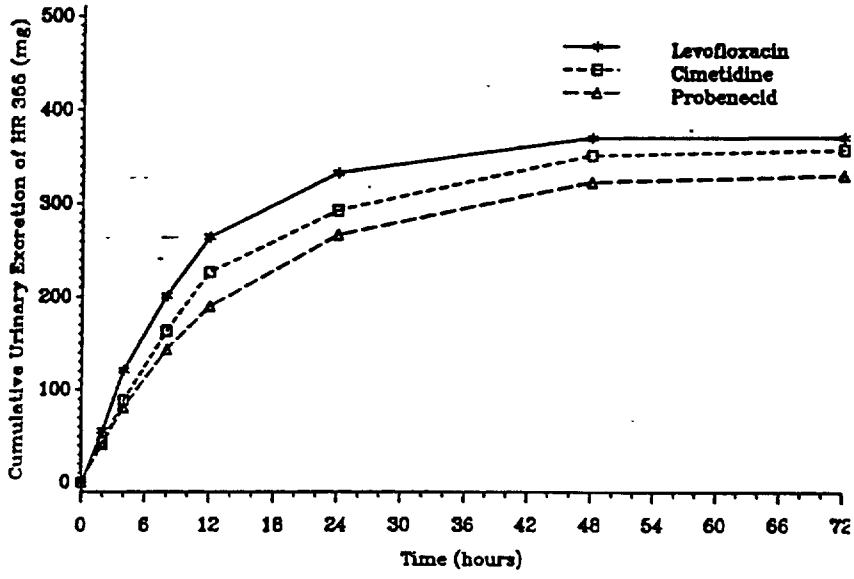
LOQ = 20 ng/ml

Figure 2
HR 355/1/GB/101/—
Serum concentrations of Levofloxacin after dosing with Levofloxacin alone, Levofloxacin and Cimetidine and Levofloxacin and Probenecid
(Semilogarithmic Scale)
Mean graph (n=12)



LOQ = 20 ng/ml

Figure 3
HR/355/1/GB/101/—
Cumulative Urinary Excretion of Levofloxacin after dosing with Levofloxacin alone, Levofloxacin and Cimetidine and Levofloxacin and Probenecid
Mean values (n=12)



STUDY TITLE: OPEN-LABEL, CROSSOVER STUDY TO DETERMINE THE PENETRATION OF LEVOFLOXACIN INTO INFLAMMATORY EXUDATE. VOLUME 1.70

PRINCIPAL INVESTIGATOR:

STUDY OBJECTIVES: This study was designed to evaluate the safety, pharmacokinetics, and penetration of levofloxacin into an inflammatory exudate (blister fluid) that mimicked skin and soft tissue infection.

STUDY DESIGN: This was an unblinded, randomized, two period, two treatment, crossover study consisting of six healthy male subjects. Subjects enrolled were assigned randomly to receive levofloxacin orally in one of two treatment sequences: (1) 500 mg q24h for three doses, followed by a six-week washout and continued on (2) 500 mg q12h for five doses, or vice versa. Each dose consisted of one 500-mg levofloxacin tablet manufactured by (Batch No. 18). Each dose was taken with ~240 mL of water. Subjects were instructed to fast for at least 2 hours before and 2 hours after dosing. On the evening of Day 2 of each treatment period, blisters were raised by strapping two 1-cm^2 cantharides plasters on the forearm of each subject.

SAMPLING: Blister fluid (~0.45 µL each) was drawn from each subject immediately prior to (0 h) the morning dose on Day 3 (last dose in each treatment period) and at 0.5, 1, 2, 4, 6, 12, and 24 hours post dose. The blister was resealed with a plastic spray dressing after each sample was taken. Blood samples were drawn from each subject at 0 (immediately prior to dosing), 0.5, 1, 1.5, 2, 4, 6, 8, 12, and 24 hours post dose on Day 3 via a venous cannula. The volume and pH of urine collected during each interval were recorded. A 20-mL aliquot of each urine sample was transferred to polypropylene tube for storage until analysis.

ANALYTICAL METHOD: Levofloxacin concentrations in these biological fluids were analyzed at the study site using a microbiological assay diffusion method within 1 hour after collection.

DEMOGRAPHICS: Six healthy male subjects participated in this study (Table 1). All completed the study.

DATA ANALYSIS: The following pharmacokinetic parameters of levofloxacin were estimated: the peak concentration (C_{max}) in plasma and blister fluid, trough concentration (C_{min}) in plasma and blister fluid, time-averaged concentration (C_{avg}) in plasma and blister fluid, time of C_{max} (T_{max}) in plasma and blister fluid, duration of absorption (To), area under the plasma and blister fluid concentration-time curve for a dosing interval (AUC), apparent total body clearance (CL/F), apparent distribution clearance between the plasma (central) and blister fluid (peripheral) compartments (CL_d/F), renal clearance (CL_R), apparent volume of distribution (Vd/F), apparent volume of the central compartment (V_c/F), apparent volume of the peripheral compartment (V_T/F), elimination rate constant from the body (ke), elimination half-life of terminal phase ($t_{1/2}$), penetration index into blister fluid (% penetration), and the amount excreted unchanged in urine (Ae).
Quantitation of the pharmacokinetic parameters was performed by the compartmental nonlinear regression method using the PCNONLIN program. The goodness of fit was evaluated by the correlation coefficient (r) between the observed and predicted concentration-time profiles (both plasma and blister fluid). The following pharmacokinetic parameters: To, Vd/F, V_c/F, V_T/F, CL/F, and Cl_d/F, K_e, $t_{1/2}$, and AUC were determined from the fit. Values of C_{max}, C_{min}, and T_{max} were

determined by inspection of the plasma and blister fluid concentration-time profiles. The total amounts of levofloxacin recovered in urine for a dosing interval (Ae) were determined on Day 3 of each treatment period. Renal clearance (CL_R) was calculated as Ae/AUC in plasma.

RESULTS: The mean (±SD) pharmacokinetic parameter estimates of the subjects following multiple 500-mg q24h or q12h oral administration of levofloxacin are summarized in Table 2. As shown in this Table, levofloxacin absorption and disposition pharamacokinetics appeared to be very similar following the once-daily and twice-daily dosing regimens. Increasing dosing frequency (q24h to q12h) resulted in predictably higher concentrations of levofloxacin attained in the plasma and blister fluid compartments.

Levofloxacin penetrated rapidly into the blister fluid following dose administration. Peak concentrations (C_{max}) in blister fluid were usually attained 1 to 2 h later than those observed in plasma. The C_{max} attained in blister fluid was ~70% of that attained in plasma following either dosing regimen. The time-averaged levofloxacin concentrations (C_{avg}) in the blister fluid and plasma over a dosing interval, however, were essentially identical under both dosing regimens. The percentage of levofloxacin that penetrated into the inflammatory exudate, calculated as the ratio between the blister fluid and plasma AUCs, was about 100% for both dosing regimens.

In two previous studies, 500 mg of levofloxacin hemihydrate (equivalent to 488 mg of anhydrous levofloxacin) were administered orally to 10 healthy male subjects at the q24h (study # K90-077) or to 20 healthy male subjects at the q12h (K90-014) dosing regimen. The pharmacokinetic parameter estimates from these two studies, where levofloxacin concentrations in plasma and urine were measured by an HPLC method, are summarized in Table 3. As shown, values of the levofloxacin pharmacokinetic parameters obtained from these studies are comparable with the results reported in the present study (Table 2), indicating a fairly good consistency between the levofloxacin concentrations measured by the two assaying methods (microbiological and HPLC) and the limited variability in levofloxacin pharmacokinetics across studies.

CONCLUSION: Levofloxacin penetration into the inflammatory exudate that mimicked skin and soft tissue infection was found to be rapid, extensive, and predictable following 500 mg q24h and q12h oral doses of levofloxacin. Levofloxacin pharmacokinetics were also similar for the two dosing regimens.

TABLE 1: Demographic and Baseline Characteristics
(All Subjects Enrolled in Study LOFBO-PHI0-095)

	Levofloxacin 500 mg q12h/500 mg q24h (N = 3)	Levofloxacin 500 mg q24h/500 mg q12h (N = 3)	Total (N = 6)
Race			
Caucasian	3	3	6
Age (yr)			
Mean ± SD	29.7 ± 7.6	26.7 ± 0.6	28.2 ± 5.1
Range			
Weight (kg)			
Mean ± SD	71.1 ± 13.1	82.0 ± 13.9	76.6 ± 13.5
Range			
Height (cm)			
Mean ± SD	179.8 ± 4.0	171.0 ± 7.2	175.4 ± 7.1
Range			

TABLE 2: Summary of Levofloxacin Pharmacokinetic Parameter Estimates (Mean ± SD)

Parameter	500 mg q24h	500 mg q12h
Plasma:		
C_{max}, µg/mL	6.55 ± 1.84	9.33 ± 2.27
C_{min}, µg/mL	0.55 ± 0.09	2.93 ± 0.95
C_{avg}, µg/mL	2.23 ± 0.43	5.00 ± 1.51
T_{max}, h	1.17 ± 0.52	1.08 ± 0.20
AUC, µg•h/mL[a]	53.5 ± 10.3	60.0 ± 18.2
Blister Fluid:		
C_{max}, µg/mL	4.33 ± 0.96	6.79 ± 2.05
C_{min}, µg/mL	0.82 ± 0.47	2.88 ± 1.08
C_{avg}, µg/mL	2.25 ± 0.61	4.66 ± 1.46
T_{max}, h	3.67 ± 1.51	2.33 ± 0.82
AUC, µg•h/mL[a]	54.1 ± 14.7	55.9 ± 17.5
% Penetration	100± 12	93.0 ± 4.7
Urine:		
Ae, % dose[a]	85.8 ± 8.1	86.9 ± 21.8
Other:		
To, h	1.14 ± 0.63	1.12 ± 0.35
Vd/F, L	102 ± 13	97.5 ± 22.3
V_c/F, L	66.4 ± 15.8	69.8 ± 18.6
V_T/F, L	35.2 ± 10.8	27.7 ± 9.4
CL/F, mL/min	161± 35	149 ± 40
CL_d/F, mL/min	348 ± 168	494 ± 197
CL_R, mL/min	138 ± 28	128 ± 45
k_e, h^{-1}	0.15 ± 0.03	0.13 ± 0.02
$t_{1/2}$, h	7.95 ± 1.35	7.91 ± 1.10

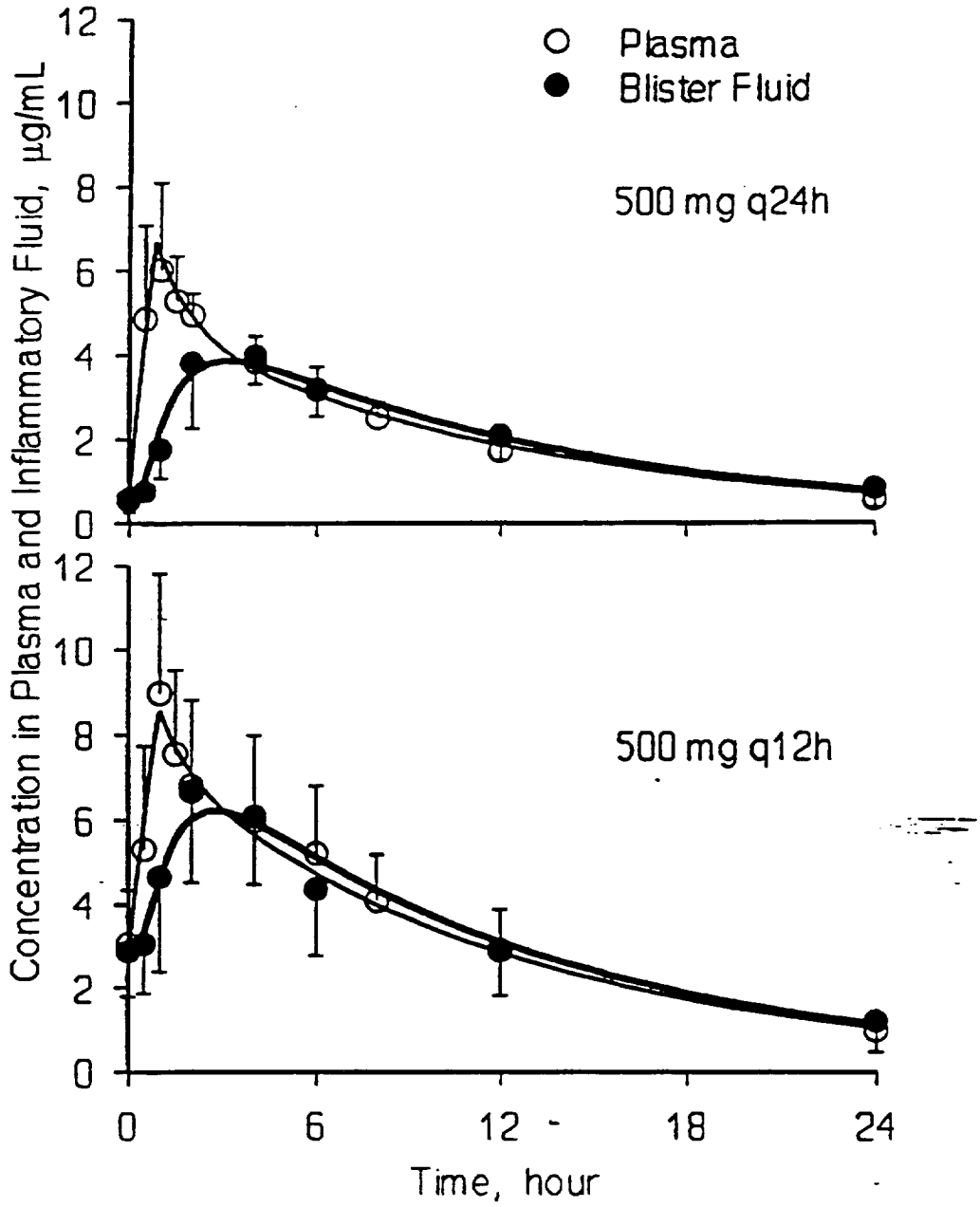
[a] AUC and Ae were calculated per dosing interval.

TABLE 3: Levofloxacin Pharmacokinetic Parameter Estimates (mean ± SD) in Healthy Subjects Following Multiple 488-mg q24h or q12h Oral Doses of Levofloxacin
(Studies K90-077 and K90-014)

Parameter	488 mg q24h	488 mg q12h
C_{max}, µg/mL	5.72 ± 1.40	7.80 ± 1.07
C_{min}, µg/mL	0.51 ± 0.17	2.97 ± 0.87
T_{max}, h	1.1 ± 0.4	1.3 ± 0.6
AUC, µg•h/mL[a]	47.5 ± 6.7	59.0 ± 11.8
Vd/F, L	102 ± 22	102 ± 16
CL, mL/min	175 ± 25	143 ± 30
CL_R, mL/min	116 ± 31	104 ± 26
$t_{1/2}$, h	7.6 ± 1.6	8.0 ± 1.1

[a] AUC per dosing interval

FIGURE 1: Mean (±SD) Levofloxacin Concentration vs. Time Profiles in Plasma and Inflammatory (Blister) Fluid Following Multiple 500-mg q24h or q12h Oral Dosing of Levofloxacin (Study LOFBO-PHI0-095).



[circles: observed data, lines: predicted curves]

TITLE: Penetration of Levofloxacin Into Bone Tissue After Oral Administration in Subjects Undergoing Total Hip Replacement (or Knee Replacement, by Amendment 1).
Volume 1.71 - 1.72.

STUDY #: HR355/1/USA/104/GP; N93-069 (PRI)

INVESTIGATOR AND STUDY SITE:

STUDY OBJECTIVE: The purpose of this study was to estimate the rate and extent of bone tissue penetration of levofloxacin in subjects undergoing total hip or knee replacement. Safety and tolerability of levofloxacin were also evaluated.

STUDY MEDICATION AND DOSAGE: Single doses of 500-mg anhydrous levofloxacin as a tablet (Batch nos. 5324 and R5826)

STUDY DESIGN: This was an open-label, randomized study planned for 30 adult males and females undergoing total hip or knee replacement. Twenty-seven were actually enrolled. Two subjects were control subjects who did not receive drug. The remaining 25 subjects were administered a single tablet containing 500 mg of anhydrous levofloxacin and assigned into groups to obtain bone tissue specimens at various postdose times (1, 2, 3, 4, 8, 12, and 24 hours). Plasma samples were collected before dosing, at the time of removal of the bone tissue, and 24 hours after dosing.

STUDY POPULATION: The planned study population was 30 subjects, between 18 and 80 years of age, undergoing total hip or knee replacement. However, twenty-seven (27) subjects (15 male and 12 female) were enrolled (Table 1).

ANALYTICAL METHOD: Concentrations of levofloxacin in plasma and bone were determined by high performance liquid chromatography with fluorescence measurement at

DATA ANALYSIS: Plasma and bone tissue concentrations of levofloxacin obtained at the various sampling times were calculated to estimate the rate and extent of penetration of levofloxacin into the bone tissue. The penetration ratio (bone tissue concentration divided by plasma concentration) was also calculated for each sampling time. The concentration of levofloxacin in bone tissue was corrected for levofloxacin in the blood that was in the bone. Corrected concentrations were compared to minimum inhibitory concentrations (MICs) already established *in vitro* against organisms commonly encountered in bone infections.

$$C_{corr.\,t} = \frac{C_t - C_p(Ht/Hb)(1-P)}{1-Ht/Hb}$$

where:

$C_{corr.\,t}$ = corrected tissue concentration of levofloxacin (µg/g),

C_t = measured concentration of levofloxacin in tissue (µg/g),

Cp = plasma concentration of levofloxacin at corresponding time of tissue procurement (µg/mL),

Ht = hemoglobin concentrations in tissue (g/100 g),

Hb = hemoglobin concentrations in blood (g/100 mL),

P = hematocrit value (%).

RESULTS: The observed maximum concentrations of levofloxacin were reached between 1.2 to 2.6 hours in cortical bone, spongiosa bone, and plasma. This indicates a fast penetration of the drug into femoral head and distal femur. The levofloxacin concentration profiles in plasma and in cortical bone and spongiosa bone of both femoral head and distal femur became almost parallel 5 hours after dose which suggests the attainment of an equilibrium. The relative magnitudes of mean levofloxacin concentration were as follows: spongiosa > plasma > cortical in the femoral head, and cortical > plasma > spongiosa in the distal femur. The difference in levofloxacin distribution between the femoral head and the distal femur could be due to a difference between these sites in surgical interruption of perfusion, drug permeability, blood perfusion rate, or tissue binding. The results are prented in Tables 2 and 3 below.

CONCLUSION: Levofloxacin penetrated well into cortical and spongiosa tissues in both the femoral head and distal femur, with mean penetration ratios between 0.34 and 1.51. The penetration of levofloxacin into bone was rapid, taking approximately 2 hours to reach the maximum concentration in bone. By 5 hours, levofloxacin seemed to have equilibrated between the bone tissues and plasma. The concentrations of levofloxacin in the bone tissues were high enough throughout the 24-hour period to be active *in vivo* against many organisms common in bone infection, which have MIC_{90} values ranging from µg/mL.

TABLE 1: Demographics.

		Age (years)		Weight (lb)		Height (in)	
Group	N	Mean	Range	Mean	Range	Mean	Range
Control (no dose)	2	48.5	47 to 50	192	123 to 260	67.0	63 to 71
	1	76.0		101		65.0	
	6	60.0		169		65.3	
	3	62.0		164		66.0	
	3	72.0		173		67.0	
	3	70.3		194		71.0	
	4	72.3		172		66.5	
	5	72.0		178		68.0	
Males	15	67.4		192		69.1	
Females	12	65.3		149		64.3	
Total	27	66.5		173		67.0	

TABLE 2: Levofloxacin Concentrations in Plasma and Femoral Head (Cortical and Spongiosa Bone) After a 500-mg Oral Dose - subjects with hip replacement.

Inv/	Sample Time	Concentration	Corrected Conc (μg/g)		Penetration Ratio	
Subject	(hrs postdose)	in Plasma (ng/mL)	Cortical	Spongiosa	Cortical	Spongiosa

Mean

x = Plasma sample was not taken simultaneously with bone sample.

* = Below detection limit.

— = Not reportable (the assay required recalibration, and there was not enough sample for reassay).

m = Sample missing (the investigator sampled only the other tissue type).

nc = Not calculated.

TABLE 3: Levofloxacin Concentrations in Plasma and Distal Femur (Cortical and Spongiosa Bone) After a 500-mg Oral Dose - subjects with knee replacement.

Inv/ Subject	Sample Time (hrs postdose)	Concentration in Plasma (ng/mL)	Corrected Conc (µg/g)		Penetration Ratio	
			Cortical	Spongiosa	Cortical	Spongiosa
Mean		2987	4.14	1.03	1.51	0.34

x = Plasma sample was not taken simultaneously with bone sample.

