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*APPLICATION NUMBER:*

**21-744**

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

## CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW

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**NDA NUMBER:** 21-744  
**SUBMISSION DATE:** 18 July 2004  
**BRAND NAME:** PROQUIN XR™  
**GENERIC NAME:** Ciprofloxacin hydrochloride  
**DOSAGE FORM AND STRENGTH(S):** Extended-release oral tablets, 500 mg  
**INDICATION(S):** treatment of uncomplicated UTI  
**SPONSOR:** DEPOMED, Inc.  
**TYPE OF SUBMISSION:** 505(b)(1)  
**OCPB DIVISION:** DPE3  
**OND DIVISION:** DSPIDP  
**REVIEWER:** Gerlie Gieser, Ph.D.  
**TEAM LEADER:** Philip M. Colangelo, Pharm.D., Ph.D.

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#### I. Executive Summary

##### A. Recommendations

Proquin™ is an extended release tablet containing 500 mg of ciprofloxacin hydrochloride. Proquin™ differs from currently marketed ciprofloxacin immediate-release and modified-release solid oral dosage forms because of its distinct absorption profile, as well as its unique interaction with food and drugs that alter ciprofloxacin absorption (e.g., antacids, omeprazole). The label of Proquin™ should adequately communicate the formulation-related PK differences of this extended-release ciprofloxacin dosage form. Patients should not substitute Proquin™ for other ciprofloxacin dosage forms unless they are properly

counseled by their physician and/or pharmacist. Proquin™ should be given with the main meal of the day, preferably the evening meal. The recommended timing of Proquin™ co-administration with antacids and omeprazole are different from the usual time of dosing recommendations for currently marketed ciprofloxacin oral dosage forms. Despite these differences, the total systemic ciprofloxacin exposure and the cumulative urinary excretion of ciprofloxacin and its active metabolites from Proquin™ 500 mg once-daily appear to be comparable to that achieved from the reference ciprofloxacin treatment (Cipro® 250 mg BID).

For the treatment of uncomplicated urinary tract infections (uUTI), the proposed Proquin™ dosing regimen is one (500 mg) tablet once daily (with a meal) for 3 consecutive days. Based on the calculated AUC/MIC and C<sub>max</sub>/MIC ratios, adequate plasma exposures, as well as urinary concentrations of ciprofloxacin are achieved from Proquin™ that during the 3-day dosing period would sustain antimicrobial activity against susceptible strains of at least the following microbes commonly encountered in uncomplicated urinary tract infections: *Escherichia coli*, *Klebsiella pneumoniae*

Age, body weight, height, gender, and race were not significant covariates of ciprofloxacin exposure from Proquin™ 500 mg once daily for 3 days. Thus dosing adjustments based on these factors are not warranted. Furthermore, based on the findings of the PK studies conducted in special populations, as well as on existing literature PK information, dosage adjustments do not appear to be necessary for elderly patients and patients with renal impairment

Although the *in vitro* study conducted to investigate the inhibitory effects of ciprofloxacin on selected CYP450 enzymes was not able to definitively demonstrate the potential of this drug to inhibit the metabolism of CYP1A2 substrates at test concentrations covering relevant plasma exposure, the label will contain a precautionary statement regarding the drug interactions of ciprofloxacin that result in decreased clearance of CYP1A2 substrates (e.g. theophylline, caffeine). Likewise, despite the inability to show a PK and/or PD interaction between single-doses of Proquin™ and warfarin (Coumadin®) in healthy volunteers, the label will indicate the potential of ciprofloxacin to increase the anticoagulant effect of warfarin, as stated in the labels of other ciprofloxacin products.

Based on a Level A IVIVC, the proposed release specifications for dissolution testing of Proquin™ extended-release tablets are acceptable.

From a clinical pharmacology and biopharmaceutics perspective, this application for Proquin™ 500 mg extended-release tablets is acceptable. Labeling recommendations in Section III should be addressed by the sponsor.

#### **B. Phase IV Commitments**

None.

#### **C. Summary of Important Clinical Pharmacology and Biopharmaceutics Findings**

All except 1 of the 18 clinical pharmacology study reports in this NDA submission for Proquin™ 500 mg extended-release ciprofloxacin oral tablets (also referred to as PROQUIN™ and Ciprofloxacin GR™) were reviewed thoroughly. The report for comparative PK Study 00-07 was not given much weight in this review because the prototype formulations used in this particular study were not the same ones used in the succeeding PK studies and pivotal clinical trials.

#### **Comparative Plasma and Urinary Ciprofloxacin Pharmacokinetics of Proquin™ 500mg OD versus Cipro® 250mg BID (on Day 1 of Treatment)**

The mean ciprofloxacin plasma concentration-time profiles of the two treatments when both were given with a high-fat meal on Day 1 are presented in Figure 1. As seen in Table 1, the total systemic ciprofloxacin exposure (AUC<sub>0-24h</sub>) from once daily Proquin™ is similar to that from twice daily immediate-release Cipro®. However, the C<sub>max0</sub> of Proquin™ is about 46% higher than the C<sub>max1</sub> from the first

dose of Cipro® but about 24% lower than the Cmax<sub>2</sub> of the second dose of Cipro®. The mean time to Cmax<sub>0</sub> of Proquin™ is longer than the mean time to Cmax<sub>1</sub> of Cipro® by about 5 hours; the difference between the median Tmax values was about 6.5 hours.

FIGURE 1  
Ciprofloxacin Pharmacokinetics on Day 1:  
Proquin™ 500mg OD versus Cipro® 250mg BID

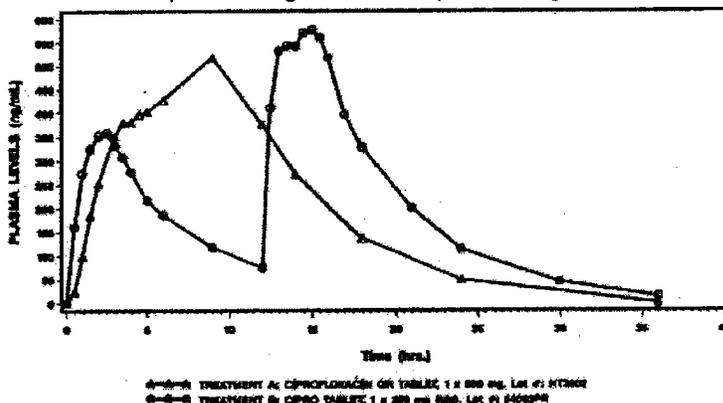
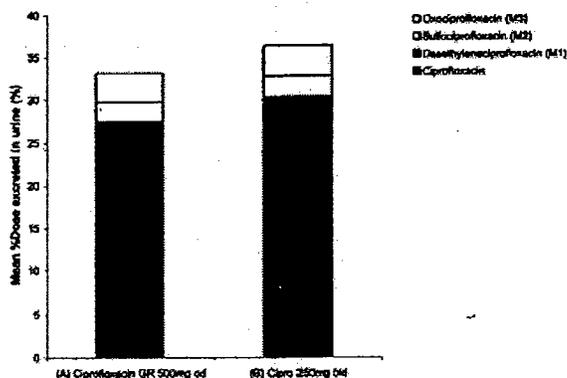


TABLE 1

Parameter	Ciprofloxacin GR™ 500 mg Tablets (single dose) (A) vs. Cipro® 250 mg Tablets (twice daily x 2 doses) (B)		
	90% C.I.	Ratio of Means (A/B)	Intra-Subject CV
AUC <sub>0-∞</sub>	85.47% to 98.98%	91.98%	15.77%
AUC <sub>0-36</sub>	86.91% to 101.19%	93.78%	16.03%
C <sub>max</sub> vs. C <sub>min</sub>	131.17% to 163.50%	146.44%	23.68%
C <sub>max</sub> vs. C <sub>min</sub>	68.10% to 84.44%	75.83%	23.11%

Figure 2 shows a comparison of the two treatments in terms of the total percentage of the dose excreted in the urine (as parent + active metabolites). The ciprofloxacin 0 - 36 hour urinary recovery was significantly lower (by ~10%, p=0.0416) from Proquin™ 500 mg QD than from Cipro® 250 mg BID. The renal clearance of ciprofloxacin was not different between the two treatments. Similar urinary excretion profiles between the two treatments were observed for the quantifiable metabolites, M1, M2, and M3.