* = Below detection limit.

m = Sample missing (the investigator sampled only the other tissue type).

nc = Not calculated.

TABLE 4: Representative susceptibility MIC data for some frequent bacterial pathogens in bone infection are as follows:

Organism	MIC_{90} (µg/mL)
Staphylococcus aureus	0.5
Streptococcus pyogenes	0.5 to 2.0
Streptococcus agalactiae	2.0
Enterobacter spp.	0.78
Salmonella spp.	0.12
Escherichia coli	0.05 to 0.06

Figure 1. Levofloxacin concentrations in plasma, cortical bone, and spongiosa bone in hip replacement subjects, following the oral administration of 500-mg levofloxacin

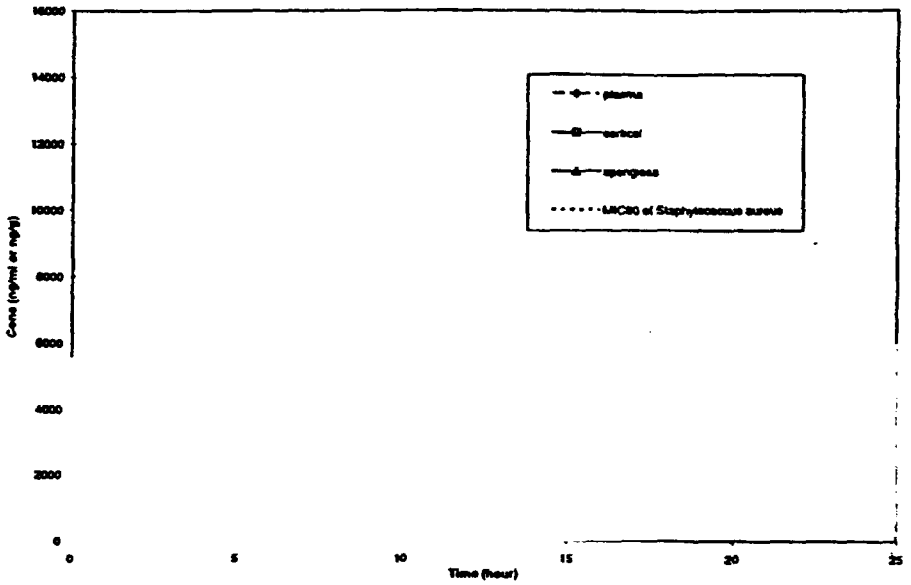


Figure 2. Levofloxacin concentrations in plasma, cortical bone, and spongiosa bone in knee replacement subjects, following the oral administration of 500-mg levofloxacin

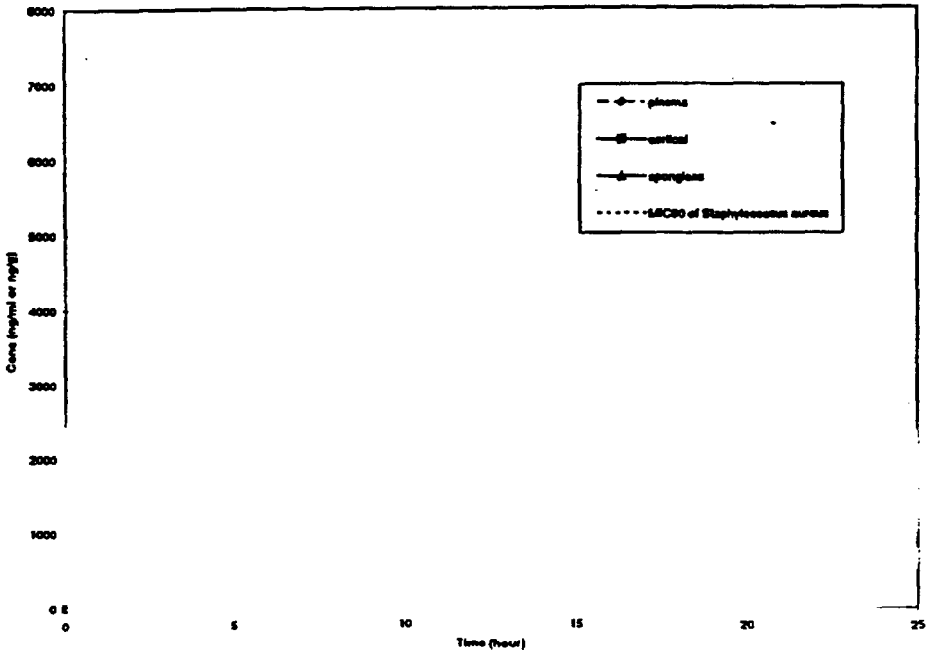


Figure 3. Penetration ratio of levofloxacin in cortical and spongiosa bones in hip replacement subjects, following the oral administration of 500-mg levofloxacin

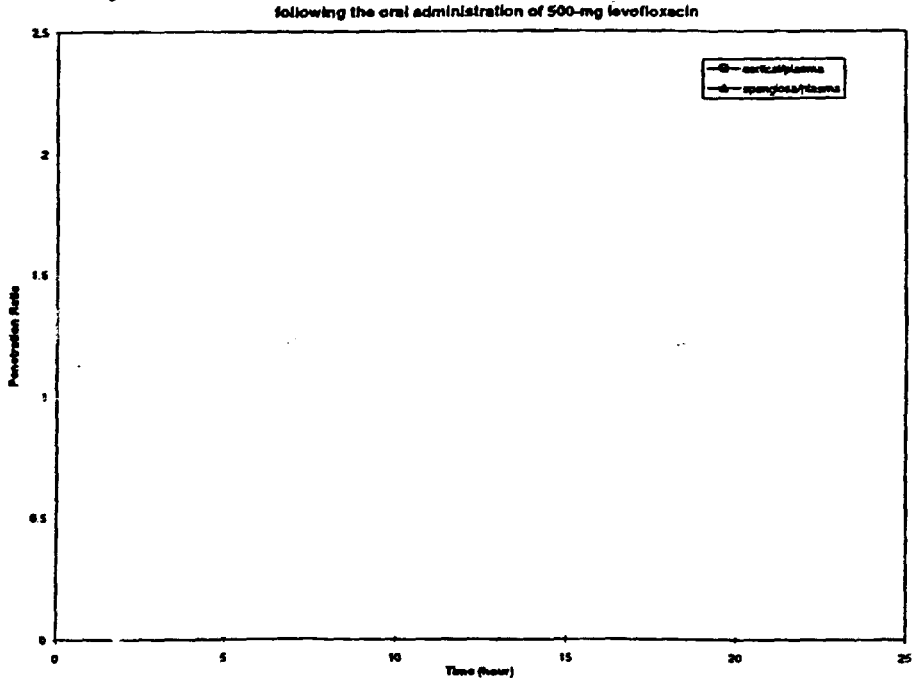


Figure 4. Penetration ratio of levofloxacin in cortical and spongiosa bones in knee replacement subjects, following the oral administration of 500-mg levofloxacin

(data of subject 108 is treated as an outlier and excluded from this plot)

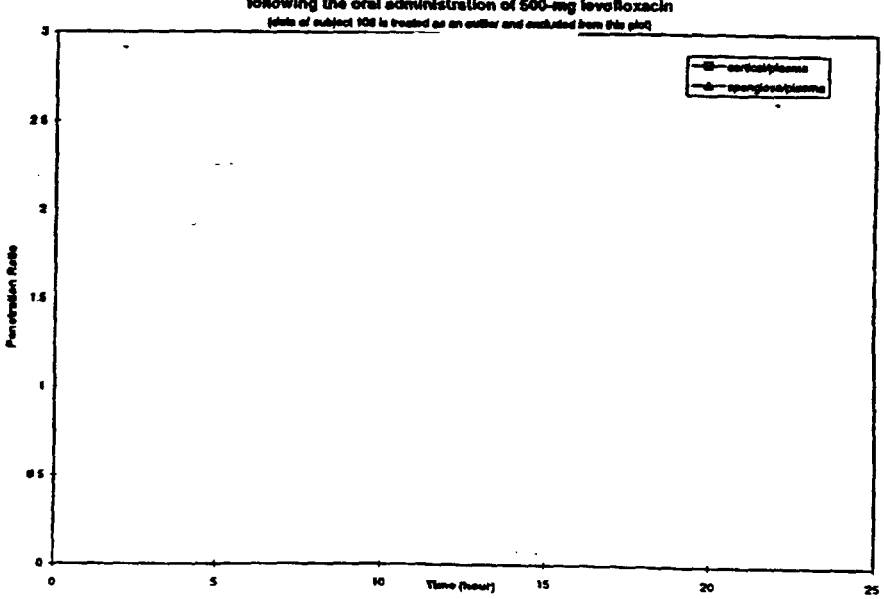
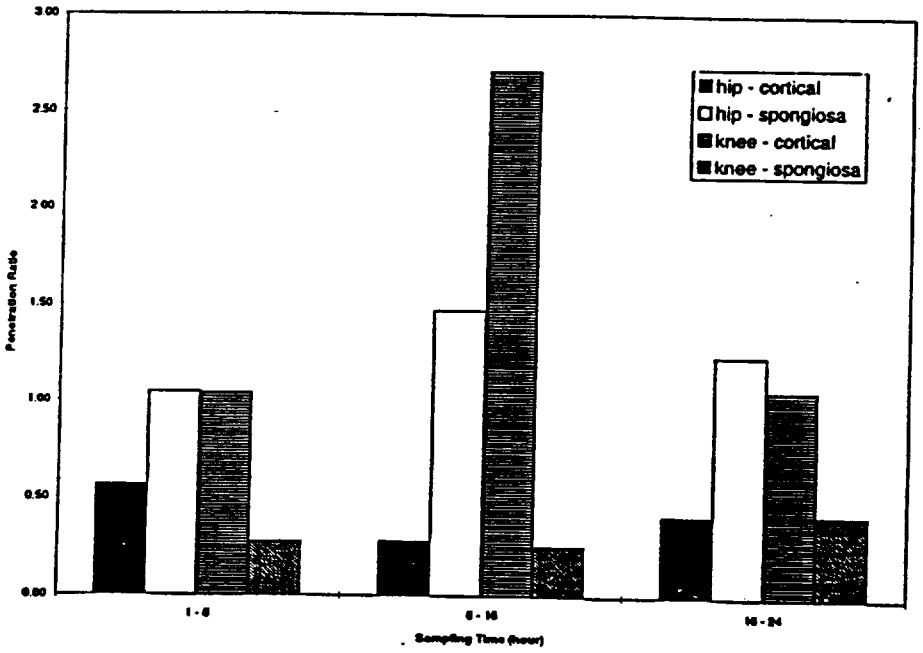


Figure 5. Penetration ratio (median) of levofloxacin into various sites of bone during different time intervals following the oral administration of 500 mg levofloxacin



ATTACHMENT

INVESTIGATORS AND STUDY SITES

INV. NO.	NAME/LOCATION
002	
005	

TITLE: Penetration of Levofloxacin Into Lung Tissue After Oral Administration in Subjects Undergoing Lung Biopsy or Lobectomy.

VOLUMES: 9.2 - 9.3

INVESTIGATORS:

OBJECTIVE: To estimate the rate and extent of lung tissue penetration of levofloxacin in subjects undergoing lung biopsy, lobectomy, or other operative procedures involving the removal of lung tissue.

FORMULATION: Single doses of 500-mg anhydrous levofloxacin as a tablet (Batch no. 5324).

STUDY DESIGN: This was an open-label study planned for 30 adult males and females undergoing lung biopsy, lobectomy, or other open operative procedure involving the removal of lung tissue. Two subjects were to be control subjects who did not receive drug. The remaining subjects were to be administered a single tablet containing 500 mg of anhydrous levofloxacin and assigned into groups to obtain lung tissue specimens at specified postdose times (1, 2, 3, 4, 8, 12, and 24 hours).

DEMOGRAPHICS: The study was discontinued after 18 of the planned 30 subjects were enrolled because the sponsor decided, considering the unanticipated slow enrollment, that sufficient data had been collected to describe qualitatively the penetration of levofloxacin into lung tissue. Twelve men and 6 women were enrolled in the study (Table 1). Thirteen subjects were white, 2 Oriental, 1 black, 1 Hispanic, and 1 other (Asian-Indian).

SAMPLING: Plasma samples were collected before dosing, at the time of removal of the lung tissue, and 24 hours after dosing with the exception of one subject who entered the study prior to Amendment 1, from whom samples were taken before dosing and at approximately 1, 2, 3, 4, 8, 12, and 24 hours posdose.

ANALYTICAL METHOD: Concentrations of levofloxacin in plasma and lung were determined by high performance liquid chromatography with fluorescence measurement.

DATA ANALYSIS: The concentration of levofloxacin in lung tissue was corrected for levofloxacin in the blood that was in the lung (**see the Attachments**). The corrected concentrations were compared with minimum inhibitory concentrations (MICs) already established *in vitro* against organisms commonly encountered in lung infections.

RESULTS: The individual plasma concentrations and the corresponding lung tissue concentrations, arranged by increasing sampling time (theoretical and actual), are shown in the table below. The above data are generally consistent with a peak in plasma concentration within 3 hours after dosing followed by a peak in lung concentration. The lung tissue concentration (ng/g) of levofloxacin consistently exceeded the plasma concentration (ng/mL) at every time point over the 24-hour period. The mean penetration ratio (corrected lung concentration/plasma concentration ratio) are 2.02, 5.02, 5.13 and 4.13 for Theoretical Hours 2 and 3, 4 and 8, 12, and 24, respectively.

The results are in agreement with previous findings that levofloxacin concentrations in most tissues or body fluids are generally higher than those observed in plasma. The penetration ratio (lung/plasma) measured in this study was similar to those observed with ofloxacin. This similarity with ofloxacin is expected since the human pharmacokinetic profile of levofloxacin is similar to that of the racemic mixture, ofloxacin. In the current study, there was one diseased (tuberculous) lung tissue sample obtained at about 22 hours postdose, for which the lung/plasma ratio was 2.13 (Table 2). This was similar to the ratio observed for healthy tissue; however, a difference of tissue penetration between healthy and diseased tissues can not be ruled out in this study.
The purpose of measuring antibiotic concentrations in different body fluid and tissues is to predict therapeutic effect. This is commonly done by comparing the concentration attained at the site of the infection with in vitro susceptibility as assessed by the MIC. For at least 24 hours after dosing, lung tissue levels of levofloxacin exceeded the MICs of organisms commonly isolated in respiratory tract infections.

CONCLUSION: In the present study, lung tissue concentrations of levofloxacin consistently exceeded the corresponding plasma concentrations over a 24-hour period after a single 500-mg, oral dose of levofloxacin.

TABLE 1: Demographic Data

Group	N	Age (years) Mean	Age (years) Range	Weight (lb) Mean	Weight (lb) Range	Height (in) Mean	Height (in) Range
A: Control (no dose)	0	NA		NA		NA	
B:	0	NA		NA		NA	
C:	2	73.0		159		66.0	
D:	3	56.3		148		68.0	
E:	2	68.0		201		70.0	
F:	2	72.0		188		69.5	
G:	6	60.3		150		64.2	
H:	3	57.7		143		66.7	
Males	12	64.1		165		68.3	
Females	6	60.2		148		63.5	
Total	18	62.8		160		66.7	

NA = Not applicable.

TABLE 2: Levofloxacin Concentrations in Plasma and Lung Tissue in Individual Subjects After a 500-mg Oral Dose

Inv/ Subject	Sampling Time (hour) Theoretical	Plasma	Lung	Corrected Concentration[a] Plasma (ng/mL)	Corrected Concentration[a] Lung (ng/g)	Penetration Ratio[b]
	2 (Group C)	2.28	2.28			
	2 (C)	2.00	2.35			
	3 (D)	3.00	3.00			
	3 (D)	3.08	3.08			
	3 (D)	3.18	3.18			
	4 (E)	4.60	4.60			
	4 (E)	4.70	4.70			
	8 (F)	6.33	6.33			
	8 (F)	—	—			
	12 (G)	10.67	10.67			
	12 (G)	11.50	11.50			
	12 (G)	11.81	12.66			
	12 (G)	12.40	—			
	12 (G)	14.25	14.25			
	12 (G)	17.42	17.38			
	24 (H)	21.50	21.58			
	24 (H)	24.63	24.63			
	24 (H)	25.43	25.43			

[a] Lung tissue concentrations were corrected for levofloxacin in the blood in the lung.
[b] Penetration ratio = corrected lung concentration (ng/g)/plasma concentration (ng/mL).
[c] Lung tissue concentration was not corrected for levofloxacin in the blood in the lung, because lung sample was too small for hemoglobin measurement.
[d] tuberculous tissue.
— Sample was not obtained.
nc = not calculated.

TABLE 3: Mean Levofloxacin Concentrations in Plasma and Lung Tissue at Specified Sampling Intervals After a 500-mg Oral Dose

Group	N	Sampling Time Range (hr)		Mean Corrected Concentration[a]		Mean Penetration Ratio[b]
		Plasma	Lung	Plasma (ng/mL)	Lung (ng/g)	
C + D	5	2.28–3.18	2.28–3.18	4,123	7,743	2.02
E + F	3	4.60–6.33	4.60–6.33	2,932	11,279	5.02
G	5	10.67–17.42	10.67–17.38	2,065[c]	9,164	5.13
H	3	21.50–25.43	21.58–25.43	717	2,429	4.13

[a] Lung tissue concentration in each subject was corrected for levofloxacin in the blood in the lung.
[b] Penetration ratio = corrected lung concentration (ng/g)/plasma concentration (ng/mL).
[c] The plasma concentration for Subject 005/0110 was excluded since there was no corresponding lung concentration.

TABLE 4. In Vitro Antibacterial Activities of Levofloxacin

Organism	Mean (weighted) MIC_{90} value (mg/L)
Haemophilus influenzae	0.02
Morexella catarrhalis	0.09
Klebsiella pneumoniae	0.18
Staphylococcus aureus (methicillin-resistant)	0.52
Streptococcus pneumoniae	1.91

INVESTIGATORS AND STUDY SITES

ATTACHMENTS

INV. NO. NAME/LOCATION

001

005

006

Formula for correcting tissue concentration of levofloxacin:

$$C_{corr.t} = \frac{C_t - C_p\,(Ht/Hb)\;(1-P)}{1-Ht/Hb}$$

where

$C_{corr.t}$	=	corrected tissue concentration of levofloxacin (ng/g),
C_t	=	measured concentration of levofloxacin in tissue (ng/g),
Cp	=	plasma concentration of levofloxacin at corresponding time of tissue procurement (ng/mL),
Ht	=	hemoglobin concentrations in tissue (g/100 g),
Hb	=	hemoglobin concentrations in blood (g/100 mL),
P	=	hematocrit value (%).

EFFECT OF GENDER ON THE PHARMACOKINETICS OF LEVOFLOXACIN – A NONMEM ANALYSIS OF POOLED DATA FROM FOUR CLINICAL PHARMACOKINETIC STUDIES

VOLUME 1.90

The main objective of this NONMEM analysis was to investigate the effect of gender on the pharmacokinetics of levofloxacin. Secondary objectives were to study the effects of other covariates like race, age, creatinine clearance, body weight, and drug interactions with digoxin, sucralfate, and cyclosporine.

Data from four clinical pharmacokinetic studies in healthy subjects were combined for the population pharmacokinetic analysis using the NONMEM program (Version IV, level 2.1). The data set comprised of complete pharmacokinetic profiles after a single oral dose of levofloxacin (500 mg) or after multiple oral doses to steady-state (500 mg q12h). Seventy-two subjects (36 males, 36 females, see Table I) provided one concentration-time profile each resulting in 1344 measured concentrations.

Table I: Demographic Summary for Subjects Included in the NONMEM Analysis

		Body Weight (kg)		CL_{CR} (mL/min)	
	No. of Subjects	Range	Mean (SD)	Range	Mean (SD)
Gender:					
Male	36		76.9 (10.4)		101 (21)
Female	36		65.0 (10.3)		84 (17)
Age:					
Age<65 yr	60		71.5 (11.5)		97.0 (17.1)
Age≥65 yr	12		72.6 (15.6)		58.2 (12.1)
Race:					
White*	48		71.6 (12.4)		89.2 (24.5)
Nonwhite*	24		71.8 (11.8)		93.1 (15.3)

* 14 Black, 9 Hispanic, and 1 Oriental

The following covariates were included in the analysis: gender, race, age, creatinine clearance, body weight, presence of cyclosporine, presence of digoxin, and presence of sucralfate.

Pharmacokinetic Model and Hypotheses Testing of Intermediate Models

Preliminary analysis using one- and two-compartment models with first order absorption and elimination indicated the one-compartment model was most appropriate. Oral absorption of levofloxacin is rapid and complete. Peak levofloxacin concentrations were reached within 1.5 hours in most cases. The limited number of concentration measurements before the peak precluded the precise estimation of the absorption rate constant (k_a) as well as the investigation of covariates which might have influenced the absorption rate of levofloxacin. This NONMEM analysis focused on the contribution of the various covariates on the apparent oral clearance (CL) and apparent volume of distribution (V).