FIGURE 2  
Percentage of Dose Excreted in the Urine (Ciprofloxacin and metabolites):  
Proquin™ 500 mg QD versus Cipro® 250 mg BID



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The mean urinary ciprofloxacin concentration values obtained in this single-day PK study of Proquin™ 500mg OD were at least 165x and 49x the MIC<sub>90</sub> values (0.016 mcg/mL and 0.045 mcg/mL) for *E.coli* isolates strain 1 and strain 4, respectively. The corresponding AUC/MIC and C<sub>max</sub>/MIC ratios were ≥139 and ≥15, respectively.

Comparative Plasma and Urinary Ciprofloxacin Pharmacokinetics of Proquin™ 500mg OD versus Cipro® 250mg BID (on Day 3 of Treatment)

The mean ciprofloxacin plasma concentration-time profiles of the two treatments when both were given with a high-fat meal on Day 3 (the proposed final day of treatment for uncomplicated UTI) are presented in Figure 3. As seen in Table 2, the total systemic ciprofloxacin exposure (AUC<sub>0-24h</sub>) from once daily Proquin™ is 98% of that from twice daily immediate-release Cipro®. Although the C<sub>max0</sub> of Proquin™ is about 45% higher than the C<sub>max1</sub> from the first dose of Cipro®, this C<sub>max0</sub> was only 12% lower than the C<sub>max2</sub> of the second dose of Cipro®. The mean time to C<sub>max0</sub> is longer than the mean time to C<sub>max1</sub> by about 3.5 hours. As expected from a longer-interval dosing regimen, the C<sub>min</sub> from once daily Proquin™ was about 55% lower than from twice daily Cipro® 250 mg.

Based on the relative bioavailability of ciprofloxacin from Proquin™ on Day 1 and Day 3, the estimated AUC<sub>0-24h</sub> accumulation ratio of ciprofloxacin on Day 3 of treatment is about 1.07.

FIGURE 3  
Ciprofloxacin Pharmacokinetics on Day 3: Proquin™ 500mg OD versus Cipro® 250mg BID

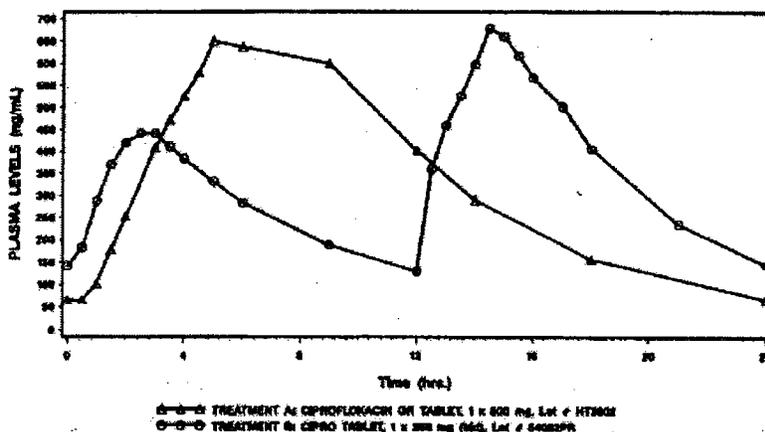


TABLE 2

Pharmacokinetic Parameters	Ciprofloxacin GR™ 500 mg Tablets (qd) (A) vs. CIPRO® 250 mg Tablets (bid) (B)		
	90% Confidence Interval	Ratio of Means	Intra-Subject CV
AUC <sub>0-24h</sub>	92.21% to 103.60%	97.74%	12.52%
C <sub>max0</sub> vs. C <sub>max1</sub>	130.67% to 160.20%	144.69%	21.89%
C <sub>max0</sub> vs. C <sub>max2</sub>	80.77% to 96.23%	88.17%	18.82%
C <sub>min</sub>	40.39% to 49.75%	44.82%	22.40%

The mean percentage of the dose excreted into the urine (as ciprofloxacin and metabolites) at steady state was similar to that obtained during Day 1 of therapy. During the three days of dosing, the %Dose, A<sub>e</sub>, and CL<sub>r</sub> of ciprofloxacin were consistently slightly higher (by 8 to 20%) from Cipro® 250 mg BID than from Proquin™ 500 mg QD but the difference was significant (p<0.05) only on Days 2 and 3.

It can be seen from Table 3 below that the AUC<sub>ss</sub>/MIC ratios for Proquin™ were greater than 100 and the C<sub>max,ss</sub>/MIC ratios were greater than 10 for the following microbial strains: *E. coli* strain 1, *E. coli* strain 4, *K. pneumoniae*, and *P. mirabilis*. For the same microorganisms, the C<sub>min,ss</sub>/MIC values were at least equal to 1.

**TABLE 3**  
Ratios for Ciprofloxacin AUC/MIC, C<sub>max</sub>/MIC and 24-h C<sub>urine</sub>/MIC  
Following a 3-Day Regimen of Proquin™ 500 mg Once Daily

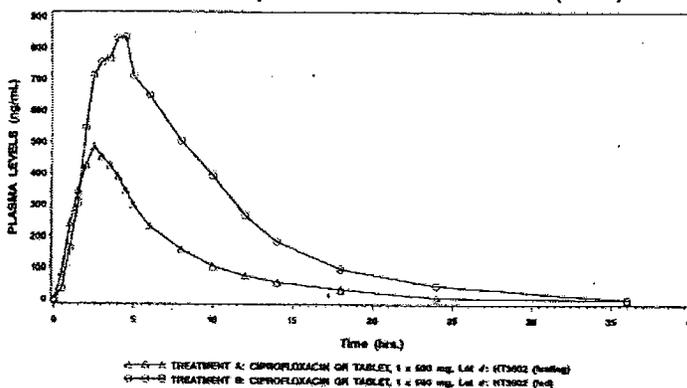
ORGANISM	MIC <sub>90</sub> (mcg/mL)	Ciprofloxacin AUC <sub>0-24h</sub> (7905 ng <sup>*</sup> h/mL)	Ciprofloxacin C <sub>max</sub> (857 ng/mL)	Ciprofloxacin C <sub>urine(0-24h)</sub> <sup>#</sup> (65.91 mcg/mL)
<i>E. coli</i> ATCC 25922 (strain 1)	0.016	494	54	4119
<i>E. faecalis</i> ATCC 29212 (strain 2)	1	8	1	65.91
<i>S. aureus</i> ATCC 29213 (strain 3)	0.5	16	2	131.8
<i>E. coli</i> N9688 (strain 4)	0.045	176	19	1465
<i>K. pneumoniae</i> N9189 (strain 5)	0.016	494	54	4119
<i>E. faecalis</i> ST12,296 (strain 6)	>32	<0.25	<0.03	<2.06
<i>S. saprophyticus</i> , SP8822 (strain 7)	0.5	16	2	131.8
<i>P. mirabilis</i> N9287 (strain 8)	0.045	176	19	1465

# C<sub>urine(0-24h)</sub> = A<sub>e0-24h</sub>/volume of urine in 24 h

#### Effect of a High-Fat Meal on Proquin™ Pharmacokinetics

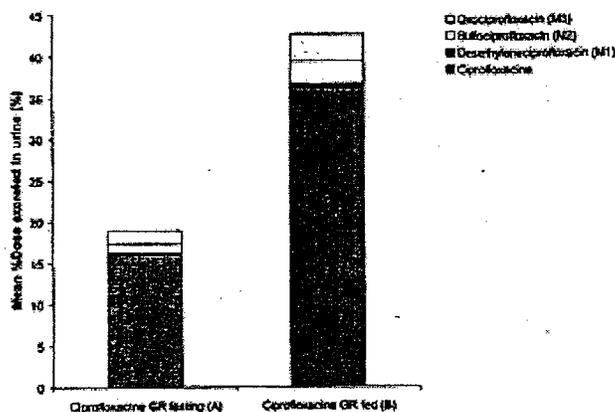
Mean ciprofloxacin plasma concentration-time profiles following Proquin™ 500mg under fasted and fed conditions are presented in Figure 4. Co-administration with a high-fat meal increased the AUC<sub>0-24h</sub> and the C<sub>max</sub> of Proquin™ by 170% and 120%, respectively. The percent coefficient of variation (% CV) about the mean AUC and C<sub>max</sub> was also lower under fed conditions (25-35%) than under fasted conditions (48-52%). With a meal, the T<sub>max</sub> of ciprofloxacin was prolonged by about 2.2 hours. Similarly, under fed conditions, the total %Dose excreted into the urine as the unchanged drug and its active metabolites increased by 125% (Figure 5).