Proportional error models were employed for the interindividual variability of k_a, CL, and V, as well as for the residual variability in the levofloxacin concentration data.

A multiple stepwise procedure was used to determine which influencing covariates should be included in the optimal model describing the population pharmacokinetics of levofloxacin by oral administration. The difference in the value of the objective function between two related NONMEM models was calculated. In the complete model, a certain θ parameter representing a covariate would be freely estimated, whereas in the reduced model it would be fixed to zero allowing the complete model to collapse to its reduced counterpart. Such a θ parameter would only be retained in the model to represent the significant influence of a certain covariate if the difference in the objective function value was at least eight. The First-Order (FO) method was used in the model building procedure. The First-Order Conditional Estimation (FOCE) method was used in addition for the optimal model to confirm the results from the FO method. An iterative stepwise procedure was employed to prevent oversights as well as redundancies in the optimal model.

The Optimal Population Model

The optimal population model was derived from the multiple stepwise procedure. As expected, the most significant covariate on CL was CL_{CR} and the most significant covariate on V was body weight. The mean CL value for subjects with normal renal function (CL_{CR} = 110 mL/min) was 10.9 L/h. This is in fair agreement with those published for healthy subjects. No other covariate was found to influence the CL.

Gender Effect

There were 36 male and 36 female subjects included in this analysis (Table I). The mean body weight and CL_{CR} of female subjects were about 16 and 17% lower, respectively, than those of male subjects. There was no significant gender effect on CL of levofloxacin in subjects with matching CL_{CR}. However, a small but significant gender effect on V was found. The mean V in female subjects was approximately 19% lower than that of male subjects with matching body weight. Monte Carlo simulations of levofloxacin plasma concentrations at steady state were performed by NONMEM for 100 male and 100 female subjects. The mean plasma levofloxacin concentration profiles and 95% population confidence intervals following a 500 mg q12h regimen was compared between male and female subjects with typical body weights and CL_{CR} (70 kg body weight and 100 mL/min

CL_{CR} for male; 60 kg body weight and 85 mL/min CL_{CR} for female). The difference in steady-state levofloxacin concentration is marginal (Figure 3).

Race Effect

There were 48 white and 24 nonwhite subjects with matching body weights and CL_{CR} included in this analysis (Table I). Race did not significantly influence either CL or V of levofloxacin.

Age Effect

Twelve of the 72 subjects were 65 years or older. Their mean CL_{CR} was about 40% lower than that of the younger subjects. The effect of age on either CL or V of levofloxacin can be explained by the difference in CL_{CR}.

Concomitant Medications

The presence of digoxin or sucralfate had no effect on either CL or V of levofloxacin. The presence of cyclosporine had no effect on the CL of levofloxacin (Fig 4). The concomitant cyclosporine dosing resulted in an increased V. This is expected to be of no clinical significance since it would have only marginal effect on levofloxacin steady-state plasma concentrations.

Table 2: Clinical Studies Included in the NONMEM Analysis

Study No.	Study Objective	Protocol No.	Levofloxacin Dose	Concentration Profiles	Males (M) Females (F)
1	Influence of age and gender on the pharmacokinetics of levofloxacin	N93-024	500 mg single oral dose	0 to 36 h	M = 12 F=12
2	Effect of levofloxacin on the pharmacokinetics of cyclosporine	N93-059	500 mg orally every 12 h to steady state	0 to 12 h	M = 6 F = 6
3	Effect of levofloxacin on the pharmacokinetics of digoxin	LOFBO-PHI0-094	500 mg orally every 12 h to steady state	0 to 12 h for two periods	M = 6 F = 6
4	Effect of food and sucralfate on the pharmacokinetics of levofloxacin	HR355/1/ USA/105	500 mg single oral dose	0 to 48 h for two periods	M = 12 F = 12

Table 3: One Way ANOVA of Pharmacokinetic Parameters of Male and Female Subjects Estimated From Model 1 by FO Posthoc Method

Parameter (Unit)	Mean Value Male	Female	%Difference (Male-Female)*100/Male	ANOVA p-Value
CL (L/h)	10.1	8.9	12	0.0099
V (Liter)	98.1	72.1	26	0.0001

Figure 1: Frequency Distribution of Creatinine Clearance of Male and Female Subjects

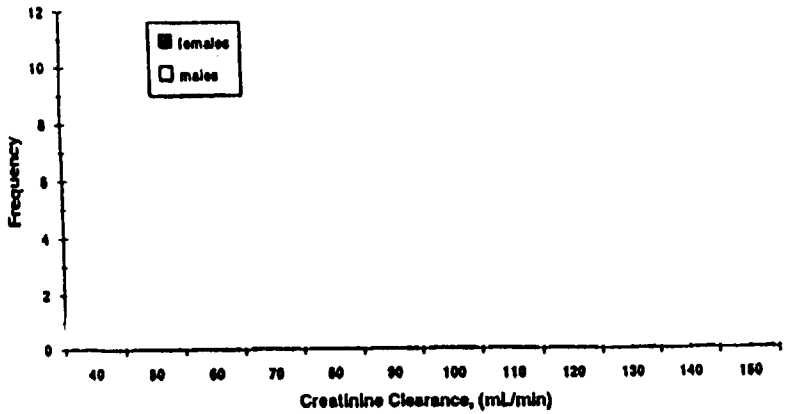


Figure 2: Frequency Distribution of Body Weight of Male and Female Subjects

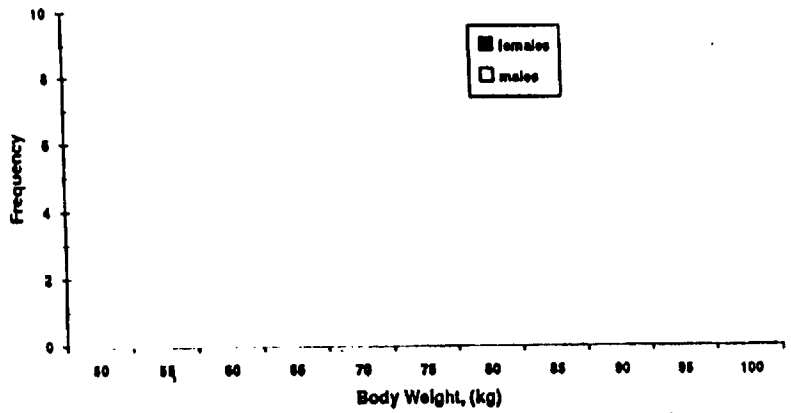


Figure 3: Monte Carlo Simulations of Levofloxacin Steady-State Plasma Concentrations for Male and Female Subjects Following Oral Administration of a 500 mg q12h Regimen. The Solid Line Represents the Mean Concentrations (N=100) and the Dashed Lines Represent the 95% Confidence Intervals of the Population.

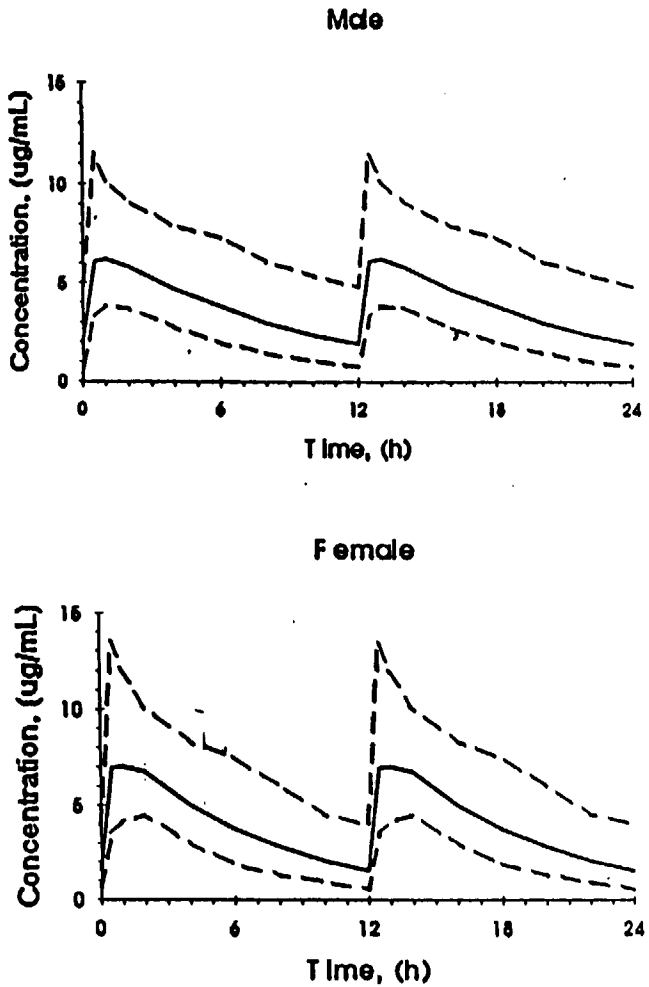


Figure 4: Comparison of Levofloxacin Steady-State Trough Concentrations Prior to Cyclosporine Dosing and After Dosing. The Solid Line and Dashed Lines Were the Mean and 95% Confidence Intervals for the Population

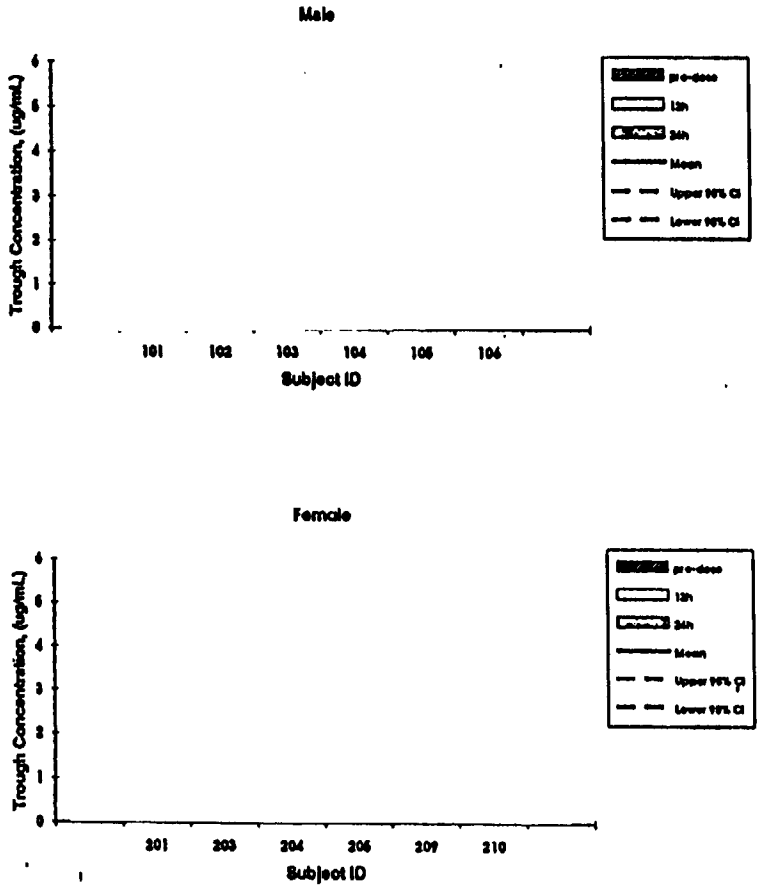


Figure 5: Simulation using parameters generated from NONMEM analys

Female - 40 kg, 75 yr, 30 ml/min (CLCR), (500 mg qd)

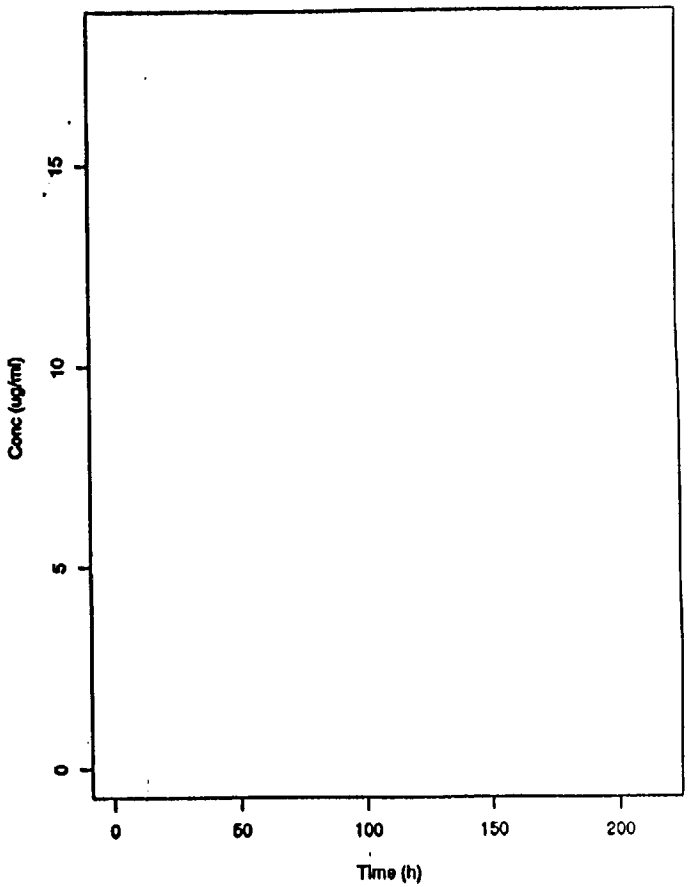


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Figure 6: Simulation using parameters generated from NONMEM analysis.

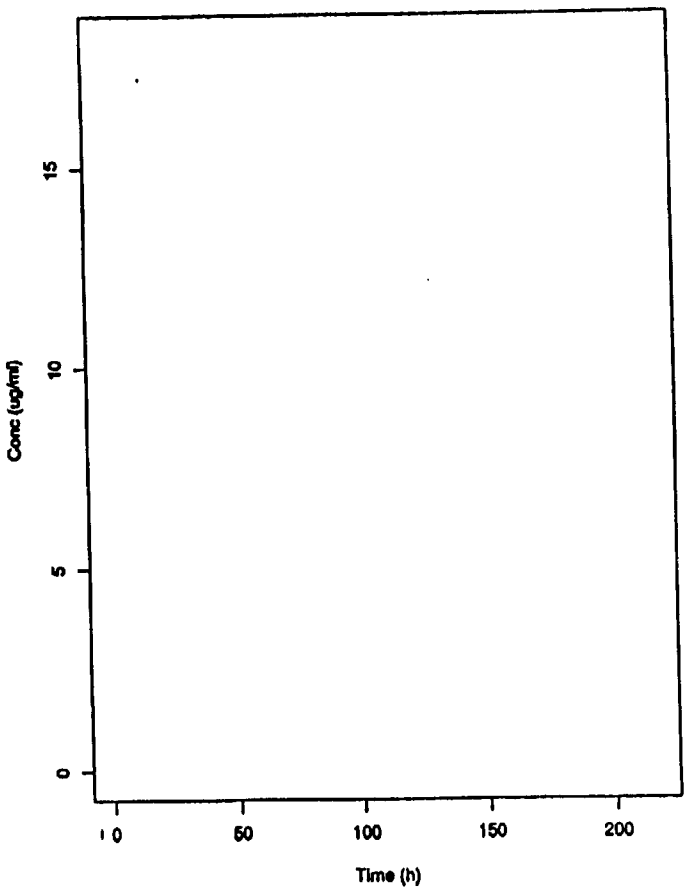
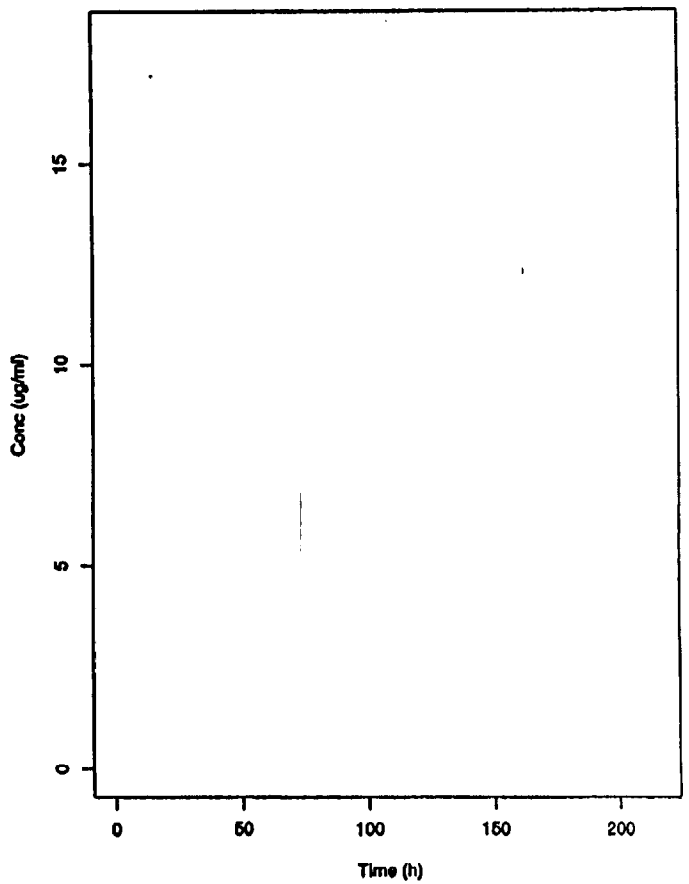


Figure 7: Simulation using parameters generated from NONMEM analysis.



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Attachment 1: Representation of Data in the NONMEM Data File

Data Label	Description
ID	This is an unique number for each subject in the data file. The number 2101, e.g., stands for subject 101 in Study 2; 4211 stands for subject 211 in Study 4.
AMT	This is the amount of levofloxacin in mg given orally at one occasion.
TIME	This is the time in hours between the oral dose and the sampling of blood for the determination of the levofloxacin plasma concentration.
DV	DV stands for "dependent variable". This is the levofloxacin plasma concentration measured in mg/L.
SS	This data item is required by the NONMEM program. A "1" indicates that the dose was given at steady-state; a "0" indicates a non steady-state dose.
II	II stands for "interdose interval". It is the time in hours between doses at steady-state.
SEX	The gender of the subjects is expressed as "0" for male and as "1" for female.
RACE	A "0" stands for "White", and a "1" stands for "Nonwhite".
WT	This represents the body weight of the subjects in kg.
AGE	The age of the subjects in years.
CL_{CR}	The renal function of the subjects is expressed as creatinine clearance with units mL/min. This parameter was calculated from the serum creatinine concentration.
CSA	"0" in the absence of cyclosporine and "1" in its presence.
DIGX	"0" in the absence of digoxin and "1" in its presence.
SUCR	"0" in the absence of sucralfate and "1" in its presence.
EVID	This data item is required by the NONMEM program. A "1" indicates a dosing event; a "0" indicates an observation event, and a "4" indicates a "reset" dosing event, i.e., a second profile in the same subject.
MDV	This data item is required by the NONMEM program. A "1" indicates a dosing event; a "0" indicates an observation event.

Attachment 2: Listing of Intermediate Models in Their Chronological Order

Model No.	Compared to Model No.	ΔObjective Function	Model Objective	Model Outcome
1	-	-	The basic one-compartment model with first-order absorption run by the FO method	Acceptable fit by the FO method, used as the reference model for the following comparisons
2	1	-	The FOCE method was used to compare with the FO method	The FOCE method results in very similar model estimates. The FO method will be used in subsequent model building
3	1	3	Test gender effect on CL	Not significant
4	1	97	Test gender effect on V	Significant/Rank = 2
5	1	24	Test race effect on CL	Significant/Rank = 9
6	1	22	Test race effect on V	Significant/Rank = 10
7	1	76	Test age effect on CL	Significant/Rank = 4
8	1	46	Test age effect on V	Significant/Rank = 5
9	1	1	Test cyclosporine effect on CL	Not significant
10	1	29	Test cyclosporine effect on V	Significant/Rank =6
11	1	2	Test digoxin effect on CL and V	Not significant
12	1	29	Test sucralfate effect on V	Significant/Rank = 7
13	1	27	Test sucralfate effect on CL	Significant/Rank = 8
14	1	121	Test influence of body weight on V	Significant/Rank = 1
15	1	22	Test influence of body weigh on CL	Significant/Rank = 11
16	1	0	Test influence of CL_{CR} on V	Not significant
17	1	83	Test influence of CL_{CR} on CL	Significant/Rank = 3
18	14	14	Add gender effect on V when body weight is already related to V	Gender effect on V is still significant
19	18	74	Add influence of CL_{CR} on CL	Influence of CL_{CR} on CL is significant

Attachment 2: Listing of Intermediate Models in Their Chronological Order (Continued)

Model No.	Compared to Model No.	Δ Objective Function	Model Objective	Model Outcome
20	19	5	Add age effect on CL	Age effect on CL is NOT significant anymore
21	19	7.3	Add age effect on V	Age effect on V is NOT significant anymore
22	19	66	Add cyclosporine effect on V	Significant
23	22	15	Add sucralfate effect on V	Significant
24	23	7	Add sucralfate effect on CL	Not significant
25	23	3	Add race effect on CL	Not significant
26	23	1	Add race effect on V	Not significant
27	23	1	Add influence of body weigh on CL	Not significant
28	23	-	The same structure model as Model 23 run by FOCE method	Model 28 and 23 included all significant covariates. The FOCE method results in similar model estimates.
29	23	24	The same structure model as Model 23 but the off-diagonal terms of the OMEGA matrix were also estimated; i.e., BLOCK(3)	The off-diagonal terms of the OMEGA matrix will be kept in subsequent models.
30	29	17	Remove sucralfate effect from V	Significant, 4% lower V which is not clinical significant
31	29	72	Remove cyclosporine effect from V	Significant, higher V in the presence of cyclosporine
32	29	32	Remove gender effect from V	Significant, lower V in female as compared to male
33	29	76	Remove influence of CL_{CR} from CL	Significant, CL is dependent on CL_{CR}.
34	29	69	Remove influence of body weight from V	Significant, V is dependent on body weight.
35	29	-	The same structure model as Model 29 run by FOCE method	The FOCE method results in similar model estimates. The FOCE method also provided esimates of individual pharmacokinetic parameters

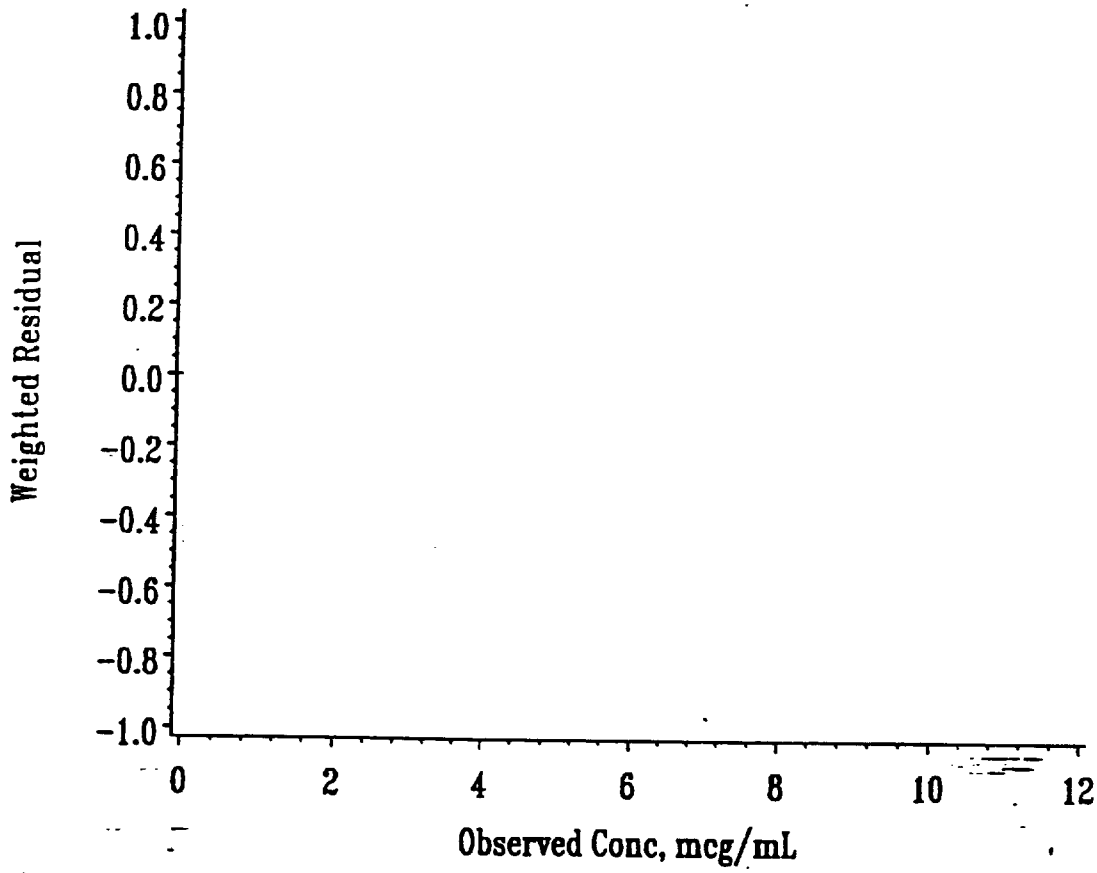
Attachment 3: The Control Stream File for the Optimal Model in NONMEM Analysis

```
$PROB  levofloxacin MODEL 35
$INPUT  ID AMT TIME DV SS II SEX RACE WT AGE CLCR CSA DIGX SUCR EVID MDV
$DATA  rjle_d02.dat(E5.0,E4.0,2E6.0,E2.0,E3.0,2E2.0,E6.0,E3.0,E4.0,5E2.0)
$SUBROUTINES ADVAN2 TRANS1
$PK
   FAGE=0
   IF (AGE.GE.65) FAGE=1
   TVKA = THETA(1)
   CL0  = THETA(2)
   CL1  = CL0*(1+THETA(3)*SEX)*(1+THETA(4)*RACE)*(1+THETA(5)*FAGE)
   CL2  = CL1*(1+THETA(6)*CSA)*(1+THETA(7)*DIGX)*(1+THETA(8)*SUCR)
   TVCL = CL2*(CLCR/110)**THETA(9)*(WT/70)**THETA(10)
   V0  = THETA(11)
   V1  = V0*(1+THETA(12)*SEX)*(1+THETA(13)*RACE)*(1+THETA(14)*FAGE)
   V2  = V1*(1+THETA(15)*CSA)*(1+THETA(16)*DIGX)*(1+THETA(17)*SUCR)
   TVVD = V2*(CLCR/110)**THETA(18)*(WT/70)**THETA(19)
   KA   = TVKA*EXP(ETA(1))
   CL   = TVCL*EXP(ETA(2))
   VD   = TVVD*EXP(ETA(3))
   K    = CL/VD
   S2   = VD
$ERROR
   IPRED=F
   Y=F*(1 + EPS(1)) + EPS(2)
$THETA (.3, 1.5, 10)   ;KA
     (3, 10, 40)      ;CL
      0 FIXED 0 FIXED 0 FIXED 0 FIXED
      0 FIXED 0 FIXED (0, 0.6, 3) 0 FIXED
     (10, 90, 500)    ;VD
       (-2, -0.2, 2) 0 FIXED 0 FIXED (-2, 1, 2)
      0 FIXED (-2, .05, 2) 0 FIXED (0, 0.7, 3)
$OMEGA  BLOCK (3) 1  0.1 0.1 .3 .006 .4
$SIGMA  0.1 0.1
;$MSFI  LEVONM1.MSF
$EST  METHOD=COND  NOABORT  SIGDIG=4  MAXEVAL=9900  PRINT=5
MSFO=LEVONM1.MSF
$COV
$TABLE ID TIME SEX RACE FAGE WT CLCR SUCR KA VD CL IPRED NOHEADER
  NOPRINT FILE=LEVONM1.TAB
$SCAT WRES VS DV
$SCAT WRES VS TIME
```

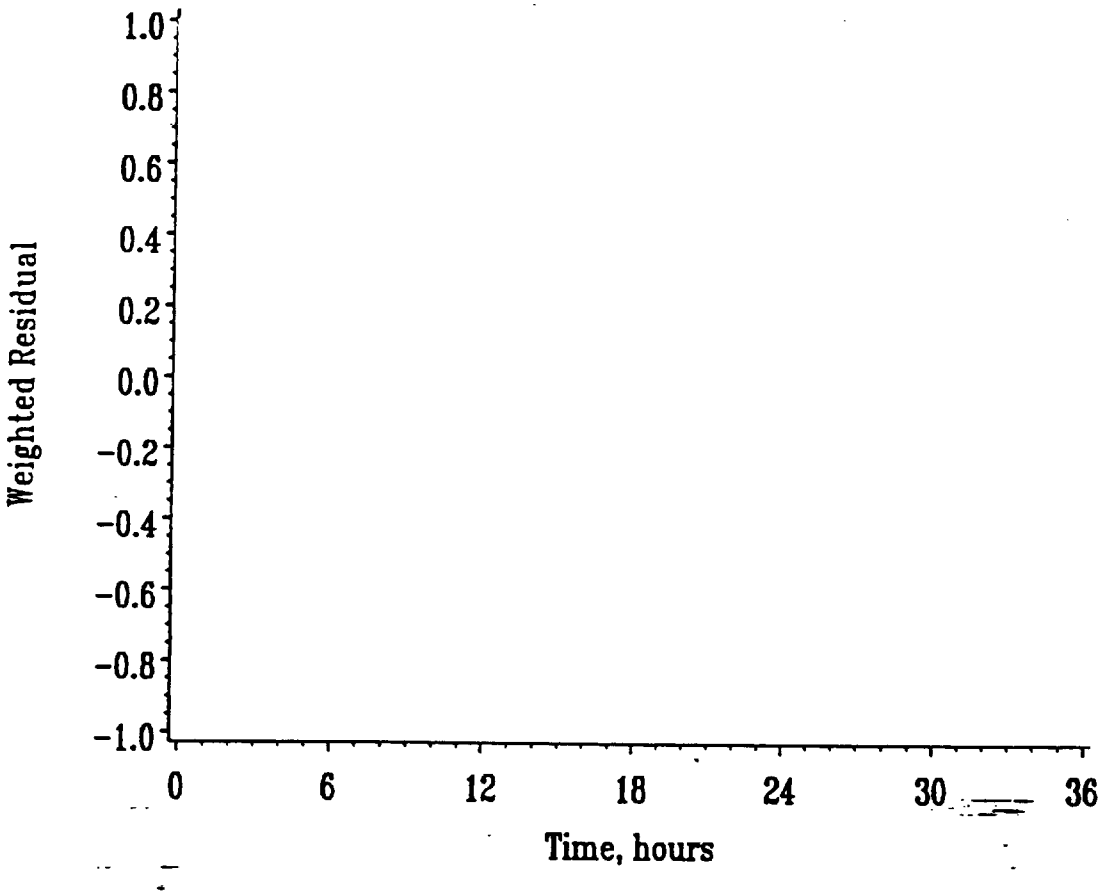
Attachment 4: Levofloxacin Pharmacokinetic Parameter Estimates Obtained by FO Method (Model 29)

Parameter	Units	Symbol	Estimate	S.E. of Estimate
k_a	1/h	θ_1	4.42	0.93
CL for normal covariates	L/h	θ_2	10.9	0.52
Power of CL_{CR} term on CL	-	θ_9	0.37	0.06
V for normal covariates	Liter	θ_{11}	94.1	5.1
Power of body weight term on V	-	θ_{19}	0.64	0.15
Fractional change in V influenced by gender	-	θ_{12}	-0.178	0.067
Fractional change in V influenced by cyclosporine	-	θ_{15}	0.99	0.16
Fractional change in V influenced by sucralfate	-	θ_{17}	-0.046	0.019
Variance of k_a	-	ω^2_{ka}	4.92	3.72
Variance of CL	-	ω^2_{CL}	0.0549	0.0205
Variance of V	-	ω^2_V	0.0178	0.0036
Residual variance	-	σ^2	0.0321	0.0068

Attachment 6: A Plot of Weighted Residuals vs. Observed Concentrations (µg/mL) for the Optimal Model by the FOCE Method



Attachment 7: A Plot of Weighted Residuals vs. Sampling Times (h)



for the Optimal Model by the FOCE Method

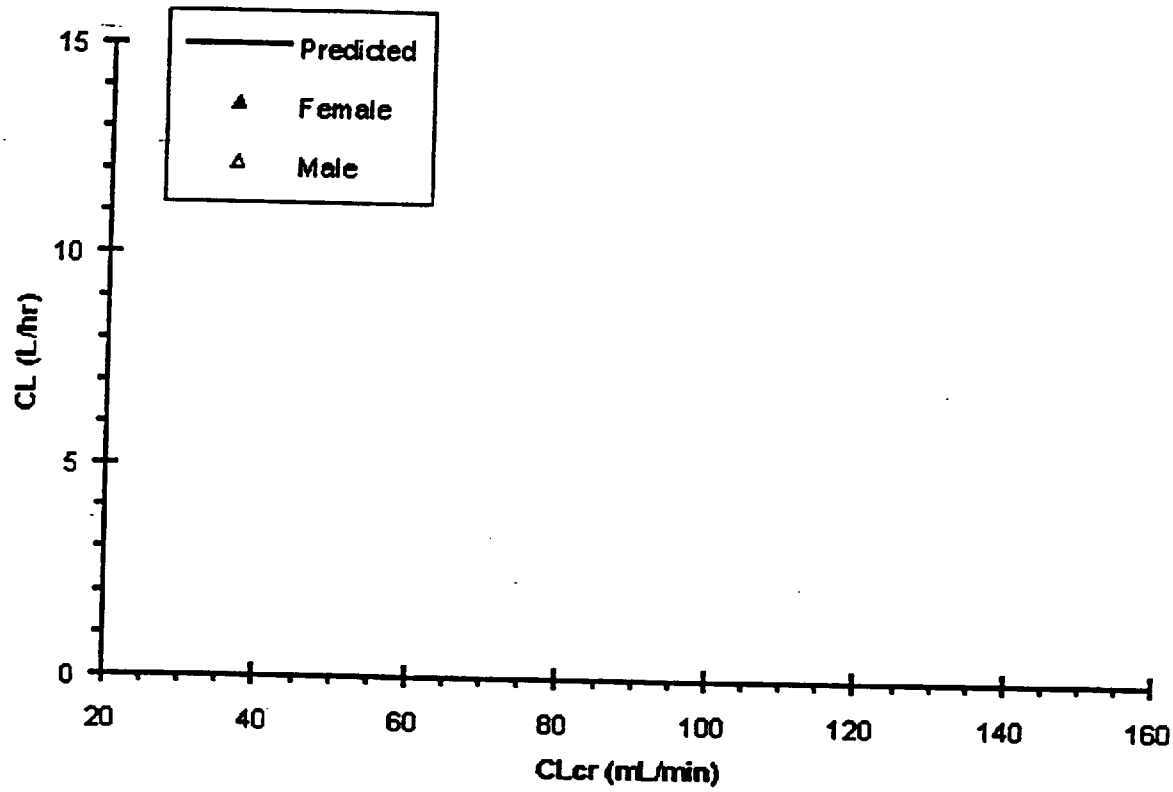
Attachment 8: A Table of Individual Levofloxacin Pharmacokinetic Parameters and Demographic Characteristics for the Optimal Model by the FOCE Method

Subject ID	Gender	Race	Age	Weight (kg)	CL_{CR} (mL/min)	K_a (1/h)	V (Liter)	CL (L/h)
	0	1	0	88				
	0	1	0	86				
	0	1	0	68				
	0	0	0	61				
	0	1	0	85				
	0	1	0	75				
	0	0	1	71				
	0	0	1	87				
	0	0	1	81				
	0	0	1	81				
	0	0	1	97				
	0	0	1	93				
	1	0	0	63				
	1	1	0	82				
	1	1	0	81				
	1	1	0	77				
	1	0	0	51				
	1	0	0	71				
	1	0	1	70				
	1	0	1	71				
	1	0	1	50				
	1	0	1	52				
	1	0	1	58				
	1	0	1	60				
	0	1	0	70				
	0	0	0	89				
	0	0	0	70				
	0	0	0	85				
	0	1	0	87				
	0	1	0	86				
	1	1	0	64				
	1	0	0	83				
	1	0	0	74				
	1	1	0	59				
	1	0	0	70				
	1	1	0	62				

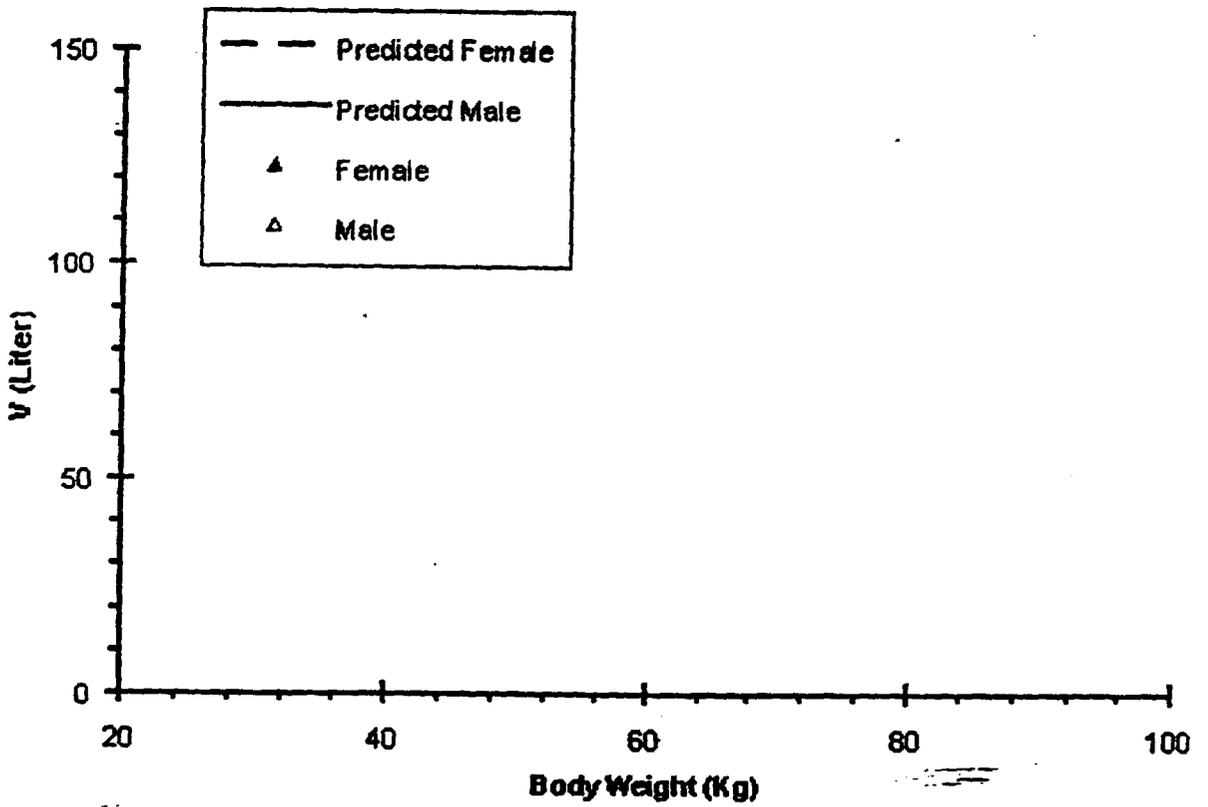
Attachment 8: A Table of Individual Levofloxacin Pharmacokinetic Parameters and Demographic Characteristics for the Optimal Model by the FOCE Method (Continued)

Subject ID	Gender	Race	Age	Weight (kg)	CL_{CR} (mL/min)	K_a (1/h)	V (Liter)	CL (L/h)
	0	0	0	72				
	0	0	0	95				
	0	0	0	77				
	0	0	0	94				
	0	1	0	65				
	0	0	0	74				
	1	0	0	86				
	1	1	0	80				
	1	0	0	64				
	1	0	0	62				
	1	0	0	79				
	1	0	0	65				
	0	0	0	68				
	0	0	0	95				
	0	1	0	69				
	0	0	0	76				
	0	0	0	71				
	0	0	0	76				
	0	1	0	79				
	0	0	0	68				
	0	0	0	60				
	0	1	0	66				
	0	0	0	67				
	0	0	0	76				
	1	1	0	56				
	1	1	0	74				
	1	0	0	70				
	1	1	0	42				
	1	0	0	60				
	1	0	0	59				
	1	1	0	58				
	1	0	0	53				
	1	1	0	65				
	1	0	0	61				
	1	0	0	60				
	1	0	0	63				

Attachment 9: A Plot of Levofloxacin Oral Clearance vs. Creatinine Clearance for the Optimal Model by the FOCE Method. The Solid Line Represents the NONMEM Calculated Values.



Attachment 10: A Plot of Levofloxacin Volume of Distribution vs. Body Weight for the Optimal Model by the FOCE Method. The Solid Line Represents the NONMEM Calculated Values.