**FIGURE 4**  
Mean Plasma Ciprofloxacin Concentrations (N=27)



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**FIGURE 5**  
**Mean Percentage of Dose Excreted in Urine Following the Administration of Proquin™ 500 mg Tablets**  
**under Fasting (Treatment A) and Fed Conditions (Treatment B)**



Later in the clinical development of Proquin™ for the treatment of uncomplicated UTI, the oral tablet was co-administered with a moderate-fat content meal. Also, in earlier clinical pharmacology studies in healthy subjects, a fluid control technique was instituted, i.e., 100mL or 200mL of water was given after the Proquin™ dose every 1 or 2 hours until 24 hours post-dose. A cross-study comparison between earlier and later PK studies suggests that such alterations in dietary and fluid conditions had only a minor effect on the over-all oral bioavailability of ciprofloxacin from Proquin™.

Because the total systemic ciprofloxacin exposure ( $AUC_{0-24h}$ ) of Proquin™ was similar to the reference Cipro® 250 mg BID regimen when both were given under fed conditions, the Proquin™ dose should be given with a substantial meal, preferably the evening meal as carried out in the pivotal clinical efficacy/safety trials.

#### Mass Balance Study

The disposition and pharmacokinetics of ciprofloxacin was characterized in non-smoking healthy volunteers following a single dose of Proquin™ 500mg with a moderate-fat content meal. The total recovery, in urine and feces, of ciprofloxacin and the metabolites, M1, M2, M3, and M4, are summarized in Table 4. The findings of this study suggest that ciprofloxacin is eliminated to a similar extent by renal and non-renal means.

**TABLE 4**  
**Mean % Recovery of Ciprofloxacin, M1, M2, M3, and M4**  
**Following a Single Dose of Proquin 500 mg (Excluding Subject 007\*)**

	Ciprofloxacin	M1	M2	M3	M4	Total
<b>Urine</b>	33.9%	0.61%	2.81%	3.29%	-	40.6
<b>Feces</b>	39.1%	0.54%	3.24%	0.37%	0.15%	43.4%
<b>Total</b>	73.0%	1.15%	6.05%	3.66%	0.15%	84.0%

\*Subject excluded because of incomplete PK sampling and very low drug concentrations in the samples collected.

#### In-Vitro Plasma Protein Binding

The mean and individual percentages of bound ciprofloxacin in human plasma at test concentrations 0.9 to 30  $\mu$ M are given in the table below. At ciprofloxacin 3  $\mu$ M ( $\approx C_{max}$  in healthy volunteers), the percentage of plasma protein binding of ciprofloxacin was about 37%. There appears to be no

concentration dependence. At higher ciprofloxacin concentrations (>3  $\mu\text{M}$ ), the magnitude of plasma protein binding decreased. The study findings ( $P_B < 50\%$ ) suggest that ciprofloxacin has a low potential for interaction with drugs that are highly plasma protein bound (e.g., warfarin) via a mechanism involving displacement from protein binding.

**TABLE 5**  
**Ciprofloxacin Plasma Protein Binding**

Concentration ( $\mu\text{M}$ )	Percentage of Radioactivity				Standard Deviation
	Unbound		Bound		
	Individual	Mean	Individual	Mean	
0.9		70.9		29.1	5.7
3		63.4		36.6	1.2
9		73.5		26.5	2.5
30		90.1		9.93	6.37

**Inhibitory Potential of Ciprofloxacin Towards Human Hepatic Microsomal Cytochrome P450 Isoenzymes (CYP1A2, CYP2C9, CYP2C19, CYP2D6, and CYP3A4)**

As seen from Table 6 below, ciprofloxacin did not produce significant inhibitory activity against any of the CYP450 enzymes included in this study because more than 50% activity relative to the control value remained in all the assays. However, the study did not include positive inhibitor controls.

At 90  $\mu\text{M}$  ( $\cong$  30-fold higher than the  $C_{\text{max,ss}}$  in healthy volunteers), there was a minor but concentration-dependent inhibition observed for CYP1A2 and CYP2C9. By contrast, in published studies, higher test concentrations (500 to 1000  $\mu\text{M}$ ) of ciprofloxacin were able to produce >70% inhibition of CYP1A2 metabolic activity *in vitro*. In addition, the potential of ciprofloxacin to decrease the clearance of CYP1A2 substrates (e.g., theophylline, caffeine, tizanidine) in humans have been demonstrated. It is not known whether ciprofloxacin concentrations achieved in hepatocytes are much higher than that achieved in systemic circulation, thereby allowing ciprofloxacin to cause substantial inhibition of the hepatic metabolism of CYP1A2 substrates *in vivo*. Thus, as with other ciprofloxacin products, the label of Proquin™ will include a precautionary statement regarding the potential of ciprofloxacin to inhibit the clearance of specific CYP1A2 substrates like theophylline.

**TABLE 6**  
**Effect of ciprofloxacin on CYP450 activity**

CYP450 enzyme	Probe substrate (concentration)	Metabolite assayed	Percent of activity remaining*						
			Ciprofloxacin concentration ( $\mu\text{M}$ )						
			0	0.3	0.9	3	9	30	90
CYP1A2	Phenacetin (100 $\mu\text{M}$ )	acetaminophen	NA	103	100	101	97.9	91.7	82.5
CYP2C9	Diclofenac (10 $\mu\text{M}$ )	4'-hydroxydiclofenac	NA	95.5	105	97.8	106	96.5	75.3
CYP2C19	S-Mephenytoin (50 $\mu\text{M}$ )	4'-hydroxymephenytoin	NA	106	105	107	104	107	115
CYP2D6	Bufuralol (10 $\mu\text{M}$ )	1'-hydroxybufuralol	NA	105	105	103	101	109	120
CYP3A4	Testosterone (50 $\mu\text{M}$ )	6 $\beta$ -hydroxytestosterone	NA	99.1	99.0	101	95.6	101	98.6
	Midazolam (5 $\mu\text{M}$ )	1'-hydroxymidazolam	NA	93.4	95.2	102	107	102	102

NA- not applicable

\* average of triplicate values

Evaluation of CYP450 Induction Potential of Ciprofloxacin Using Primary Cultures of Human Hepatocytes: CYP1A, CYP2C, CYP3A

Table 7 summarizes the fold-induction data on CYP1A2, CYP2C9 and CYP3A enzyme activities by ciprofloxacin (0.45  $\mu$ M to 45  $\mu$ M), as well as by the positive inducer controls. Ciprofloxacin (at concentrations of 0.45 to 45  $\mu$ M) did not induce CYP2C or CYP3A activities of primary cultures of human hepatocytes. At 45  $\mu$ M (approximately equivalent to 18x the  $C_{max,ss}$  in healthy volunteers who received Proquin™ 500 mg OD for 3 days), ciprofloxacin showed a weak induction effect on CYP1A2. Because the effect was <40% of that produced by the positive inducer control (omeprazole 30  $\mu$ M), ciprofloxacin is not projected to cause *in vivo* induction of the metabolism of CYP1A2 substrates. To date, the literature provides no evidence of such metabolic induction interactions with CYP1A2 substrates precipitated by ciprofloxacin *in vitro* or *in vivo*.