Attachment 11: The Control Stream File for the NONMEM Simulation

```
$PROB   levofloxacin SIMULATION
$INPUT  ID AMT TIME DV SEX SS II RACE WT0 AGE CR0 CSA DIGX SUCR EVID MDV
$DATA   LEVOSIM2.dat
$SUBROUTINES ADVAN2 TRANS1

$PK
    WT   = WT0*EXP(ETA(4))
    CLCR = CR0*EXP(ETA(5))
    FAGE=0
    IF (AGE.GE.65) FAGE=1
    TVKA = THETA(1)
    CL0  = THETA(2)
    CL1  = CL0*(1+THETA(3)*SEX)*(1+THETA(4)*RACE)*(1+THETA(5)*FAGE)
    CL2  = CL1*(1+THETA(6)*CSA)*(1+THETA(7)*DIGX)*(1+THETA(8)*SUCR)
    TVCL = CL2*(CLCR/110)**THETA(9)*(WT/70)**THETA(10)
    V0   = THETA(11)
    V1   = V0*(1-THETA(12)*SEX)*(1+THETA(13)*RACE)*(1+THETA(14)*FAGE)
    V2   = V1*(1+THETA(15)*CSA)*(1+THETA(16)*DIGX)*(1-THETA(17)*SUCR)
    TVVD = V2*(CLCR/110)**THETA(18)*(WT/70)**THETA(19)
    KA   = TVKA*EXP(ETA(1))
    CL   = TVCL*EXP(ETA(2))
    VD   = TVVD*EXP(ETA(3))
    K    = CL/VD
    S2   = VD
$ERROR
    IPRED=F
    Y=F*(1 + EPS(1)) + EPS(2)
$THETA (.3, 4.88, 10)   ;KA
      (3, 10.9, 40)     ;CL
       0 FIXED 0 FIXED 0 FIXED 0 FIXED
       0 FIXED 0 FIXED 0.353 0 FIXED
      (10, 92, 500)     ;VD
      (-2, 0.189, 2) 0 FIXED 0 FIXED (-2, .775, 2)
       0 FIXED (-2, 0.0448, 2) 0 FIXED (0, 0.63, 3)
$OMEGA  1.42 0.0451 0.0142 0.0225 0.0225
$SIGMA  0.0329 0.000573
$SIMUL (2345) SUBPROBLEMS=100 ONLYSIMULATION
;$MSFI   LEVONM1.MSF
;$EST NOABORT MAXEVAL=9900  PRINT=5 MSFO=LEVONM1.MSF
;$COV
$TABLE ID TIME DV SEX RACE FAGE WT CLCR KA VD CL NOHEADER
  NOPRINT FILE=LEVOSIM1.TAB
$SCAT WRES VS DV
$SCAT WRES VS TIME
```

Attachment 12: The Summary Statistics of Pharmacokinetic Parameters and Demographic Characteristics in Monte Carlo Simulations

Male

Variable	N	Mean	SD	Minimum	Maximum
WT	100	71.2456800	10.8417762	49.9620000	103.0100000
CL_{CR}	100	101.1293900	14.5232440	68.3540000	145.1800000
VD	100	93.6301100	13.1855608	72.1420000	130.1900000
CL	100	10.6841250	2.5136575	5.7219000	21.5700000

Female

Variable	N	Mean	SD	Minimum	Maximum
WT	100	60.5362700	8.9173002	42.8330000	88.9730000
CL_{CR}	100	84.8962800	13.5644238	55.6550000	133.5500000
VD	100	68.5503900	9.5677139	44.8510000	101.5400000
CL	100	10.1544370	1.9356045	5.7431000	15.2000000

TITLE OF STUDY: EVALUATION OF THE PHARMACOKINETICS AND PHARMACODYNAMICS (SAFETY) OF LEVOFLOXACIN FROM A MULTICENTER, OPEN-LABEL STUDY IN PATIENTS WITH BACTERIAL INFECTIONS. (PROTOCOL LOFBIV-MULT-001). VOLUMES 9.4 - 9.5; 9.8 - 9.9.

PRINCIPAL INVESTIGATORS AND LOCATIONS:

OBJECTIVES: The objectives of this report were: 1.) to examine the pharmacokinetics of levofloxacin in patients with bacterial infections; and 2.) to examine the quantitative relationships between measures of exposure to levofloxacin (pharmacokinetics) and the incidence of adverse events (pharmacodynamics) in an infected patient population.

STUDY DESIGN: This was a multicenter, open-label, noncomparative study. Subjects who met the entry criteria were assigned to receive 250 or 500 mg levofloxacin once daily for 5 ~~to 14~~ days, depending on the type of infection being treated. Subjects with moderate renal impairment (creatinine clearance, CL_{CR} of 20 to 50 mL/min) and infections of the respiratory tract or skin received 500 mg levofloxacin q48h. No dosage adjustment was made for renally impaired patients receiving the 250-mg daily dose. A minimum of three full doses of intravenous levofloxacin were to be administered, after which the subject could be switched to oral levofloxacin for the duration of therapy. For intravenous levofloxacin (Formula FD-25213-097-D-45, Batch 5270), the appropriate dose (250 or 500 mg) was reconstituted in 5% dextrose and water by the hospital pharmacist to yield a final concentration of 5 mg/mL. The entire contents of the bag were to be infused into the subject over a 60-minute period. For subjects receiving oral levofloxacin, one 500-mg clinical tablet (Formula FD-25213-097-G-22, Batch R5826) or two 125-mg clinical tablets (Formula FD-25213-097-H-22, Batch 5520) were administered.

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[a] Did not enroll any subjects in the study

SAMPLING: Blood samples were to be collected at trough (predose), end of infusion, and at 2, 6.75, 7.75, and 9.25 hours postdose on Day 3 or 4 of the intravenous levofloxacin therapy. Additional blood samples for checking dosing compliance for oral therapy were collected at trough, 0.5, and 1 hour postdose on any day during the course of oral therapy.

ANALYTICAL METHOD: Levofloxacin plasma concentrations were determined by a validated reversed-phased HPLC method at Samples analyzed were used for pharmacokinetic analysis.

DEMOGRAPHICS: Three hundred thirteen subjects were enrolled in the study at 22 centers (Table 1). Of the 313 subjects enrolled in the study, 272 subjects had sufficient plasma concentration data for pharmacokinetic analysis. The adverse events of the 272 subjects were used for pharmacodynamic (safety) analysis. The demographic and baseline characteristics of the subjects for pharmacokinetic/pharmacodynamic (pk/pd) evaluations are also presented in Table 1.

Table 1: Demographic and Baseline Characteristics: Intent-to-Treat Subjects and Subjects Included in Pharmacokinetic/Pharmacodynamic Evaluations
(Study LOFBIV-MULT-001)

	Intent-to-Treat Subjects (N =313)		PK/PD Subjects (N =272)	
	No.	(%)	No.	(%)
Sex				
Men	179	(57.2)	163	(59.9)
Women	134	(42.8)	109	(40.1)
Race				
Caucasian	182	(58.1)	161	(59.2)
Black	89	(28.4)	80	(29.4)
Hispanic	40	(12.8)	29	(10.7)
Other	2	(0.6)	2	(0.7)
Age (Years)				
≤45	170	(54.3)	153	(56.3)
46-64	66	(21.1)	58	(21.3)
≥65	77	(24.6)	61	(22.4)
Mean±SD	47.6±18.8		46.8±18.6	
Range	[redacted]		[redacted]	
Weight (lb)				
N	303		263	
Mean±SD	168.7±41.1		170.6±41.0	
Range	[redacted]		[redacted]	
Missing	10		9	
Height (in.)				
N	290		252	
Mean±SD	67.6±4.12		67.9±3.99	
Range	[redacted]		[redacted]	
Missing	23		20	
Primary Bacterial Infection				
Bronchitis	101	(32.3)	87	(32.0)
Pneumonia	97	(31.0)	89	(32.7)
Skin	56	(17.9)	52	(19.1)
Complicated UTI/Acute Pyelonephritis	41	(13.1)	31	(11.4)
Sinusitis	18	(5.8)	13	(4.8)
Second Bacterial Infection*				
Bronchitis	2	(0.6)	1	(0.4)
Skin	2	(0.6)	2	(0.7)
Complicated UTI/Acute Pyelonephritis	1	(0.3)	1	(0.4)
None	308	(98.4)	268	(98.5)

* Present at study admission

PHARMACOKINETIC RESULTS: Plasma concentration data from intravenous administration were analyzed using the Non-Parametric Expectation Maximization (NPEM2) approach. A two-compartment open model with first-order elimination from the central compartment and a zero-order intravenous infusion was employed. Estimates of the intercompartmental transfer rate constants (K_{CP} and K_{PC}), volume of distribution of the central compartment (V_C) and total body clearance (CL) are summarized in Table 2. These values were similar to values in subjects without bacterial infections in previous Phase I clinical studies. Maximum a-posteriori probability (MAP) Bayesian estimation was used to generate Bayesian posterior parameter values for each individual. Excellent correlation was seen between the observed and predicted plasma concentrations for the 272 subjects included in the pharmacokinetic analysis (r^2 =0.966).

Table 2: Summary of Levofloxacin Population Pharmacokinetic Parameter Estimates in Patients with Bacterial Infections (Study LOFBIV-MULT-001)

	K_{CP} (h^{-1})	K_{PC} (h^{-1})	V_C (L/kg)	CL (L/h)
Mean	0.487	0.647	0.836	9.27
Median	0.384	0.596	0.795	9.01
SD	0.378	0.391	0.429	4.31

Population demographic models for prediction of the levofloxacin pharmacokinetic parameters (peak concentration, CL, V_C, K_{CP}, and K_{PC}) from demographic data (site of infection, gender, race, age, body weight, serum creatinine, and CL_{CR}) of the patients were examined using the general linear model module of the SYSTAT program. Models were developed based on the data obtained from 172 subjects and validated by the data from the remaining 100 subjects included in the pk/pd evaluations. The demographic model for prediction of CL explained a reasonable amount of the variance in CL of the patient population (r^2 =0.396). The median bias and precision for prediction of CL by the demographic model were 0.5% and 18.3%, respectively. CL_{CR}, race, and age were included in the demographic model with CL_{CR} explaining most of the population variance in CL. The mean volume of distribution of the central compartment was 0.836 L/kg while the mean plasma clearance was 9.27 L/hr. These values are comparable to those previously obtained from normal volunteers data. Mean (+SD) for C_{max} and AUC normalized to dose and dosing interval of 500 mg q24hr were 8.67 (3.99) and 72.53 (51.17), respectively.

PHARMACODYNAMIC ANALYSIS: The individual Bayesian parameter estimates were employed in the simulation module of ADAPT II to allow calculation of the individual AUC and to simulate the C_{min} and C_{max} for each patient. The following ratios were estimated C_{max}/MIC, AUC/MIC and Time above the MIC. These data was analyzed using logistic regression for examining their effect on the clinical outcome (cured & improved as successful outcome and failed patients as unsuccessful) and the microbiological outcome (eradicated or persisted). Breakpoints of pharmacodynamic variables such as C_{max}/MIC ratio and AUC/MIC ratio which divided patients into lower and higher probability groups for positive clinical and microbiological outcome were determined using the Classification And Regression Tree (CART) analysis aproach This method of analysis uses a recursive partitioning alogarithm which performs tree growing/pruning and sets breakpoints that best divide dichotomous or polytomous by independent variables.

PHARMACODYNAMIC RESULTS:

i. Clinical outcome analysis: The C_{max}/MIC, AUC/MIC, and Time above MIC are virtually indistinguishable in their ability to alter the probability of a good outcome (Table 4). The C_{max}/MIC and AUC/MIC ratios are highly correlated with an r value (Spearman rank correlation) of 0.942. The

C_{max}/MIC and Time above MIC had a Spearman's correlation of 0.605. Probability plots from the point estimates of parameter values are presented in Figure 4. The breakpoint from the CART analysis is 12.2 for C_{max}/MIC ratio. Clinical success rates for patients achieving a C_{max}/MIC ratio of >12.2 and < 12.2 were 99% and 83.3%, respectively.

ii. Microbiological outcome: Five predictive variables were observed to significantly affect the probability of a positive microbiological outcome (Table 5). These predictors were among the ones which were selected for the clinical outcome analysis along with AUC. However, when these were examined for model expansion, the final model selected by the log-likelihood ratio test included only C_{max}/MIC ratio plus AUC (Table 6) and finally, C_{max}/MIC ratio alone. The breakpoint from the CART analysis is 12.2 for C_{max}/MIC ratio. Microbiological success rates for patients achieving a C_{max}/MIC ratio of >12.2 and < 12.2 were 100% and 80%, respectively. Probability plots for successful microbiological outcome for C_{max}/MIC ratio and C_{max}/MIC ratio plus AUC are presented in Figures 5 & 6, respectively.

iii. Adverse events: Two pharmacodynamic analyses were performed, one using all adverse events regardless of relationship to drug, and the second using only those subjects with adverse events assessed by the investigator as definitely, probably, or possibly related to drug. Adverse events of the central nervous system (including psychiatric disturbances), gastrointestinal tract, and skin were analyzed in relation to the gender, race, site of infection, age, peak and trough plasma concentrations, and AUC of the patients, using the logistic regression module of SYSTAT. No pharmacologic (drug related) covariates were found to significantly affect the probability of occurrence of an adverse event when gastrointestinal, skin and CNS systems were examined. The probability of a CNS adverse event was influenced by the site of infection (all the explanatory power was in the sinus infection and was likely due to the nature of the disease). The probability of a skin adverse event was influenced by patient's race with 50% of the events occurring in the Hispanic population.

CONCLUSION: Levofloxacin pharmacokinetics in hospitalized patients with serious community acquired infection were similar to those observed in healthy volunteers investigated previously in Phase I studies. Creatinine clearance, age, and race were included in the demographic model for prediction of levofloxacin clearance of the subjects, with creatinine clearance explaining most of the population variance. For both Clinical and microbiological outcomes, the breakpoint from the CART analysis is 12.2 for the C_{max}/MIC ratio. Fom the results, it could be said that the probality of a successful clinical and microbiological outcome for patients that achieve a C_{max}/MIC ratio of >12.2 is greater than 95%. No pharmacologic (drug related) predictors were shown to associate significantly to the probability of occurrence of an adverse event.

Table 3: Demographic Models from a General Linear Model Procedure for Prediction of Levofloxacin Pharmacokinetic Parameters in Patients with Bacterial Infections. (Study LOFBIV-MULT-001).

Parameter	Covariate	Coefficient	Standard Error	P-value	r^2
CL	Constant	5.945			0.396
	Race			0.017	
	Caucasian	-1.486	0.332		
	Black	-0.484	0.579		
	Hispanic	-3.167	0.855		
	Other	5.137	3.504		
	CL_{cr}	0.070	0.012	<0.001	
	Age	-0.032	0.019	0.095	
V_c	Constant	72.10			0.132
	Gender			0.008	
	male	6.482	8.067		
	female	-6.482	8.434		
	Race			0.022	
	Caucasian	10.03	2.944		
	Black	-3.421	4.892		
	Hispanic	-10.45	7.431		
	Other	3.844	30.121		
	Age	-0.332	0.124	0.008	
K_{cp}	Constant	0.308			0.065
	Weight	0.003	0.002	0.029	
	Race			0.044	
	Caucasian	-0.127	0.034		
	Black	0.061	0.057		
	Hispanic	-0.074	0.087		
	Other	0.140	0.360		
K_{pc}	Constant	0.430			0.087
	Age	0.005	0.002	0.002	
	Site			0.064	
	pulmonary	-0.066	0.035		
	skin/skin structure	0.112	0.067		
	urinary tract	-0.046	0.082		

Table 4

Logistic Regression Analysis Examining Clinical Outcome

Single Covariates				Final Model			
Covariate*	Estimate	Standard Error	Significance†	Covariate*	Estimate	Standard Error	McFadden's Rho-Squared
MIC	-0.105	0.050	p = 0.004	CONSTANT	0.970	0.876	0.337
PEAK/MIC	0.148	0.063	p < 0.001	PEAK/MIC	0.140	0.064	
AUC/MIC	0.011	0.006	p = 0.006	SITE‡			
TIME > MIC	0.040	0.011	p < 0.001	Pulmonary	0	-	
SITE‡				Skin/soft tissue	- 1.06	0.876	
Pulmonary	0	-		Urinary tract	36.516	>100	
Skin/soft tissue	-1.674	0.902	p = 0.032				
Urinary tract	37.871	> 100					
AGE	-0.042	0.021	p = 0.045				

n = 134

* MIC = minimum inhibitory concentration, PEAK/MIC = the ratio of peak serum concentration of drug at the end of a 1 hour infusion to MIC, AUC/MIC = the ratio of area under the serum concentration versus time curve to MIC, TIME > MIC = the time serum concentration of drug remains above the MIC, SITE = site of infection

† chi-squared p values represent the log-likelihood ratio test for model expansion from a constant-only model

‡ for categorical variables, the estimate is added to the logit.

Table 5

Logistic Regression Analysis Examining Microbiological Outcome

Single Variables				Final Model			
Covariate*	Estimate	Standard Error	Significance†	Covariate*	Estimate	Standard Error	McFadden's Rho-Squared
PEAK/MIC	0.252	0.108	p <0.001	CONSTANT	0.226	0.830	0.343
AUC/MIC	0.017	0.009	p = 0.005	PEAK/MIC	0.252	0.108	
TIME > MIC	0.046	0.013	p<0.001				
AUC	-0.016	0.007	p = 0.045				
AGE	-0.048	0.025	p = 0.046				

n = 116

* Definitions of covariates are listed in Table 2.

† chi-squared p-values represent the log-likelihood ratio test for expansion from a constant-only model

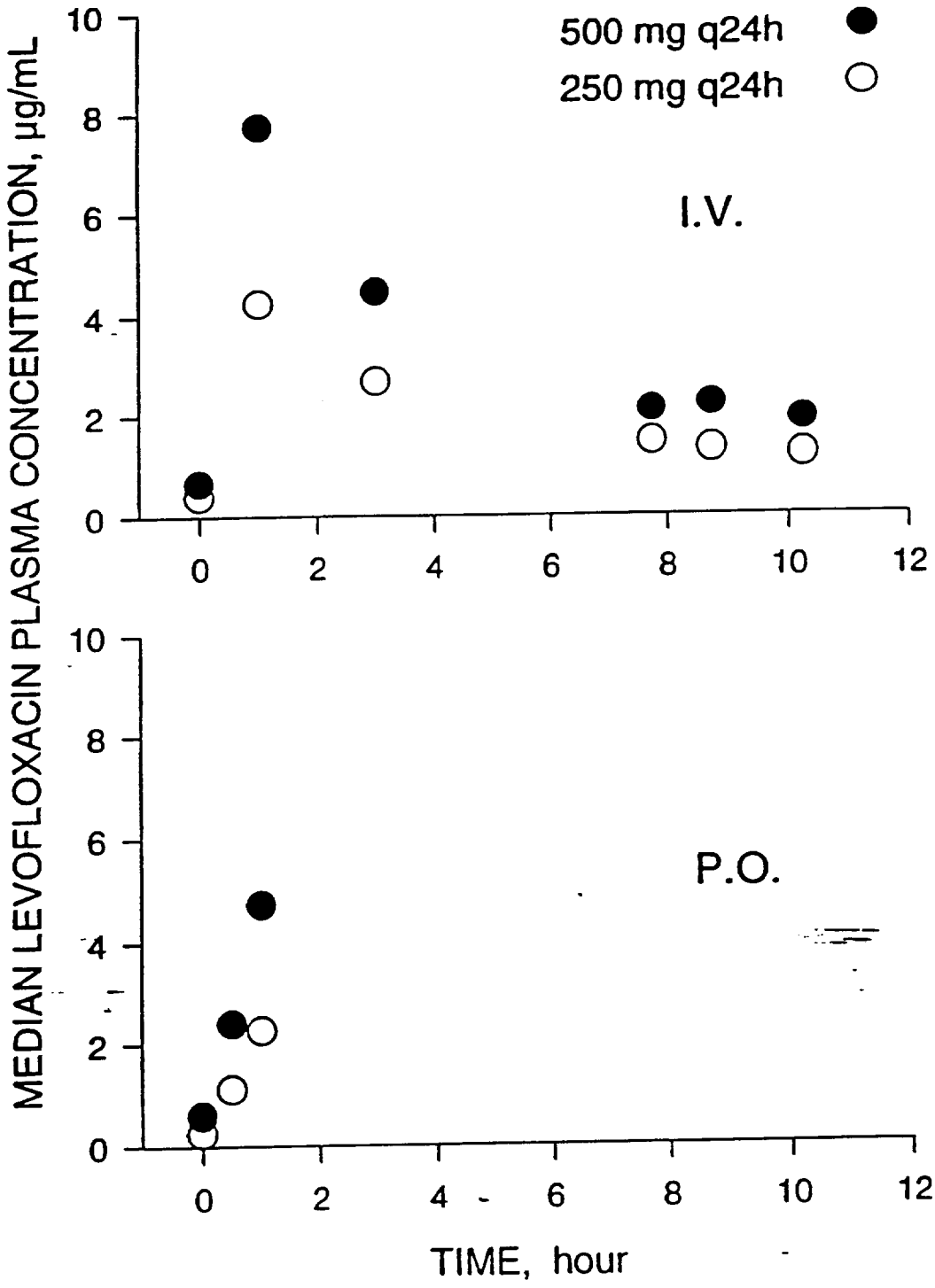
Table 6

Alternate Final Model Selection from Covariates Shown to be Significant Univariately for Microbiological Outcome