**TABLE 7**  
**Fold-induction on CYP1A2, CYP2C9 and CYP3A enzyme activities**  
**by ciprofloxacin (0.45  $\mu$ M to 45  $\mu$ M), in comparison with the positive inducer controls**

CYP1A2	0.5% v/v DMSO	Omeprazole (30 $\mu$ M)	Ciprofloxacin		
			0.45 $\mu$ M	4.5 $\mu$ M	45 $\mu$ M
mean	0	12.90	0.90	1.33	1.80
sd	0	7.72	0.10	0.25	0.46
CYP2C9	0.5% v/v DMSO	Rifampin (50 $\mu$ M)	Ciprofloxacin		
			4.5 $\mu$ M	4.5 $\mu$ M	4.5 $\mu$ M
mean	0	4.10	1.00	1.20	1.00
sd	0	0.80	0.36	0.46	0.30
CYP3A	0.5% v/v DMSO	Rifampin (50 $\mu$ M)	Ciprofloxacin		
			4.5 $\mu$ M	4.5 $\mu$ M	4.5 $\mu$ M
mean	0	3.43	1.13	1.20	1.17
sd	0	1.33	0.31	0.44	0.15

Ciprofloxacin Pharmacokinetics in Elderly (>65 years) Subjects Given a Single Dose of Proquin™

The sponsor compared the PK parameters in elderly patients of this study to historical younger ( $\leq 65$  years) subject controls from Studies 81-0024, 81-0025, 81-0029, and 81-0032. The sponsor's findings (as given in Table 8 below) suggest that the  $C_{max}$  and AUC values for ciprofloxacin following Proquin™ in elderly subjects were higher, 39% and 31% respectively, as compared to younger healthy subjects. However, the ciprofloxacin half-lives were similar in the elderly and younger healthy subjects.

In the reviewer's own analysis, only the PK data of healthy subjects from a study (Study 81-0028) that had similar clinical study protocol conditions as that of the elderly PK study were used for PK comparison. Table 9 below compares the plasma and urinary PK parameters of Proquin™ in elderly subjects of this study to that of healthy volunteers (< 65 years old) in Study 81-0028. Based on this analysis, it appears that the ciprofloxacin  $AUC_{0-t}$  and  $C_{max}$  values in elderly subjects were indeed slightly higher (but only by 20 and 24%, respectively) compared to those in younger subjects. Similar to the sponsor's findings, both the mean/median  $T_{max}$  values and the elimination half-lives of elderly subjects were comparable to those in the younger subjects of the reference study. However, the percentage of the ciprofloxacin dose excreted into the urine of elderly subjects was lower by about 11% than in younger subjects, suggesting that the difference in PK could be related to the decreased renal clearance of ciprofloxacin in elderly patients. Using the Cockcroft-Gault formula to calculate individual creatinine clearance values, it was

revealed that 75% (12 of the 16) elderly subjects enrolled in this study had mild renal impairment (CLcr = 51-80 mL/min). However, these slight changes in the plasma and urinary PK of ciprofloxacin in elderly subjects do not warrant a dosage adjustment recommendation for Proquin™ in the 3-day treatment of uUTI.

**Table 8**  
**Summary of Ciprofloxacin Plasma Pharmacokinetic Parameters by**  
**Age: Subjects Receiving Ciprofloxacin GR 500 mg (Single Dose) in**  
**Studies 81-0024, 81-0025, 81-0029, and 81-0032**

Pharmacokinetic Parameter	Statistics	Treatment Group		p-value <sup>a</sup>
		Ciprofloxacin GR 500 mg < 65 Years	Ciprofloxacin GR 500 mg ≥ 65 Years	
AUC <sub>0-4</sub> (ng·hr/mL)	n Geometric Mean (%CV)	68 6886.7 (28.8)	18 9028.6 (30.5)	0.001
AUC <sub>0-∞</sub> (ng·hr/mL)	n Geometric Mean (%CV)	66 7213.7 (28.6)	18 9429.5 (29.9)	0.001
C <sub>max</sub> (ng/mL)	n Geometric Mean (%CV)	68 917.5 (42.8)	18 1273.7 (26.5)	<0.001
T <sub>max</sub> (hr)	n Median Mean ± SD	68 4.50 5.52 ± 3.07	18 4.50 4.20 ± 0.81	0.002
T <sub>1/2</sub> (hr)	n Median Mean ± SD	66 4.72 4.74 ± 0.94	18 4.89 5.03 ± 0.96	0.258
Renal Clearance (L/hr)	n Median Mean ± SD	52 <sup>b</sup> 23.47 23.01 ± 5.79	17 <sup>b</sup> 16.26 17.45 ± 4.74	<0.001

- a. The p-value for the between group comparison was based on the two-sample t-test.  
b. Urinary PK Samples were not collected in 81-0029

**TABLE 9**  
**Ciprofloxacin Pharmacokinetic Parameters in Elderly Subjects**  
**versus Healthy Subjects in Study 81-0028 who received Proquin™ alone**

PHARMACOKINETIC PARAMETER (UNIT)	ELDERLY (>65 YEARS) (STUDY 81-0032) (N = 16)	HEALTHY VOLUNTEERS (<65 YEARS OLD) (STUDY 81-0028) <sup>B</sup> (N = 26)
Proquin™ Dose (mg)	500 (single-dose)	1000 (without antacids; single-dose)
Fat-content of meal	moderate	moderate
Fluid control measure	Yes	Yes
AUC <sub>0-4</sub> (ng·h/mL)	8853.2 (32.2)	7405 <sup>a</sup>
AUC <sub>0-∞</sub> (ng·h/mL)	9256.0 (31.7)	7598 <sup>a</sup>
C <sub>max</sub> (ng/mL)	1285.5 (26.8)	1041 <sup>a</sup>
T <sub>max</sub> (hr)	1.19 ± 0.81 4.50	4.45 ± 1.69 4.50
t <sub>1/2</sub> (hr)	4.89 ± 0.80	5.11 ± 0.99
T <sub>max</sub> Rate (hr)	5.25 ± 1.44	5.78 ± 2.36
Max Rate (mg/hr)	24.16 ± 6.80	48.24 ± 18.33
Ae (mg)	149.9 ± 17.7	162.4 <sup>a</sup>
% Dose	30	33.4 <sup>a</sup>

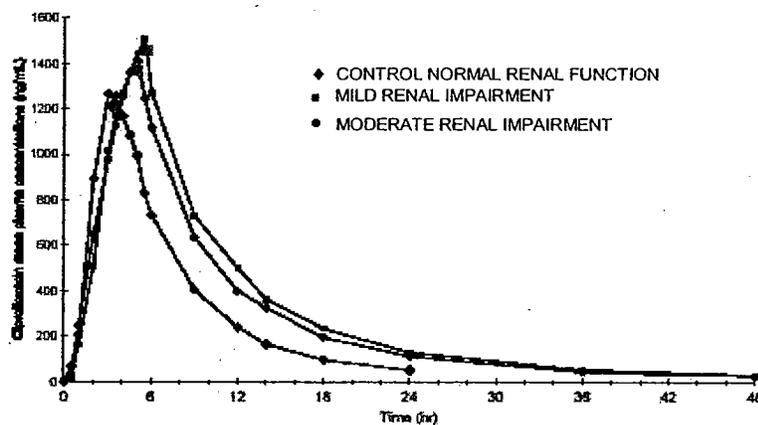
<sup>a</sup> normalized to 500 mg

<sup>b</sup> values in parentheses (% CV); values after "±" are standard deviation values

### Single Dose Pharmacokinetics of Proquin™ 500 mg Tablets in Subjects with Normal Renal Function and in Subjects with Mild and Moderate Renal Impairment

Mean ciprofloxacin plasma concentration-time profiles are presented in Figure 6.

**FIGURE 6**  
Mean Plasma Ciprofloxacin Concentration-Time Profiles in Various Renal Function Groups



The plasma pharmacokinetic parameters of ciprofloxacin (Proquin™) obtained for various renal function groups and the findings of statistical analysis are summarized in Table 10 below.

**TABLE 10**

Pharmacokinetic Parameter	<i>Group 1 (Mild Renal Impairment) n = 10 Mean ± SD</i>	p-Values <sup>†</sup>	<i>Group 2 (Moderate Renal Impairment) n = 10 Mean ± SD</i>	p-Values <sup>†</sup>	<i>Group 3 (Normal Renal Function) n = 10 Mean ± SD</i>
AUC <sub>0-4</sub> (ng·hr/mL)*	12314.9 (29.4)	0.0453	13403.5 (37.7)	0.0119	8722.4 (22.0)
AUC <sub>0-∞</sub> (ng·hr/mL)*	12778.8 (28.1)	0.0397	13854.2 (37.0)	0.0105	9059.6 (21.6)
C <sub>max</sub> (ng/mL)*	1545.5 (28.6)	0.6204	1752.4 (38.9)	0.1859	1363.0 (23.7)
T <sub>max</sub> (hr) <sup>‡</sup>	4.25 (2.00 - 5.50)	0.1557	4.50 (3.00 - 6.00)	0.0348	3.25 (2.00 - 5.00)
t <sub>1/2</sub> (hr)	7.74 ± 1.09	0.0001	7.54 ± 2.15	0.0001	4.54 ± 0.40
CL/F (mL/min)	41.1 ± 15.3	0.0397	38.6 ± 15.4	0.0105	56.4 ± 13.1

Source: Appendix 3.1.1.