Covariate*	Estimate	Standard Error	McFadden's Rho-Squared
CONSTANT	2.055	1.17	0.491
PEAK/MIC	0.282	0.119	
AUC	-0.027	0.011	

n = 116

Figure 1: Median Plasma Concentration vs. Time Profiles of Levofloxacin in Subjects Following 250 or 500 mg Once-Daily Intravenous Doses and 250 or 500 mg Once-Daily Oral Doses of Levofloxacin



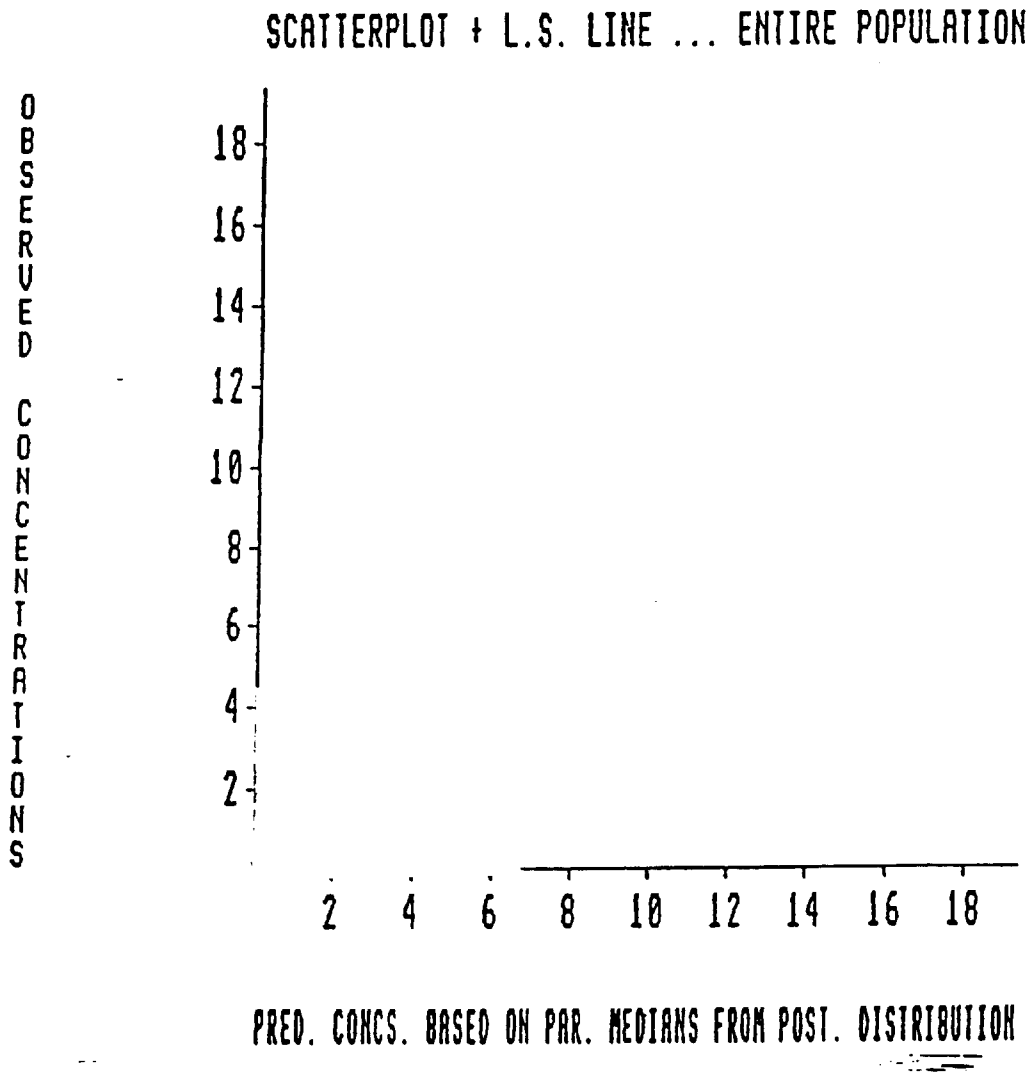


Figure 2: Observed vs. MAP-Bayesian Predicted (Based on Population Parameter Medians) Plasma Concentrations of Levofloxacin for All 272 Subjects Included in the Pharmacokinetic/Pharmacodynamic Evaluations

Figure 3: Levofloxacin Plasma Clearances Determined from Maximum a-posteriori Probability (MAP) Bayesian Pharmacokinetic Parameter Estimation vs. Plasma Clearances Determined from Demographic Model Prediction for 100 Subjects Used in Model Validation

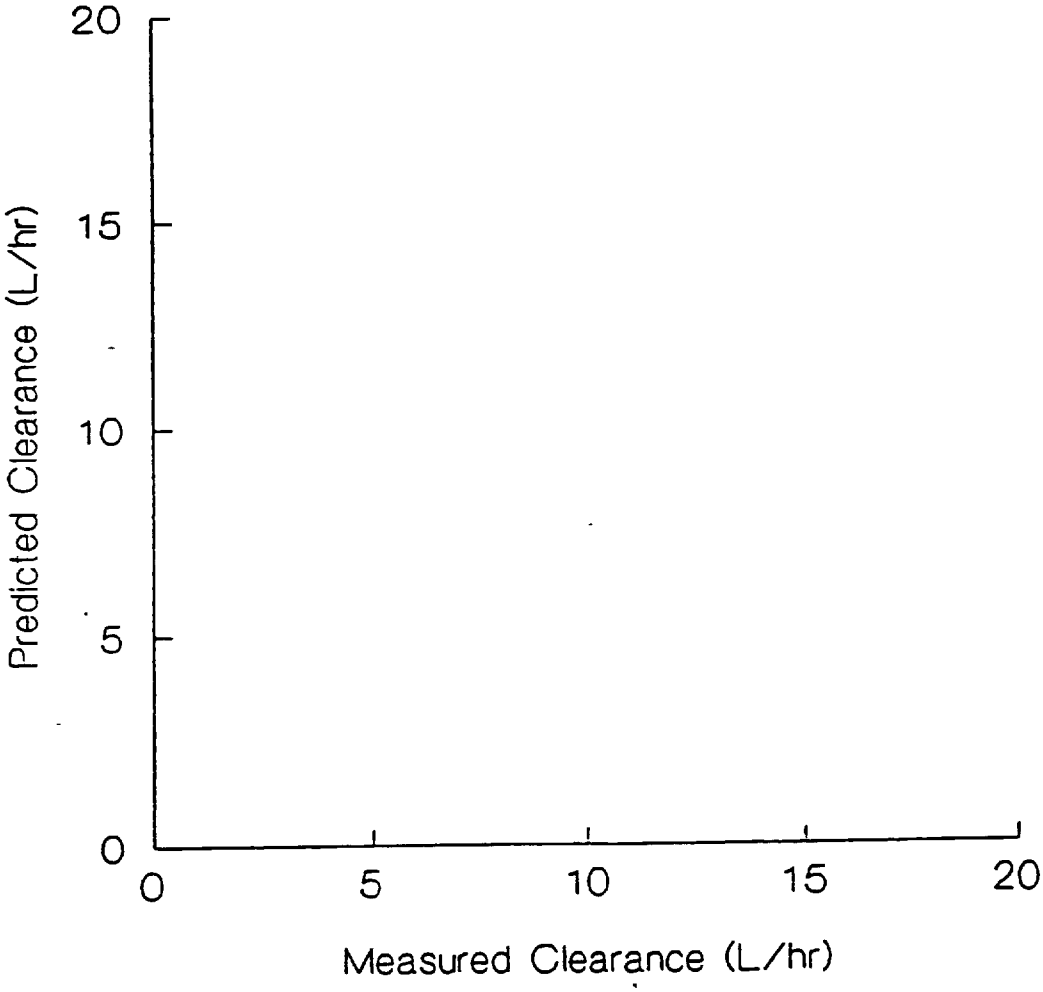
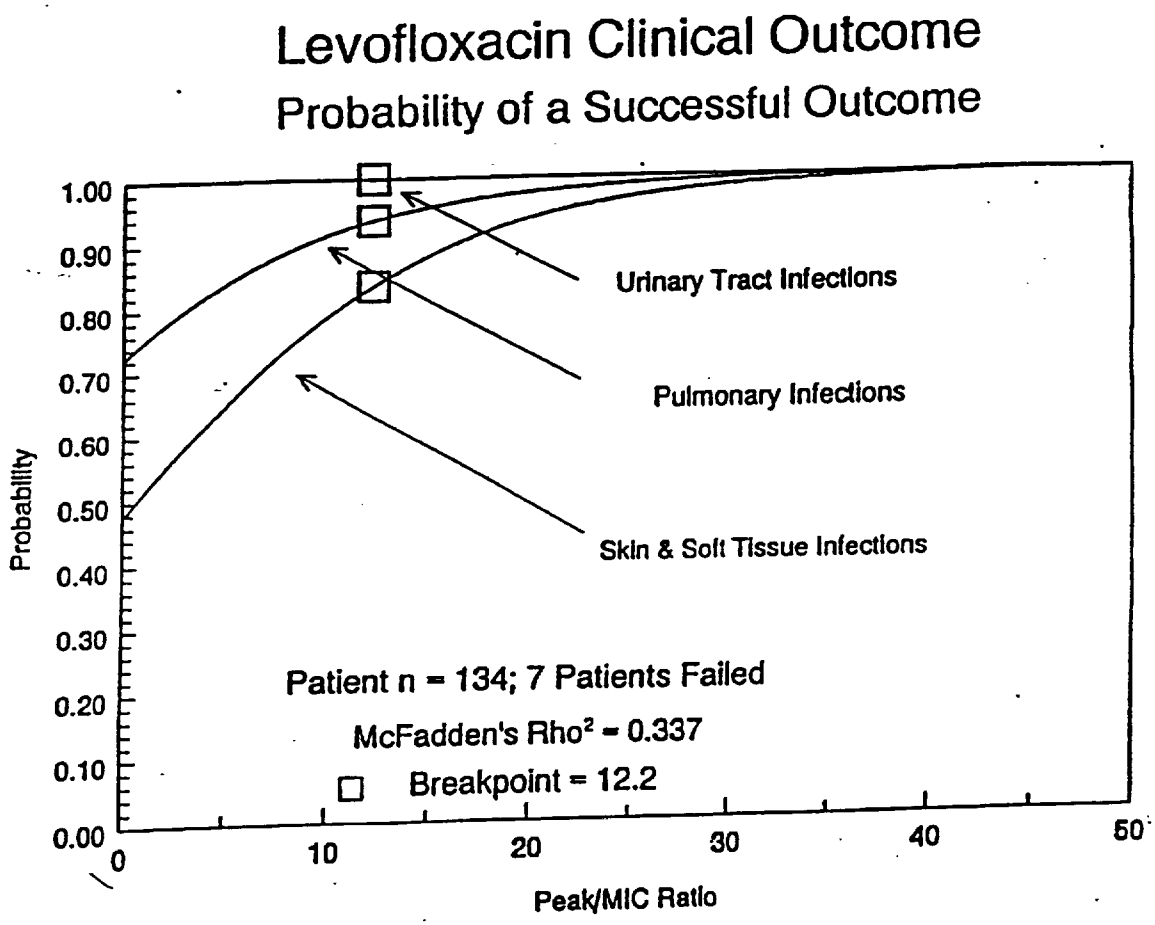
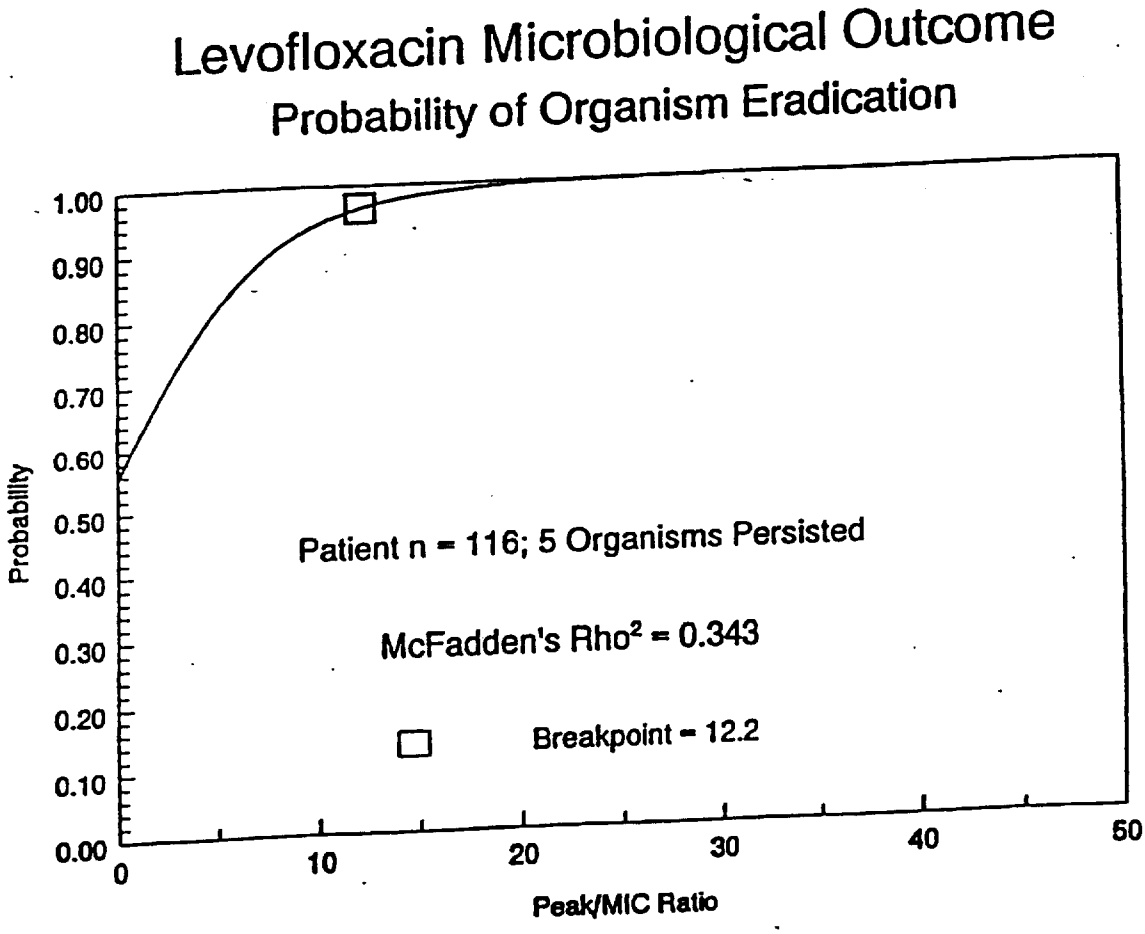


Figure 4



The probability curve for successful clinical outcome versus PEAK/MIC ratio is shown. Breakpoint values for the pharmacologic variables are displayed, indicating the value for which there is a significantly increased probability of successful outcome as determined by CART. The McFadden's Rho-squared value is also displayed. The figure illustrates the probability curves for successful clinical outcome including PEAK/MIC ratio and three different sites (skin/soft tissue, pulmonary, and urinary tract).

Figure 5

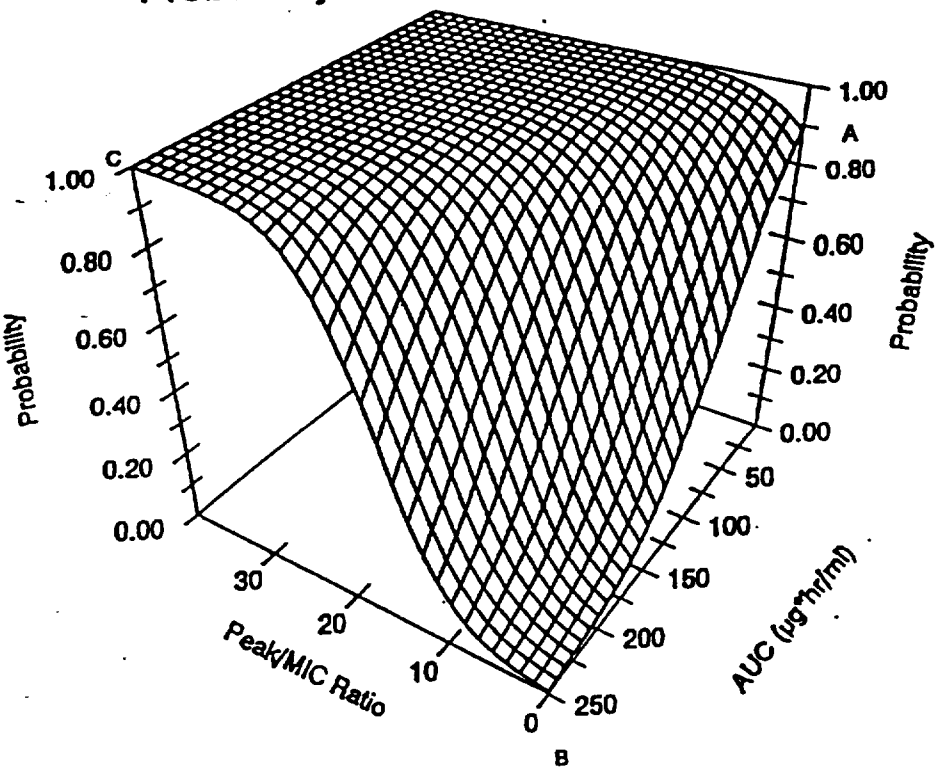


The probability curve for organism eradication versus PEAK/MIC ratio is shown. Breakpoint values for the pharmacologic variables are displayed, indicating the value above which there is a significantly increased probability of organism eradication as determined by CART. The McFadden's Rho-squared value is also displayed.

Figure 6

Levofloxacin Microbiological Outcome

Probability of Organism Eradication



An alternative model for the probability of eradication involves Peak/MIC Ratio and AUC, with AUC showing decreased probability of eradication with higher AUC value (non-physiologic). Point A represents the no exposure point (Peak/MIC ratio = 0.0, AUC = 0.0). The positive probability of eradication probably reflects host defenses. Point B would be a patient with an AUC of 250 and a Peak/MIC ratio which is vanishingly small (very resistant organism). Point C represents the case where there is a large AUC and a moderate peak/MIC ratio (40/1). In this case the probability of eradication is very high, indicating that the AUC effect is a relatively weak one.