\* Geometric means (%CV)

<sup>‡</sup> Median (Min - Max)

<sup>†</sup> p-values relative to Group 3 (subjects with normal renal function)

The systemic exposures (as AUC<sub>0-4</sub>) of ciprofloxacin in subjects with mild and moderate renal impairment were 42% and 54% higher, respectively, compared to subjects with normal renal function. That the total clearance of ciprofloxacin is not dependent only on renal excretion is evident from the lack of a significant difference in ciprofloxacin clearance values between the mildly and moderately renally impaired groups (41 and 39 mL/min, respectively). Therefore, dosage reduction is not needed for patients with mild to moderate renal impairment.

In the treatment of uncomplicated urinary tract infections (uUTI), the currently recommended ciprofloxacin dosage for patients with severe renal impairment is up to 500 mg q18h and for dialysis patients, 500mg q24h. Such dosage could also be justified for Proquin™ because of the following reasons: (1) As shown by the findings of the mass balance study, the elimination of ciprofloxacin from Proquin™ is not only via renal excretion; about an equal percentage of the dose is excreted by non-renal means. (2) As shown by the findings of this PK in Renal Impairment Study, the total clearance of ciprofloxacin is not dependent on renal function. In addition, the 2-fold increase in the ciprofloxacin elimination half-life previously seen in subjects with end-stage renal disease (CL<sub>cr</sub> < 10 mL/min; Drusano et al., 1987) versus healthy control subjects is similar to that seen in subjects with mild and moderate renal impairment (1.70-fold and 1.66-fold, respectively; Study 81-0036). (3) Based on the findings of the single-dose and multiple-dose studies, the resulting total daily systemic exposure from Proquin™ 500 mg extended release tablets is not expected to be greater than that achievable from the immediate-release Cipro® regimen at the dosage recommended for those with severe renal impairment or those undergoing dialysis. (4) Based on the combined findings of the single-dose and steady state PK studies, the AUC<sub>0-24</sub> accumulation ratio on Day 3 of treatment is negligible (R = 1.07) in subjects with normal renal function. Thus, based on the comparable PK parameters of subjects in various renal function groups, it does not appear necessary to adjust dosage in severely renally impaired uUTI patients who will receive Proquin™ 500 mg daily for 3 days.

#### Drug Interaction with Warfarin

Study 81-0035 was conducted to investigate the two-way, single dose, pharmacokinetic and pharmacodynamic interaction between Proquin™ 500 mg tablets and warfarin (Coumadin®) 7.5 mg tablets when both were given to healthy volunteers with a moderate-fat content meal. Table 11 presents the pharmacokinetic parameters of Proquin™ alone and when given with Coumadin®. Tables 12 and 13 compare the PK parameters of S-warfarin and R-warfarin when Coumadin® was given alone and when co-administered with Proquin™. Table 14 shows the pharmacodynamic parameters of Coumadin® alone and when given with Proquin®.

TABLE 11  
Pharmacokinetic Parameters of Ciprofloxacin with or without Coumadin®

Pharmacokinetic Parameter	Ciprofloxacin GR™ 500 mg Tablets and Coumadin® 7.5 mg Tablets (Treatment A) (n=18)	Ciprofloxacin GR™ 500 mg Tablets (Treatment C) (n=18)	p-value <sup>f</sup>
AUC <sub>0-24</sub> (ng·hr/mL)	7519.1 (26.9) <sup>ff</sup>	7241.6 (23.6) <sup>ff</sup>	0.344 <sup>e</sup>
AUC <sub>0-8</sub> (ng·hr/mL)	7924.8 (25.8) <sup>ff</sup>	7616.0 (23.3) <sup>ff</sup>	0.291 <sup>e</sup>
C <sub>max</sub> (ng/mL)	862.7 (20.9) <sup>ff</sup>	818.7 (19.9) <sup>ff</sup>	0.382 <sup>e</sup>
T <sub>max</sub> (hr)	4.50 ± 0.98 <sup>g</sup>	4.89 ± 1.94 <sup>g</sup>	0.420
t <sub>1/2</sub> (hr)	5.02 ± 0.70 <sup>g</sup>	5.07 ± 0.84 <sup>g</sup>	0.803
CL/F (mL/min)	1072.59 ± 206.15 <sup>g</sup>	1120.67 ± 253.81 <sup>g</sup>	0.297
Vd/F (L)	461.56 ± 91.82 <sup>g</sup>	486.63 ± 115.35 <sup>g</sup>	0.211

<sup>f</sup> Geometric mean (%CV)

<sup>g</sup> Mean ± SD

<sup>e</sup> The p-value is from ANOVA on ln-transformed data

<sup>f</sup> Manually rounded from values obtained in Appendix 3

No significant changes in the AUC and C<sub>max</sub> values of ciprofloxacin R-warfarin, and S-warfarin were observed when single doses of Proquin™ and Coumadin® were administered together in healthy volunteers. However, a small but statistically significant increase in R-warfarin elimination half-life was observed when Coumadin® was co-administered with Proquin™ although this did not obviously translate to changes in the pharmacodynamics of single-dose warfarin. The ability of a single-dose study to detect any drug interactions between warfarin and ciprofloxacin may be limited because the approximate time to steady state of warfarin is ≥ 5 days. Furthermore, other prospective single-dose and multiple dose interaction studies have shown similar results but those studies involved healthy subjects or patients who were not being treated for an infection. Regardless of the findings of the single-dose drug interaction study conducted by the sponsor, several case reports submitted to FDA indicate that ciprofloxacin co-administration could increase warfarin's hypoprothrombinemic effect especially in those patients with risk factors (old age, fever, infection, CHF, thyroid disease, polypharmacy); the reported average time to coagulopathy was 5.5 days. Thus, as is the case with other products of ciprofloxacin, the label of Proquin

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™ will carry a precautionary statement regarding the potential of ciprofloxacin to increase the anticoagulant effect of warfarin.

TABLE 12  
Pharmacokinetic Parameters of R-Warfarin with or without Proquin™

Pharmacokinetic Parameter	Ciprofloxacin GR™ 500 mg Tablets and Coumadin® 7.5 mg Tablets (Treatment A) (n=18)	Coumadin® 7.5 mg Tablets (Treatment B) (n=18)	p-value <sup>†</sup>
AUC <sub>0-4</sub> (ng·hr/mL)	18875.1 (17.5) <sup>‡§</sup>	18638.8 (20.1) <sup>‡§</sup>	0.554 <sup>‡</sup>
AUC <sub>0-24</sub> (ng·hr/mL)	23935.1 (25.6) <sup>‡§</sup>	23311.5 (23.5) <sup>‡§</sup>	0.178 <sup>‡</sup>
C <sub>max</sub> (ng/mL)	312.1 (17.7) <sup>‡§</sup>	316.4 (18.2) <sup>‡§</sup>	0.630 <sup>‡</sup>
T <sub>max</sub> (hr)	6.75 ± 5.05 <sup>‡</sup>	5.89 ± 2.45 <sup>‡</sup>	0.497 <sup>‡</sup>
t <sub>1/2</sub> (hr)	52.56 ± 12.48 <sup>‡</sup>	50.10 ± 9.23 <sup>‡</sup>	0.029 <sup>‡</sup>
CL/F (mL/min)	5.37 ± 1.28 <sup>‡</sup>	5.50 ± 1.33 <sup>‡</sup>	0.111 <sup>‡</sup>
Vd/F (L)	23.54 ± 4.13 <sup>‡</sup>	23.22 ± 4.04 <sup>‡</sup>	0.733 <sup>‡</sup>

<sup>‡</sup> Geometric mean (%CV)