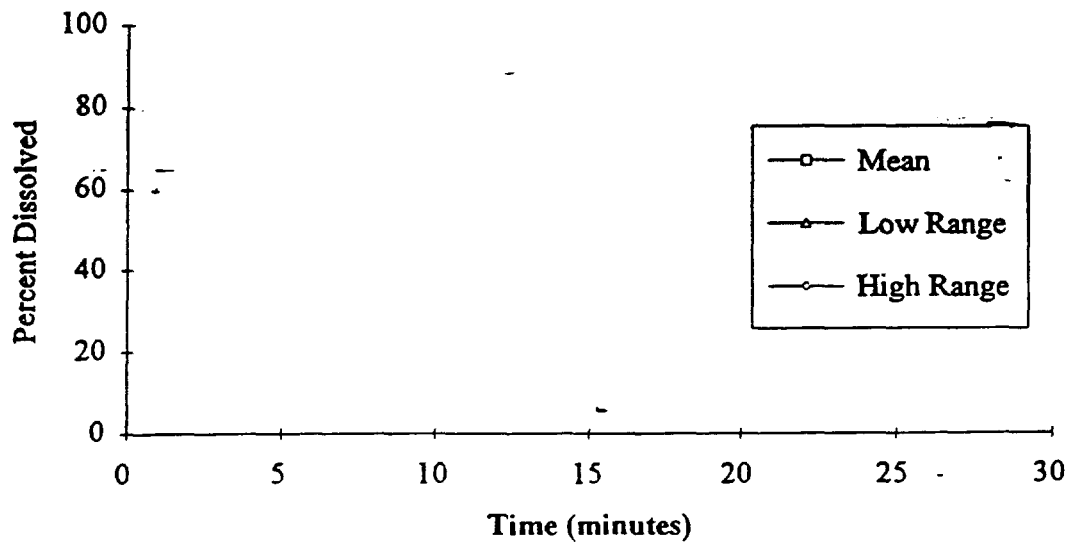
ATTACHMENT 1: Levofloxacin Bayesian Posterior Pharmacokinetic Parameter Estimates for All 272 Subjects Included in the Pharmacokinetic/Pharmacodynamic Evaluations (Continued)
(Study LOFBIV-MULT-001)

Descriptive Statistics for the Dose-Independent Pharmacokinetic Parameters (N =272):

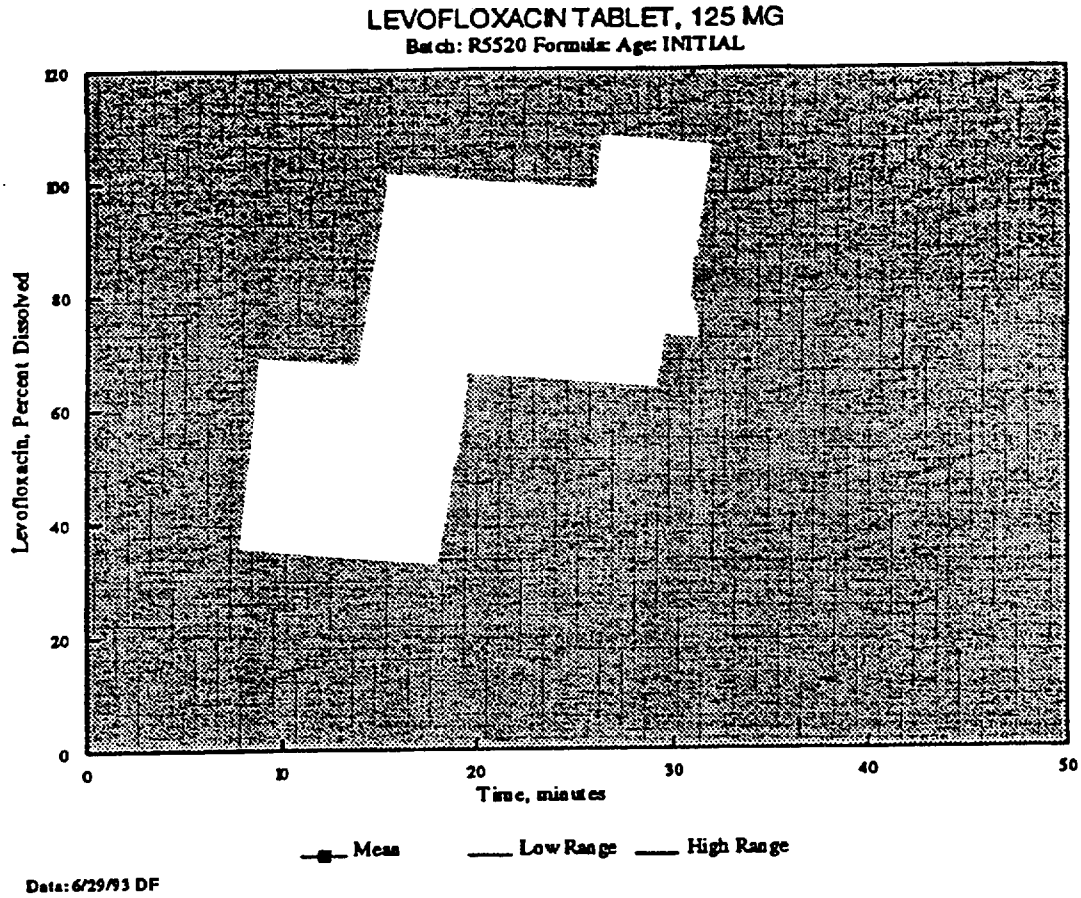
	Weight (kg)	K_{cp} (1/h)	K_{pc} (1/h)	V_c (L)	V_c/kg (L/kg)	V_{ss}[a] (L)	CL (L/h)
Mean	77.5	0.490	0.647	62.2	0.829	111.4	9.25
Median	74.9	0.403	0.594	57.1	0.789	99.9	9.02
SD	18.4	0.370	0.390	30.4	0.425	58.2	4.30

[a] V_{ss} values of subjects were too extreme (>700 L) and were not included in descriptive statistics; these extreme values were probably due to model misspecification.

ATTACHMENT 2 : Dissolution Profile for Levofloxacin 500-mg Clinical Tablet, Formula FD-25213-097-G-22, Batch R5826
(Study LOFBIV-MULT-001)



ATTACHMENT 3 : Dissolution Profile for Levofloxacin 125-mg Clinical Tablet, Formula FD-25213-097-H-22, Batch 5520 (Study LOFBIV-MULT-001)



ATTACHMENT 4: Levofloxacin Bayesian Posterior Pharmacokinetic Parameter Estimates for All 272 Subjects Included in the Pharmacokinetic/Pharmacodynamic Evaluations. (Study LOFBIV-MULT-001).

Index No.	Subject No.	Dosing Regimen	Weight (kg)	K_{cp} (1/h)	K_{pc} (1/h)	V_c (L)	V_c/kg (L/kg)	V_{ss}[a] (L)	CL (L/h)	C_{max} (µg/mL)	C_{min} (µg/mL)	AUC (µg•h/mL)
1		500 mg q24h	45.9	0.848	1.260	43.2	0.941	72.3	9.74	8.32	0.32	51
2		500 mg q24h	80.4	0.931	0.241	14.9	0.185	72.5	6.82	19.59	0.89	73
3		500 mg q24h	62.7	0.671	0.086	23.7	0.378	208.6	3.86	17.30	3.16	130
4		500 mg q24h	53.2	0.172	0.723	43.5	0.818	53.8	3.50	12.75	2.54	143
5		500 mg q24h	65.9	0.109	0.312	63.1	0.958	85.1	9.69	7.42	0.46	52
6		500 mg q24h	84.1	0.345	1.290	76.9	0.914	97.5	3.98	8.62	3.11	126
7		250 mg q24h	63.6	0.472	0.334	42.7	0.671	103.0	5.92	5.26	0.81	42
8		500 mg q24h	88.2	0.660	0.408	36.0	0.408	94.2	7.28	10.64	1.03	69
9		500 mg q24h	62.7	0.071	0.220	61.8	0.986	81.7	8.30	7.91	0.63	60
10		500 mg q48h	42.7	0.463	0.594	28.0	0.656	49.8	1.81	16.51	2.17	138
11		500 mg q24h	62.7	0.752	0.925	46.5	0.742	84.3	4.52	10.10	2.30	111
12		500 mg q24h	70.0	0.412	1.220	67.3	0.961	90.0	8.24	6.79	0.73	61
13		500 mg q24h	90.9	0.280	0.966	58.5	0.644	75.5	2.82	11.88	4.57	177
14		500 mg q24h	61.4	0.087	0.048	60.2	0.980	169.3	2.21	12.36	5.17	226
15		500 mg q24h	58.6	0.061	1.170	52.5	0.896	55.2	6.11	9.46	0.73	82
16		500 mg q24h	52.3	0.407	0.381	52.8	1.010	109.2	8.99	8.08	0.77	56
17		500 mg q24h	60.9	0.576	1.050	34.7	0.570	53.7	5.98	11.62	0.75	84
18		500 mg q24h	71.8	0.729	0.277	29.4	0.409	106.8	4.02	14.60	3.03	124
19		500 mg q24h	68.8	1.070	1.060	35.3	0.513	70.9	2.78	13.95	4.52	180
20		500 mg q24h	99.1	0.506	0.559	48.8	0.492	93.0	11.17	7.88	0.37	45
21		500 mg q24h	77.3	0.332	0.374	61.4	0.794	115.9	11.25	6.95	0.51	44
22		500 mg q24h	80.0	0.142	0.312	69.0	0.863	100.4	6.22	8.00	1.47	80
23		500 mg q24h	84.5	1.320	1.300	56.9	0.673	114.7	11.64	5.87	0.45	43
24		500 mg q24h	59.1	0.374	0.466	42.5	0.719	76.6	5.12	11.10	1.68	98
25		500 mg q24h	64.1	0.354	1.030	59.6	0.930	80.1	8.09	7.54	0.65	62
26		250 mg q24h	60.9	0.878	0.648	37.7	0.619	88.8	12.07	4.30	0.14	21
27		500 mg q24h	72.7	0.472	0.334	48.8	0.671	117.8	5.92	9.61	1.79	85
28		500 mg q24h	97.7	1.010	0.633	78.6	0.805	204.0	5.11	6.86	2.80	98
29		500 mg q24h	87.3	0.010	0.490	104.8	1.200	106.9	12.55	4.76	0.32	40
30		500 mg q24h	79.5	0.566	1.070	69.8	0.878	106.7	4.35	8.43	2.84	115
31		500 mg q24h	59.5	0.357	0.574	40.6	0.682	65.9	3.68	12.80	2.73	136

[a] $V_{ss} = (1 + K_{cp}/K_{pc}) \cdot V_c$

ATTACHMENT 4: *Levofloxacin Bayesian Posterior* Pharmacokinetic Parameter Estimates for All 272 Subjects Included in the Pharmacokinetic/Pharmacodynamic Evaluations (Continued)
(Study LOFBIV-MULT-001)

Index No.	Subject No.	Dosing Regimen	Weight (kg)	K_{cp} (1/h)	K_{pc} (1/h)	V_c (L)	V_c/kg (L/kg)	V_{ss}[a] (L)	CL (L/h)	C_{max} (µg/mL)	C_{min} (µg/mL)	AUC (µg·h/mL)
32		500 mg q24h	76.4	0.105	0.124	98.6	1.291	182.1	11.87	5.18	0.67	42
33		500 mg q24h	70.4	0.086	0.110	71.8	1.020	127.9	9.73	6.91	0.69	51
34		250 mg q24h	128.2	0.749	0.352	27.9	0.218	87.3	11.96	4.70	0.15	21
35		500 mg q24h	65.9	1.270	0.401	14.0	0.212	58.3	7.51	18.22	0.53	67
36		250 mg q24h	69.1	0.254	0.145	48.4	0.700	133.2	12.33	4.30	0.24	20
37		500 mg q24h	65.9	0.161	1.040	55.8	0.847	64.4	6.92	8.58	0.68	72
38		500 mg q24h	118.6	0.736	0.028	27.3	0.230	744.9[a]	4.47	13.50	1.63	112
39		500 mg q24h	81.8	0.712	0.449	34.2	0.418	88.4	10.11	10.06	0.45	50
40		250 mg q24h	70.4	0.479	0.331	46.5	0.661	113.8	5.90	4.96	0.88	42
41		500 mg q24h	52.3	0.363	0.091	43.1	0.824	215.0	6.60	10.70	1.72	76
42		500 mg q24h	74.5	0.325	0.236	42.9	0.576	102.0	10.26	9.51	0.54	49
43		500 mg q24h	113.6	0.372	1.140	118.1	1.040	156.6	14.38	3.90	0.42	35
44		500 mg q24h	83.6	0.368	1.220	57.7	0.690	75.1	14.57	6.88	0.08	34
45		500 mg q24h	43.2	0.117	0.201	71.3	1.650	112.8	9.30	6.91	0.73	54
46		500 mg q24h	65.9	1.040	0.472	15.0	0.228	48.1	9.81	17.32	0.16	51
47		500 mg q24h	82.7	0.931	0.627	48.2	0.583	119.8	7.37	8.04	1.26	68
48		500 mg q24h	77.3	1.140	0.615	47.8	0.618	136.4	12.59	6.62	0.49	40
49		500 mg q24h	120.4	0.076	1.060	105.0	0.872	112.5	7.55	5.54	1.15	66
50		500 mg q24h	56.4	0.252	0.246	66.6	1.181	134.8	4.16	9.50	3.18	120
51		500 mg q24h	79.5	0.248	0.382	85.9	1.081	141.7	15.55	5.08	0.31	32
52		500 mg q24h	65.9	0.590	0.692	74.5	1.131	138.0	13.57	5.32	0.41	37
53		500 mg q24h	75.0	0.472	0.334	50.3	0.671	121.4	5.92	9.42	1.82	85
54		500 mg q24h	68.2	0.194	0.353	59.4	0.871	92.0	9.05	7.75	0.61	55
55		500 mg q24h	72.7	0.074	0.057	33.5	0.461	77.0	8.93	13.02	0.39	56
56		500 mg q24h	77.3	0.325	1.250	65.9	0.853	83.0	5.21	8.22	1.77	96
57		500 mg q24h	71.8	0.774	1.240	65.7	0.915	106.7	15.67	5.50	0.16	32
58		500 mg q24h	72.7	1.090	0.899	46.2	0.635	102.2	13.19	6.88	0.27	38
59		500 mg q24h	55.4	0.072	1.230	80.9	1.460	85.6	6.92	6.72	1.02	72
60		500 mg q24h	54.1	0.278	1.120	74.6	1.379	93.1	5.86	7.33	1.57	85
61		500 mg q24h	43.6	0.055	0.174	93.3	2.140	122.8	8.51	5.88	0.94	59
62		500 mg q24h	69.5	0.702	0.100	9.2	0.132	73.8	4.26	34.30	1.95	117

[a] $V_{ss} = (1 + K_{cp}/K_{pc}) \cdot V_c$

ATTACHMENT 4: Levofloxacin Bayesian Posterior Pharmacokinetic Parameter Estimates for All 272 Subjects Included in the Pharmacokinetic/Pharmacodynamic Evaluations (Continued)
(Study LOFBIV-MULT-001)

Index No.	Subject No.	Dosing Regimen	Weight (kg)	K_{cp} (1/h)	K_{pc} (1/h)	V_c (L)	V_c/kg (L/kg)	V_{ss}[a] (L)	CL (L/h)	C_{max} (µg/mL)	C_{min} (µg/mL)	AUC (µg•h/mL)
63		500 mg q24h	73.2	1.270	0.401	15.6	0.213	65.0	7.51	16.81	0.62	67
64		500 mg q24h	69.5	0.023	0.392	72.3	1.040	76.5	10.32	6.64	0.29	48
65		500 mg q24h	78.2	1.130	0.590	28.0	0.358	81.6	10.17	10.49	0.39	49
66		500 mg q24h	79.5	1.130	0.591	28.5	0.358	83.0	10.17	10.35	0.40	49
67		500 mg q24h	75.9	0.044	0.043	53.7	0.708	108.6	8.53	8.94	0.55	59
68		500 mg q24h	72.7	0.300	0.669	41.2	0.567	59.7	12.23	9.47	0.09	41
69		500 mg q24h	121.8	1.380	1.090	61.1	0.502	138.5	14.91	5.11	0.32	34
70		500 mg q24h	75.4	0.829	1.200	81.4	1.080	137.6	14.64	4.66	0.33	34
71		500 mg q24h	72.7	1.240	1.210	58.0	0.798	117.4	13.71	5.62	0.30	37
72		500 mg q24h	64.5	0.174	0.315	52.2	0.809	81.0	10.29	8.40	0.37	49
73		500 mg q24h	84.1	0.140	0.128	119.4	1.420	250.0	19.90	3.93	0.33	25
74		500 mg q24h	51.8	0.038	0.913	49.9	0.963	52.0	6.16	9.86	0.63	81
75		500 mg q24h	86.4	0.686	1.130	92.4	1.069	148.5	13.65	4.44	0.44	37
76		500 mg q48h	60.1	0.229	1.300	75.1	1.250	88.3	4.21	6.63	0.66	59
77		500 mg q24h	77.3	0.212	1.100	51.1	0.661	60.9	6.08	9.37	0.87	82
78		500 mg q24h	70.4	0.524	1.010	39.4	0.560	59.8	3.15	13.36	3.36	159
79		500 mg q24h	114.1	0.610	0.989	54.1	0.474	87.5	2.52	12.57	5.59	198
80		500 mg q24h	40.9	1.150	1.020	33.4	0.817	71.1	9.49	9.46	0.34	53
81		250 mg q24h	46.1	0.591	0.335	28.0	0.607	77.4	8.12	6.40	0.31	31
82		250 mg q24h	84.1	0.022	0.789	105.1	1.250	108.0	7.21	2.84	0.60	35
83		500 mg q24h	68.2	0.100	0.296	53.5	0.784	71.6	16.22	7.78	0.06	31
84		500 mg q24h	118.2	1.070	0.860	67.8	0.574	152.2	14.42	5.04	0.41	35
85		500 mg q24h	56.8	0.142	0.312	49.0	0.863	71.3	6.22	9.97	1.04	80
86		500 mg q24h	70.3	0.374	1.070	69.6	0.990	93.9	6.85	7.10	1.16	73
87		250 mg q24h	115.9	0.248	0.382	125.2	1.080	206.5	15.55	1.92	0.25	16
88		500 mg q24h	86.7	0.734	1.160	68.8	0.794	112.3	18.14	5.19	0.11	28
89		500 mg q24h	69.8	0.008	0.513	56.6	0.811	57.5	5.21	9.48	1.17	96
90		500 mg q24h	133.6	0.474	1.240	88.7	0.664	122.6	12.70	4.88	0.40	39
91		500 mg q24h	79.5	0.347	0.896	56.6	0.712	78.5	7.09	8.13	0.87	71
92		500 mg q24h	74.8	0.325	1.260	63.8	0.853	80.3	5.21	8.38	1.71	96
93		500 mg q24h	77.3	1.340	1.080	39.3	0.508	88.1	14.88	7.30	0.13	34

[a] $V_{ss} = (1 + K_{cp}/K_{pc}) \cdot V_c$

ATTACHMENT 4: Levofloxacin Bayesian Posterior Pharmacokinetic Parameter Estimates for All 272 Subjects Included in the Pharmacokinetic/Pharmacodynamic Evaluations (Continued) (Study LOFBIV-MULT-001)

Index No.	Subject No.	Dosing Regimen	Weight (kg)	K_{cp} (1/h)	K_{pc} (1/h)	V_c (L)	V_c/kg (L/kg)	V_{ss}[a] (L)	CL (L/h)	C_{max} (µg/mL)	C_{min} (µg/mL)	AUC (µg•h/mL)
94		500 mg q24h	77.3	0.063	0.094	44.3	0.573	74.0	3.63	13.02	2.65	138
95		500 mg q24h	97.7	0.797	0.828	52.1	0.533	102.2	6.36	8.21	1.45	79
96		500 mg q24h	77.3	1.040	0.709	46.5	0.602	114.7	13.03	6.89	0.35	38
97		500 mg q24h	92.3	0.310	0.733	86.4	0.936	122.9	9.37	5.63	0.81	53
98		500 mg q24h	86.4	0.246	0.097	100.2	1.160	354.3	6.84	5.99	1.87	73
99		500 mg q24h	69.1	0.810	1.120	53.5	0.774	92.2	4.68	9.08	2.32	107
100		500 mg q24h	70.4	0.002	0.739	97.2	1.380	97.5	12.10	5.09	0.29	41
101		500 mg q24h	70.4	0.230	0.062	149.2	2.120	702.7[a]	3.38	4.90	2.31	148
102		500 mg q24h	75.0	0.383	0.942	158.3	2.110	222.7	21.33	2.83	0.27	23
103		500 mg q24h	71.7	0.153	1.290	73.9	1.030	82.7	6.48	7.21	1.13	77
104		500 mg q24h	78.2	0.077	0.034	66.6	0.852	217.4	16.27	6.66	0.26	31
105		500 mg q24h	68.2	0.488	0.072	199.1	2.920	1548.6[a]	4.34	3.01	1.25	115
106		500 mg q24h	79.5	0.131	0.388	112.1	1.410	149.9	15.79	4.22	0.32	32
107		500 mg q24h	79.5	0.902	0.899	59.5	0.748	119.2	15.69	5.69	0.22	32
108		500 mg q24h	77.3	0.529	1.210	63.7	0.824	91.5	11.68	6.33	0.30	43
109		500 mg q24h	86.4	0.355	0.043	110.6	1.280	1023.7[a]	1.11	5.55	2.17	451
110		500 mg q24h	90.9	0.164	0.401	105.4	1.160	148.5	16.17	4.37	0.29	31
111		500 mg q24h	61.4	0.126	0.820	63.2	1.030	72.9	1.67	15.64	8.83	299
112		500 mg q24h	75.0	0.457	1.130	56.5	0.753	79.4	10.08	7.29	0.35	50
113		500 mg q24h	95.4	0.720	0.576	79.3	0.831	178.4	14.77	4.83	0.47	34
114		500 mg q24h	74.1	0.760	0.665	56.1	0.757	120.2	8.64	7.13	0.93	58
115		500 mg q24h	67.7	0.036	0.046	94.8	1.400	169.0	14.24	5.11	0.32	35
116		500 mg q24h	84.5	0.278	0.396	70.1	0.829	119.3	15.95	3.21	0.01	31
117		500 mg q24h	50.0	0.150	0.092	89.5	1.790	235.4	17.04	5.12	0.40	29
118		250 mg q24h	62.7	0.184	0.081	91.5	1.460	299.4	2.38	4.37	2.21	105
119		250 mg q24h	86.4	0.213	0.454	84.4	0.977	124.0	15.35	2.59	0.13	16
120		500 mg q24h	90.2	0.834	0.297	34.6	0.384	131.8	2.15	15.82	6.54	233
121		500 mg q24h	69.1	1.030	1.110	55.6	0.805	107.2	9.91	6.54	0.61	51
122		500 mg q24h	129.5	0.076	1.060	121.0	0.934	129.7	7.55	5.12	1.30	66
123		500 mg q24h	93.6	1.360	0.594	18.2	0.194	59.9	11.73	13.29	0.14	43
124		250 mg q24h	60.0	0.332	0.374	47.6	0.794	89.9	11.25	4.24	0.18	22