<sup>§</sup> Mean ± SD

<sup>†</sup> The p-value is from ANOVA on ln-transformed data

<sup>‡</sup> n = 17

<sup>‡</sup> Manually rounded from values obtained in Appendix 3

TABLE 13  
Pharmacokinetic Parameters of S-Warfarin with or without Proquin™

Pharmacokinetic Parameter	Ciprofloxacin GR™ 500 mg Tablets and Coumadin® 7.5 mg Tablets (Treatment A) (n=18)	Coumadin® 7.5 mg Tablets (Treatment B) (n=18)	p-value <sup>†</sup>
AUC <sub>0-4</sub> (ng·hr/mL)	11742.9 (20.6) <sup>‡§</sup>	11894.1 (20.3) <sup>‡§</sup>	0.539 <sup>‡</sup>
AUC <sub>0-24</sub> (ng·hr/mL)	13361.1 (22.7) <sup>‡§</sup>	13512.9 (22.5) <sup>‡§</sup>	0.667 <sup>‡</sup>
C <sub>max</sub> (ng/mL)	287.3 (20.2) <sup>‡§</sup>	291.9 (21.5) <sup>‡§</sup>	0.555 <sup>‡</sup>
T <sub>max</sub> (hr)	4.03 ± 1.12 <sup>‡</sup>	4.53 ± 2.16 <sup>‡</sup>	0.315
t <sub>1/2</sub> (hr)	39.28 ± 5.89 <sup>‡</sup>	39.03 ± 5.31 <sup>‡</sup>	0.842
CL/F (mL/min)	9.55 ± 1.88 <sup>‡</sup>	9.44 ± 1.88 <sup>‡</sup>	0.663
Vd/F (L)	32.10 ± 6.39 <sup>‡</sup>	31.48 ± 5.78 <sup>‡</sup>	0.386

<sup>‡</sup> Geometric mean (%CV)

<sup>§</sup> Mean ± SD

<sup>†</sup> The p-value is from ANOVA on ln-transformed data

<sup>‡</sup> Manually rounded from values obtained in Appendix 3

TABLE 14  
Pharmacodynamic Parameters of Coumadin® with or without Proquin™

Pharmacodynamic Parameter	Ciprofloxacin GR™ 500 mg Tablets and Coumadin® 7.5 mg Tablets (Treatment A) (n=18) (mean ± SD)	Coumadin® 7.5 mg Tablets (Treatment B) (n=18) (mean ± SD)	p-value
T <sub>max</sub> PT (hr) <sup>‡</sup>	29.0 ± 25.6	30.1 ± 31.9	0.872
PT <sub>max</sub> (sec) <sup>‡</sup>	12.6 ± 0.9	12.4 ± 0.8	0.079
AUCPT (hr*sec) <sup>‡</sup>	1428.9 ± 71.2	1419.0 ± 70.6	0.142
AUCaPTT (hr*sec) <sup>‡</sup>	3439.2 ± 204.0	3406.3 ± 210.4	0.180

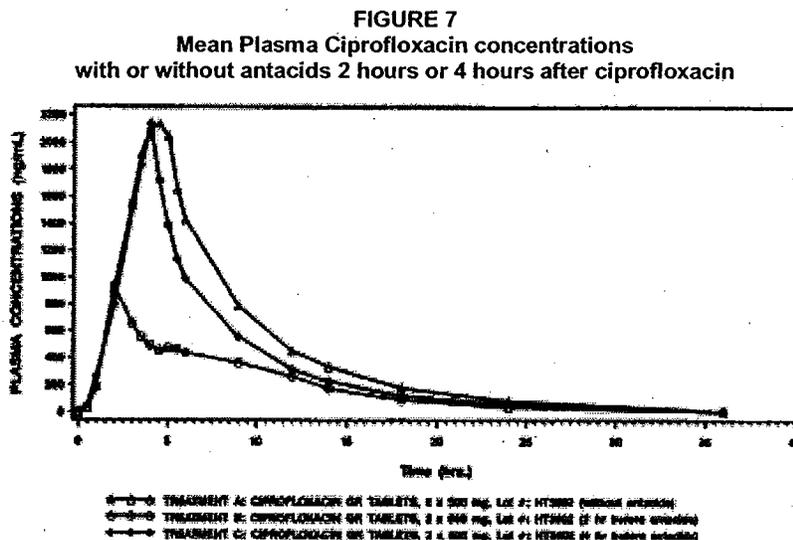
<sup>‡</sup> Manually rounded from values obtained in Appendix 3

**Drug Interaction with Antacids:** Determination of the appropriate times of co-administration. Antacids are known to decrease the absorption of ciprofloxacin via chelation and/or gastric pH-altering mechanisms. Thus, two studies were conducted to investigate the effect of timing of antacids co-administration on the pharmacokinetics of Proquin™. When the antacids were given 2 hours before or 6 hours after the Proquin™ dose, the plasma and urinary pharmacokinetics of ciprofloxacin were not altered

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(data not shown). However, when the antacids were given 2 hours after or 4 hours after the Proquin™ dose, the PK of ciprofloxacin were significantly affected.

The mean plasma concentration-time profiles of ciprofloxacin, with and without antacids (2 hours after or 4 hours after the ciprofloxacin dose) are presented in Figure 7. The summary of pharmacokinetic parameter and the findings of the statistical analysis are presented in Tables 15 and 16.



**TABLE 15**  
Pharmacokinetic parameters for Ciprofloxacin  
(without and with antacids 2 hours after or 4 hours after ciprofloxacin)

Pharmacokinetic Parameters	Ciprofloxacin GR™ 2 x 500 mg Tablets (Without Antacids)	Ciprofloxacin GR™ 2 x 500 mg Tablets (Ciprofloxacin administered 2 hours before antacids)	Ciprofloxacin GR™ 2 x 500 mg Tablets (Ciprofloxacin administered 4 hours before antacids)
	(A) (n=22) Geometric mean (%CV)	(B) (n=22) Geometric mean (%CV)	(C) (n=22) Geometric mean (%CV)
AUC <sub>0-24</sub> (ng·hr/mL)‡	14898.3 (26.3)	5572.0 (53.9) p-value < 0.0001†	11558.8 (30.3) p-value = 0.0003†
AUC <sub>0-8</sub> (ng·hr/mL)‡	15373.5 (29.4)	3893.8 (54.1) p-value < 0.0001†	11954.9 (29.3) p-value = 0.0004†
C <sub>max</sub> (ng/mL)‡	2412.7 (32.9)	876.6 (72.7) p-value < 0.0001†	2133.7 (34.8) p-value = 0.1736†
T <sub>max</sub> (hr)	4.10 ± 0.84† 4.00*	3.64 ± 1.78† 2.00* p-value = 0.2464†	3.79 ± 0.34† 4.00* p-value = 0.4594†
t <sub>1/2</sub> (hr)	5.05 ± 1.06†	4.74 ± 0.82† p-value = 0.0938†	5.19 ± 1.16† p-value = 0.4264†

\* median values  
 † Arithmetic mean ± SD  
 ‡ The p-value is from ANOVA data and is based on the comparison with Treatment A

Co-administration of antacids 2 hours after a ciprofloxacin dose decreased the AUC and Cmax of ciprofloxacin by 62% and 63%, respectively. Antacids administered 4 hours after a Proquin™ dose decreased the AUC and Cmax of ciprofloxacin by 22% and 11% compared to when Proquin™ was given alone. Therefore, based on the PK findings of the Antacids-Proquin™ Interaction Study 2, Proquin™ may be administered at least 4 hours before antacids but Proquin™ may not be administered 2 hours before antacids. This recommendation is in contrast with that recommended in the Cipro® IR and XR labels, i.e., it is advisable to administer Cipro® dosage forms 2 hours before antacids.

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**TABLE 16**  
**Bioequivalence assessments for Ciprofloxacin**  
**(with and without antacids 2 hours or 4 hours after ciprofloxacin)**

Ciprofloxacin GR™ 2 x 500 mg Tablets (Ciprofloxacin administered two hours before antacids) (B) versus Ciprofloxacin GR™ 2 x 500 mg Tablets (Without Antacids) (A)			
Parameters	90% C.I.	Ratio of Means (B:A)	Intra-Subject CV
AUC <sub>0-24</sub>	33.43% - 42.15%	37.55%	26.28%
AUC <sub>0-12</sub>	34.43% - 43.01%	38.49%	25.23%
C <sub>max</sub>	31.72% - 42.29%	36.63%	32.68%

Ciprofloxacin GR™ 2 x 500 mg Tablets (Ciprofloxacin administered four hours before antacids) (C) versus Ciprofloxacin GR™ 2 x 500 mg Tablets (Without Antacids) (A)			
Parameters	90% C.I.	Ratio of Means (C:A)	Intra-Subject CV
AUC <sub>0-24</sub>	69.09% - 87.05%	77.59%	26.28%
AUC <sub>0-12</sub>	69.33% - 86.84%	77.71%	25.23%
C <sub>max</sub>	76.93% - 102.54%	88.82%	32.68%

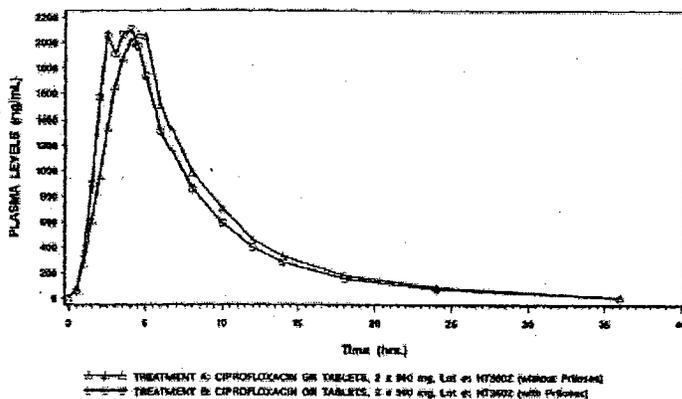
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Based on the combined findings of the two drug interaction studies conducted, it is recommended that Proquin™ be administered 2 hours after antacids or at least 4 hours before antacids. In addition, the label should highlight this important difference between Proquin™ and other currently marketed dosage forms of ciprofloxacin.

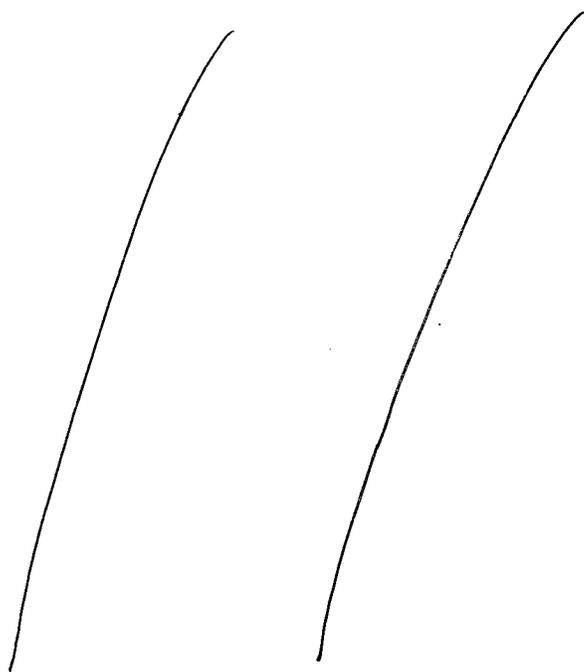
#### Drug Interaction with Omeprazole

The administration of omeprazole 2 hours before CIPRO XR® is known to decrease the AUC of ciprofloxacin by about 20% and the C<sub>max</sub> by about 23%. Study 81-0027 was specifically conducted to investigate the effect omeprazole given 2 hours before the Proquin™ dose, on the pharmacokinetics of ciprofloxacin from Proquin™ given with a meal. The mean plasma concentration-time profiles of ciprofloxacin, with or without omeprazole are presented in Figure 8. The findings of the statistical analysis are presented in Table 17. The summary of urinary pharmacokinetic parameters and the findings of the statistical analysis are presented in Table 18 below. The systemic and urinary exposures of Proquin™ when given with omeprazole 2 hours before Proquin™ were not statistically significantly different when compared to Proquin™ alone. Even the apparent elimination half-lives were similar between the two treatments.

**FIGURE 8**  
**Mean Plasma Ciprofloxacin concentrations**  
**(with or without Omeprazole, 2 hours before Proquin™)**



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3. *What is the proposed therapeutic indication(s)? What are the proposed dosage(s) and route(s) of administration?*

For the treatment of uncomplicated urinary tract infections (acute cystitis) caused by susceptible strains of *E. coli*, *K. pneumoniae*,

Proquin™ 500 mg oral tablets should be given once daily for 3 consecutive days, to be administered with a meal, preferably the evening meal.

**B. General Clinical Pharmacology**

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

All (except two) of the ten clinical pharmacology studies conducted by the sponsor of Proquin™ were randomized, open-label, single-dose or multiple-dose, cross-over studies, where the test and/or comparator treatments were given to healthy volunteers with a (high-fat or moderate-fat) meal, in the presence or absence of a fluid control technique. Only two of these PK studies, i.e., those involving elderly subjects, and those subjects with varying degrees of renal impairment were (as expected) not cross-over studies.

The two clinical efficacy/safety studies conducted were randomized, double-blind, parallel-group, active controlled trials that compared Proquin™ 500mg QD x 3 days to Cipro® 250mg BID x 3 days in the treatment of patients with uncomplicated urinary tract infections (uUTI). Both these trials did not have pharmacokinetic endpoints.

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

The microbiological eradication rates, rates of new infection, and clinical cure rates of uUTI patients taking the test and control treatments were compared. Clinical cure was assessed on the Test-of-Cure Visit ( $7 \pm 2$  days after completing the study medication) by physical examination, by clinical assessment of signs and symptoms of acute uUTI, AE and severe AEs, urinalysis, pregnancy test, blood chemistry and hematology.

3. Are the active moieties in the plasma (or other biological fluid) appropriately identified and measured to assess pharmacokinetic parameters and exposure response relationships?

Yes, refer to II. F, Analytical Section.

4. Exposure-response

Is the dose and dosing regimen selected by the sponsor consistent with the known relationship between dose-concentration-response, and are there any unresolved dosing or administration issues?

Like other fluoroquinolones, ciprofloxacin shows concentration-dependent killing of bacteria *in vitro*. *In vivo* studies in animals and humans demonstrated that a 24-hour AUC/MIC ratio of at least 100 and a Cmax/MIC ratio of at least 10 are often associated with maximal clinical and bactericidal effect in the treatment of (uncomplicated) urinary tract infections caused by gram-negative microbes. Based on the sponsor's PK/PD analysis, the administration of Proquin™ 500mg OD with a high-fat meal for three consecutive days produces the following AUC/MIC and Cmax/MIC values in Table 21 (measured on Day

**TABLE 21**  
Ratios for Ciprofloxacin AUC/MIC, Cmax/MIC, Cmin/MIC and 24-h C<sub>urine</sub>/MIC  
Following a 3-Day Regimen of Proquin™ 500 mg Once Daily

ORGANISM	MIC <sub>90</sub> (mcg/mL)	Ciprofloxacin AUC <sub>0-24h</sub> (7905 ng*h/mL)	Ciprofloxacin Cmax (857 ng/mL)	Ciprofloxacin Cmin (67.7 ng/mL)	Ciprofloxacin C <sub>urine(0-24h)</sub> (65.91 mcg/mL)
<i>E. coli</i> ATCC 25922 (strain 1)	0.016	494	54	4	4119
<i>E. faecalis</i> ATCC 29212 (strain 2)	1	8	1	0.1	65.91
<i>S. aureus</i> ATCC 29213 (strain 3)	0.5	16	2	0.1	131.8
<i>E. coli</i> N9688 (strain 4)	0.045	176	19	2	1465
<i>K. pneumoniae</i> N9189 (strain 5)	0.016	494	54	4	4119
<i>E. faecalis</i> ST12,296 (strain 6)	>32	<0.25	<0.03	<0.002	<2.06
<i>S. saprophyticus</i> , SP8822 (strain 7)	0.5	16	2	0.1	131.8
<i>P. mirabilis</i> N9287 (strain 8)	0.045	176	19	2	1465

$$C_{urine(0-24h)} = A_{e0-24h} / \text{volume of urine in 24 h}$$

3 of therapy) for the pathogens commonly found in uncomplicated urinary tract infections (uUTI). Based on these calculated surrogate PK/PD parameters, i.e., AUC/MIC and Cmax/MIC, the proposed dosage regimen for Proquin™ appears to produce sufficient systemic exposures to ciprofloxacin to successfully

treat urinary tract infections caused by microbes that are similar in susceptibility to *E. coli* strain 1 and strain 4, *K. pneumoniae*, and *P. mirabilis*. The trough ciprofloxacin concentrations (Cmin) achieved at steady state following 3 daily doses of Proquin™ 500mg were at least equivalent to the MIC<sub>90</sub> of these four susceptible microbial strains. Furthermore, it was observed that the measured mean urinary concentrations of ciprofloxacin were substantially higher in urine than in plasma, suggesting that exposure to ciprofloxacin at the organ sites involved in uncomplicated urinary tract infection (uUTI) will also be adequate, at least when the four susceptible microbial strains are involved.