[a] $V_{ss} = (1 + K_{cp}/K_{pc}) \cdot V_c$

ATTACHMENT 4: Levofloxacin Bayesian Posterior Pharmacokinetic Parameter Estimates for All 272 Subjects Included in the Pharmacokinetic/Pharmacodynamic Evaluations (Continued)
(Study LOFBIV-MULT-001)

Index No.	Subject No.	Dosing Regimen	Weight (kg)	K_{cp} (1/h)	K_{pc} (1/h)	V_c (L)	V_c/kg (L/kg)	V_{ss}[a] (L)	CL (L/h)	C_{max} (µg/mL)	C_{min} (µg/mL)	AUC (µg•h/mL)
125		500 mg q24h	100.4	0.797	0.828	53.5	0.533	105.0	6.36	8.07	1.48	79
126		500 mg q24h	88.6	0.708	0.238	31.0	0.350	123.2	5.26	13.05	2.15	95
127		500 mg q24h	102.7	0.739	0.252	10.6	0.103	41.7	5.65	28.07	0.69	89
128		500 mg q24h	123.2	0.208	0.254	88.0	0.714	160.1	6.82	6.60	1.70	73
129		500 mg q24h	102.2	1.060	0.511	29.4	0.288	90.4	8.57	10.69	0.69	58
130		500 mg q24h	70.0	0.076	1.060	65.4	0.934	70.1	7.55	7.58	0.62	66
131		500 mg q24h	136.4	0.484	0.582	64.9	0.476	118.9	19.93	5.63	0.11	25
132		500 mg q24h	59.3	0.244	0.417	29.1	0.490	46.1	4.55	15.49	1.22	110
133		500 mg q24h	118.2	0.101	0.284	115.8	0.980	157.0	19.89	3.96	0.19	25
134		500 mg q48h	86.4	1.010	0.868	41.6	0.481	90.0	2.63	10.00	1.82	95
135		500 mg q24h	70.4	0.004	1.190	200.6	2.850	201.3	15.50	2.84	0.48	32
136		500 mg q48h	63.6	0.385	0.365	35.8	0.563	73.6	2.89	12.60	1.25	87
137		500 mg q24h	62.3	0.286	1.170	57.8	0.927	71.9	11.35	7.31	0.18	44
138		500 mg q48h	56.4	0.478	0.484	39.1	0.694	77.7	3.25	11.11	1.03	77
139		500 mg q24h	90.0	0.003	0.739	124.2	1.380	124.7	12.10	4.24	0.46	41
140		500 mg q24h	104.5	0.183	0.003	61.1	0.585	3788.2[a]	3.20	7.63	0.42	156
141		500 mg q24h	70.9	0.437	0.406	40.6	0.572	84.3	5.72	10.99	1.48	87
142		500 mg q24h	66.6	0.726	0.350	17.3	0.260	53.2	7.88	17.96	0.40	64
143		500 mg q24h	75.0	0.983	0.758	95.3	1.270	218.9	5.71	5.93	2.50	88
144		500 mg q48h	76.4	0.158	0.979	92.4	1.210	107.3	5.38	5.42	0.48	47
145		500 mg q24h	58.2	0.933	0.229	22.1	0.380	112.1	10.49	13.08	0.58	48
146		500 mg q24h	59.5	0.212	0.465	46.5	0.782	67.7	11.68	8.87	0.16	43
147		500 mg q24h	68.2	0.356	0.046	95.5	1.400	834.6[a]	14.24	4.77	0.73	35
148		500 mg q24h	72.7	0.081	0.581	78.5	1.080	89.4	10.48	6.12	0.39	48
149		250 mg q24h	47.7	0.570	0.177	139.8	2.930	590.0	18.74	1.62	0.33	13
150		500 mg q24h	86.4	0.930	0.689	54.3	0.628	127.6	14.90	6.09	0.29	34
151		250 mg q24h	76.4	0.066	0.059	88.6	1.160	187.7	14.64	2.69	0.18	17
152		500 mg q24h	61.4	0.610	0.356	36.5	0.594	99.0	8.12	10.41	0.86	62
153		500 mg q24h	102.7	0.660	0.408	42.0	0.409	109.9	7.28	9.52	1.19	69
154		500 mg q24h	54.5	0.171	1.110	66.5	1.220	76.7	4.06	9.33	2.60	123
155		500 mg q24h	72.7	0.569	0.278	34.3	0.472	104.5	10.58	10.42	0.52	47

[a] $V_{ss} = (1 + K_{cp}/K_{pc}) \cdot V_c$

ATTACHMENT 4: Levofloxacin Bayesian Posterior Pharmacokinetic Parameter Estimates for All 272 Subjects Included in the Pharmacokinetic/Pharmacodynamic Evaluations (Continued)
(Study LOFBIV-MULT-001)

Index No.	Subject No.	Dosing Regimen	Weight (kg)	K_{eo} (1/h)	K_{pc} (1/h)	V_c (L)	V_c/kg (L/kg)	V_{ss}* (L)	CL (L/h)	C_{max} (µg/mL)	C_{min} (µg/mL)	AUC (µg•h/mL)
156		500 mg q24h	90.4	0.154	1.290	93.1	1.030	104.2	6.48	6.28	1.43	77
157		500 mg q24h	70.4	0.653	0.657	41.4	0.588	82.5	6.84	9.69	1.01	73
158		500 mg q24h	103.2	0.419	0.976	80.7	0.782	115.3	8.69	5.90	0.88	58
159		500 mg q24h	72.7	1.270	0.401	15.5	0.213	64.6	7.51	16.89	0.61	67
160		500 mg q24h	94.5	0.071	0.220	93.2	0.986	123.3	8.30	5.92	1.01	60
161		500 mg q24h	53.6	0.052	1.190	75.0	1.400	78.3	8.15	6.75	0.60	61
162		500 mg q24h	74.1	0.386	0.353	56.2	0.758	117.7	6.55	8.57	1.51	76
163		500 mg q48h	78.2	1.120	1.250	42.7	0.546	81.0	2.94	9.34	1.33	85
164		250 mg q24h	66.8	0.482	0.695	50.9	0.762	86.2	8.10	4.13	0.36	31
165		500 mg q24h	59.1	0.588	0.715	43.5	0.736	79.3	6.24	9.72	1.17	80
166		500 mg q24h	73.6	0.147	1.160	59.5	0.809	67.0	5.48	8.81	1.27	91
167		500 mg q24h	61.4	0.314	0.273	42.2	0.688	90.7	4.96	11.64	2.00	101
168		500 mg q24h	90.9	0.701	0.486	48.2	0.530	117.7	4.81	9.97	2.80	104
169		250 mg q24h	77.7	0.618	0.729	38.0	0.489	70.2	6.63	5.23	0.44	38
170		250 mg q24h	48.9	0.618	0.729	23.9	0.489	44.2	6.63	7.52	0.20	38
171		250 mg q24h	62.5	1.090	1.080	48.1	0.769	96.6	5.22	4.43	0.99	48
172		250 mg q24h	48.4	0.001	1.140	76.5	1.580	76.6	8.99	3.28	0.22	28
173		250 mg q24h	81.8	0.061	1.170	71.1	0.869	74.8	6.11	3.75	0.59	41
174		250 mg q24h	101.4	0.308	0.137	47.5	0.468	154.3	3.97	5.90	1.63	63
175		500 mg q24h	70.9	0.130	0.399	85.8	1.210	113.8	12.12	5.51	0.40	41
176		500 mg q24h	85.9	0.123	0.261	85.6	0.996	125.9	11.12	5.71	0.57	45
177		250 mg q24h	50.0	0.250	0.952	45.6	0.911	57.6	2.43	7.25	2.50	103
178		500 mg q24h	68.2	0.053	1.180	108.4	1.590	113.3	11.82	4.67	0.42	42
179		500 mg q24h	88.6	0.110	0.360	101.9	1.150	133.0	13.35	4.75	0.40	38
180		500 mg q24h	75.0	0.447	0.470	70.6	0.941	137.7	2.85	10.49	5.12	175
181		500 mg q24h	90.9	0.447	0.084	49.3	0.542	311.6	2.30	11.78	4.36	217
182		500 mg q24h	75.0	1.030	1.110	60.4	0.805	116.4	9.91	6.16	0.67	51
183		500 mg q24h	68.2	0.357	0.574	46.5	0.682	75.4	3.68	11.82	3.00	136
184		500 mg q24h	77.3	0.348	0.252	79.6	1.030	189.5	16.36	5.26	0.40	31
185		500 mg q24h	52.3	0.989	1.200	52.8	1.010	96.3	8.08	7.27	0.84	62
186		500 mg q24h	95.4	0.077	0.098	110.7	1.160	197.7	14.81	4.50	0.45	34

* $V_{ss} = (1 + K_{eo}/K_{pc}) \cdot V_c$

ATTACHMENT 4: Levofloxacin Bayesian Posterior Pharmacokinetic Parameter Estimates for All 272 Subjects Included in the Pharmacokinetic/Pharmacodynamic Evaluations (Continued)
(Study LOFBIV-MULT-001)

Index No.	Subject No.	Dosing Regimen	Weight (kg)	K_{cp} (1/h)	K_{pc} (1/h)	V_c (L)	V_c/kg (L/kg)	V_{ss}* (L)	CL (L/h)	C_{max} (µg/mL)	C_{min} (µg/mL)	AUC (µg•h/mL)
187		500 mg q24h	71.8	0.232	1.140	51.8	0.722	62.3	4.85	9.93	1.53	103
188		500 mg q24h	95.4	0.088	0.087	135.5	1.420	272.6	17.07	3.75	0.45	29
189		500 mg q24h	50.0	0.151	0.958	85.0	1.700	98.4	4.70	7.70	2.41	106
190		250 mg q24h	122.7	0.035	0.986	99.6	0.812	103.1	10.02	2.61	0.27	25
191		500 mg q24h	72.7	0.385	0.416	58.4	0.803	112.4	14.08	6.77	0.28	36
192		500 mg q24h	84.1	0.081	0.585	90.8	1.080	103.4	10.48	5.48	0.50	48
193		500 mg q24h	97.3	0.587	1.020	25.5	0.262	40.2	7.61	14.17	0.17	66
194		500 mg q24h	72.3	0.898	0.301	20.4	0.282	81.3	10.28	14.09	0.41	49
195		500 mg q24h	95.4	0.620	0.331	27.3	0.286	78.4	9.75	12.44	0.43	51
196		500 mg q24h	108.2	0.298	0.139	126.6	1.170	398.0	9.67	4.57	1.36	52
197		500 mg q24h	88.6	0.870	0.897	70.8	0.799	139.5	11.62	5.41	0.59	43
198		500 mg q24h	71.8	0.329	0.151	66.1	0.921	210.1	10.06	7.01	1.01	50
199		500 mg q24h	82.7	0.920	0.714	47.5	0.574	108.7	10.44	7.36	0.55	48
200		500 mg q24h	62.3	0.849	1.260	58.6	0.940	98.1	9.74	6.58	0.55	51
201		500 mg q24h	92.7	0.367	1.110	94.6	1.020	125.9	14.32	4.61	0.30	35
202		500 mg q24h	74.5	0.480	0.535	69.5	0.933	131.9	14.45	5.70	0.33	35
203		500 mg q24h	97.3	0.615	0.959	64.8	0.666	106.4	10.97	6.19	0.47	46
204		500 mg q24h	65.9	0.397	0.318	42.9	0.651	96.5	11.87	8.96	0.35	42
205		500 mg q24h	68.2	0.720	0.201	16.3	0.239	74.7	10.56	17.42	0.36	47
206		500 mg q24h	78.2	0.053	1.180	124.3	1.590	129.9	11.82	4.24	0.51	42
207		500 mg q24h	47.3	0.322	1.030	46.4	0.981	60.9	4.02	11.28	2.19	124
208		500 mg q24h	64.5	0.713	0.450	26.9	0.417	69.5	10.11	12.13	0.31	50
209		500 mg q24h	63.2	0.747	0.764	57.8	0.914	114.3	10.87	6.55	0.53	46
210		500 mg q24h	77.3	1.290	1.040	57.2	0.740	128.2	11.68	5.81	0.53	43
211		500 mg q24h	61.4	0.155	1.280	74.9	1.220	84.0	10.14	6.27	0.37	49
212		500 mg q24h	81.8	1.210	0.820	36.9	0.451	91.4	9.09	8.64	0.60	55
213		500 mg q24h	63.6	0.147	1.160	51.5	0.809	58.0	5.48	9.73	1.05	91
214		500 mg q24h	77.3	0.154	0.275	57.9	0.749	90.3	11.52	7.62	0.33	43
215		500 mg q24h	91.8	0.187	0.215	59.9	0.653	112.0	8.06	8.09	0.97	62
216		500 mg q24h	76.4	0.566	1.070	67.0	0.877	102.4	4.35	8.61	2.78	115
217		500 mg q24h	95.4	1.270	1.010	46.1	0.483	104.1	9.25	7.26	0.69	54

* $V_{ss} = (1 + K_{cp}/K_{pc}) \cdot V_c$

ATTACHMENT 4: Levofloxacin Bayesian Posterior Pharmacokinetic Parameter Estimates for All 272 Subjects Included in the Pharmacokinetic/Pharmacodynamic Evaluations (Continued)
(Study LOFBIV-MULT-001)

Index No.	Subject No.	Dosing Regimen	Weight (kg)	K_{ep} (1/h)	K_{pc} (1/h)	V_c (L)	V_c/kg (L/kg)	V_{ss}* (L)	CL (L/h)	C_{max} (µg/mL)	C_{min} (µg/mL)	AUC (µg-h/mL)
218		500 mg q24h	125.0	0.283	0.556	82.0	0.656	123.7	9.61	5.86	0.77	52
219		500 mg q24h	94.6	1.140	0.964	23.9	0.253	52.2	8.68	12.57	0.23	58
220		500 mg q24h	61.4	0.290	0.308	29.3	0.477	56.9	10.05	13.01	0.22	50
221		500 mg q24h	72.7	0.017	1.190	67.1	0.923	68.1	10.79	7.00	0.18	46
222		500 mg q24h	54.1	0.425	1.120	50.0	0.924	69.0	8.22	8.45	0.48	61
223		500 mg q24h	75.0	0.126	0.188	86.3	1.150	144.1	7.27	6.59	1.42	69
224		500 mg q24h	95.4	0.758	0.352	19.9	0.209	62.8	11.94	14.40	0.17	42
225		500 mg q24h	61.4	0.472	0.334	41.2	0.671	99.4	5.92	10.78	1.58	85
226		500 mg q24h	85.0	0.446	0.146	50.0	0.588	202.7	9.83	8.42	1.02	51
227		250 mg q24h	119.5	0.101	0.284	117.1	0.980	158.7	19.89	1.96	0.10	13
228		500 mg q24h	63.6	0.609	0.742	63.1	0.992	114.9	8.67	6.76	0.89	58
229		500 mg q24h	127.3	0.292	0.297	85.5	0.672	169.6	13.72	5.24	0.51	36
230		500 mg q24h	61.4	1.200	1.300	62.0	1.010	119.2	11.87	5.61	0.45	42
231		500 mg q24h	120.4	1.330	0.792	61.2	0.508	164.0	16.19	4.98	0.34	31
232		500 mg q24h	101.4	0.527	0.598	56.1	0.553	105.5	9.94	7.23	0.59	50
233		250 mg q24h	63.6	0.071	0.220	62.7	0.986	82.9	8.30	3.91	0.32	30
234		500 mg q24h	68.2	0.003	0.184	161.6	2.370	164.2	16.88	3.20	0.30	30
235		500 mg q24h	95.0	0.441	1.300	72.2	0.760	96.7	16.17	5.51	0.11	31
236		500 mg q24h	77.3	0.215	0.392	72.0	0.932	111.5	7.82	6.99	1.05	64
237		500 mg q24h	71.4	0.341	0.489	100.0	1.400	169.7	19.58	4.17	0.22	26
238		500 mg q24h	76.4	0.560	0.925	65.3	0.855	104.8	7.02	7.13	1.23	71
239		500 mg q24h	95.4	1.380	1.240	50.1	0.525	105.9	12.24	6.29	0.35	41
240		500 mg q24h	63.6	0.878	0.649	39.4	0.619	92.7	12.07	8.30	0.30	41
241		500 mg q24h	80.9	0.318	0.860	109.2	1.350	149.6	14.03	4.21	0.42	36
242		500 mg q24h	80.0	0.671	1.140	87.2	1.090	138.5	13.68	4.64	0.40	37
243		500 mg q24h	114.1	0.045	0.032	103.0	0.903	247.8	12.20	4.96	0.52	41
244		500 mg q24h	55.0	0.438	0.394	42.2	0.768	89.1	9.38	9.40	0.55	53
245		500 mg q24h	105.4	0.388	1.260	79.2	0.751	103.6	13.34	5.36	0.25	38
246		500 mg q24h	56.8	0.560	0.925	48.6	0.855	78.0	7.03	8.71	0.88	71
247		500 mg q24h	84.5	1.270	1.010	40.8	0.483	92.1	9.25	7.94	0.58	54
248		500 mg q24h	97.7	0.720	0.201	23.2	0.237	106.3	10.55	13.47	0.54	47

* $V_{ss} = (1 + K_{ep}/K_{pc}) \cdot V_c$

ATTACHMENT 4: Levofloxacin Bayesian Posterior Pharmacokinetic Parameter Estimates for All 272 Subjects Included in the Pharmacokinetic/Pharmacodynamic Evaluations (Continued)
(Study LOFBIV-MULT-001)

Index No.	Subject No.	Dosing Regimen	Weight (kg)	K_{ep} (1/h)	K_{pc} (1/h)	V_c (L)	V_c/kg (L/kg)	V_{ss}[a] (L)	CL (L/h)	C_{max} (µg/mL)	C_{min} (µg/mL)	AUC (µg•h/mL)
249		500 mg q24h	72.7	0.740	0.240	21.7	0.298	88.6	9.32	14.49	0.57	54
250		500 mg q24h	79.1	0.477	0.534	73.9	0.934	139.9	14.44	5.44	0.36	35
251		500 mg q24h	72.3	0.398	0.316	46.7	0.646	105.5	11.85	8.38	0.40	42
252		500 mg q24h	72.7	0.890	0.891	54.8	0.754	109.5	15.70	6.09	0.18	32
253		500 mg q24h	75.0	0.245	0.383	81.0	1.080	132.8	15.57	5.32	0.28	32
254		500 mg q24h	77.3	0.720	0.201	18.3	0.237	83.9	10.55	16.03	0.42	47
255		500 mg q24h	90.0	1.200	0.920	54.7	0.608	126.0	11.32	6.13	0.55	44
256		500 mg q24h	96.4	0.055	0.393	95.7	0.993	109.1	14.38	4.94	0.23	35
257		500 mg q24h	77.3	1.060	0.514	22.4	0.290	68.6	8.58	13.16	0.46	58
258		500 mg q24h	86.4	1.150	0.890	34.9	0.404	80.0	4.82	11.02	1.97	104
259		500 mg q24h	111.4	0.860	0.832	47.9	0.430	97.4	14.49	6.93	0.18	35
260		500 mg q24h	60.0	0.931	0.627	35.0	0.583	87.0	7.37	10.07	0.92	68
261		500 mg q24h	59.1	0.076	1.060	55.2	0.934	59.2	7.55	8.64	0.45	66
262		250 mg q24h	66.9	0.339	1.160	46.6	0.696	60.2	2.98	6.39	1.86	84
263		500 mg q24h	80.0	0.457	1.130	60.2	0.753	84.5	10.08	6.94	0.39	50
264		500 mg q24h	80.0	0.218	1.250	54.7	0.684	64.2	3.41	11.16	3.09	147
265		500 mg q24h	73.6	0.443	0.594	75.8	1.030	132.3	17.90	5.13	0.18	28
266		500 mg q24h	80.0	0.466	0.817	42.2	0.528	66.3	3.00	13.32	3.88	167
267		500 mg q24h	73.6	0.142	0.312	63.4	0.862	92.3	6.22	8.34	1.36	80
268		500 mg q24h	73.6	0.182	0.680	52.0	0.706	65.9	8.80	8.57	0.36	57
269		500 mg q48h	54.5	0.078	0.991	58.9	1.080	63.5	3.69	8.50	0.53	68
270		500 mg q24h	80.0	1.340	0.481	22.6	0.283	85.6	9.11	11.95	0.56	55
271		500 mg q24h	73.6	0.610	0.989	34.9	0.474	56.4	2.52	15.63	4.66	198
272		500 mg q24h	73.6	0.546	0.649	30.8	0.419	56.7	5.04	13.37	1.26	99

[a] $V_{ss} = (1 + K_{ep}/K_{pc}) \cdot V_c$