5. What are the PK characteristics of the drug and its major metabolites?

a) What are the single dose and multiple dose PK parameters?

The following tables summarize the plasma and urine pharmacokinetic parameters of ciprofloxacin and three of its active metabolites, following single dose and multiple doses of Proquin™ 500 mg once daily for 3 consecutive days, co-administered with a high-fat meal.

**TABLE 22**  
Summary of Plasma Pharmacokinetic Parameters of Ciprofloxacin  
Following Proquin™ 500mg OD x 3 Days Co-administered with a High-Fat Meal (N=27)

Pharmacokinetic Parameter, unit (Geometric Mean & %CV)	DAY 1 (Study 81-0025)	DAY 3 (Study 81-0026)
AUC <sub>0-24</sub> (ng*h/mL)	6236.7 (29.1)	7667.6 (24.8)
AUC <sub>0-inf</sub> (ng*h/mL)	6535.5 (28.5)	
Cmax (ng/mL)	691.6 (31.0)	824.1 (28.4)
Cmin (ng/mL)	-	62.59 (42.449)
Tmax (h)	7.04 ± 3.31 <sup>a</sup> 9.00 <sup>b</sup>	6.06 ± 2.63 <sup>a</sup> 5.00 <sup>b</sup>
t <sub>1/2</sub> (h)	4.49 ± 0.83	-
MRT (h)	-	9.29 ± 1.18 <sup>a</sup>

<sup>a</sup> arithmetic mean

<sup>b</sup> median

**TABLE 23**  
Summary of Urinary Pharmacokinetic Parameters of Ciprofloxacin and Three of Its Active Metabolites  
Following Proquin™ 500mg OD x 3 Days Co-administered with a High-Fat Meal (N=27)<sup>b,c</sup>

Pharmacokinetic Parameter, unit (Mean ± SD)	Ciprofloxacin	Desethylene-ciprofloxacin (M1)	Sulfo-ciprofloxacin (M2)	Oxo-ciprofloxacin (M3)
<b>DAY 1</b>				
Tmax rate (h)	8.19 ± 3.00	10.04 ± 3.01	8.33 ± 2.94	8.56 ± 2.79
Max Rate (mg/h)	20.35 ± 9.29	0.25 ± 0.11	2.57 ± 1.25	2.05 ± 1.02
Ae (mg)	134.4 (30.4) <sup>a</sup>	2.0 (35.8) <sup>a</sup>	14.5 (41.5) <sup>a</sup>	14.1 (38.0) <sup>a</sup>
% Dose	28.34 ± 8.63	0.46 ± 0.17	2.59 ± 1.08	2.91 ± 1.11
<b>DAY 3</b>				
Tmax rate (h)	7.22 ± 2.62	8.11 ± 2.74	7.52 ± 2.52	7.37 ± 2.66
Max Rate (mg/h)	19.54 ± 8.32	0.30 ± 0.10	2.55 ± 1.01	2.31 ± 0.88
Ae (mg)	131.8 (31.7) <sup>a</sup>	2.5 (30.7) <sup>a</sup>	14.1 (44.0) <sup>a</sup>	15.9 (33.9) <sup>a</sup>
CLr (L/h)	18.24 ± 5.68			
% Dose	27.97 ± 8.87	0.58 ± 0.18	2.55 ± 1.12	3.25 ± 1.10

Geometric mean (%CV)

<sup>a</sup> Metabolite M4 (Formylciprofloxacin) levels were below the limit of quantification of the assay.

<sup>c</sup> Study 81-0026

- b) Compare the plasma and urinary ciprofloxacin exposures following 3-day therapy with Proquin™ 500 mg OD and Cipro® 250 mg BID.

Based on comparative single-dose and steady-state PK data, when both given with a high-fat meal, Proquin™ 500mg QD produces a plasma ciprofloxacin AUC<sub>0-24h</sub> that is comparable to Cipro® 250mg BID (Table 24A); the AUC measured for Proquin™ was about 92% of the reference treatment on Day 1, and about 98% on Day 3. As expected from a longer treatment interval ( $\tau$ ) dosing regimen, the ciprofloxacin C<sub>min</sub> from the Proquin™ QD treatment was about 55% lower than that after the Cipro® BID treatment. Table 24B provides a statistical comparison of the dose-dependent PK parameters of ciprofloxacin in plasma following the two treatments.

**TABLE 24A**  
Statistical Comparison of Ciprofloxacin Pharmacokinetics:  
Proquin™ 500 mg OD versus Cipro® 250 mg BID  
(Day 1 of Therapy)

Parameter	Ciprofloxacin GR™ 500 mg Tablets (single dose) (A) vs. Cipro® 250 mg Tablets (twice daily x 2 doses) (B)		
	95% C.I.	Ratio of Means (A:B)	Intra-Subject CV
AUC <sub>0-24</sub>	85.47% to 98.98%	91.98%	15.77%
AUC <sub>inf</sub>	86.91% to 101.19%	93.78%	16.03%
C <sub>max1</sub> vs. C <sub>max2</sub>	131.17% to 163.50%	146.44%	23.68%
C <sub>max1</sub> vs. C <sub>max2</sub>	68.10% to 84.44%	75.83%	23.11%

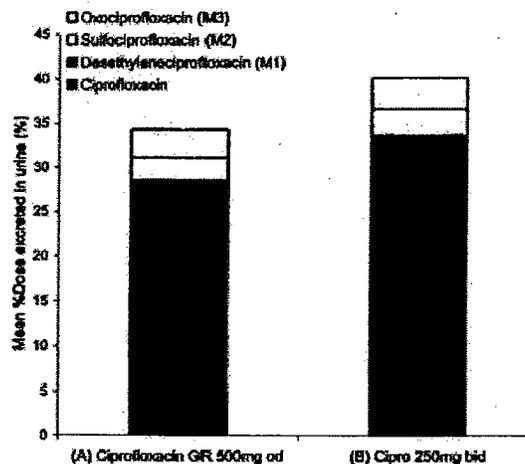
**TABLE 24B**  
Statistical Comparison of Ciprofloxacin Pharmacokinetics:  
Proquin™ 500 mg OD versus Cipro® 250 mg BID  
(Day 3 of Therapy)

Pharmacokinetic Parameters	Ciprofloxacin GR™ 500 mg Tablets (qd) (A) vs. CIPRO® 250 mg Tablets (bid) (B)		
	90% Confidence Interval	Ratio of Means	Intra-Subject CV
AUC <sub>0-24</sub>	92.21% to 103.60%	97.74%	12.52%
C <sub>max1</sub> vs. C <sub>max2</sub>	130.67% to 160.20%	144.69%	21.89%
C <sub>max1</sub> vs. C <sub>max2</sub>	89.77% to 96.23%	88.17%	18.82%
C <sub>min</sub>	49.39% to 49.75%	44.82%	22.40%

Based on the exposure-response relationship known for Cipro XR®, efficacy in the treatment of uncomplicated urinary tract infections (uUTI) depends upon antimicrobial concentrations in the urine rather than in the serum. Based on the %Dose (as parent + 3 metabolites) excreted into the urine on Day 1 and Day 3 of therapy, Cipro® 250 mg BID produced a consistently slightly higher but comparable urinary concentrations of the ciprofloxacin active moieties compared to Proquin™ OD (9% and 11%, respectively). Figure 11 provides a comparison of the % total dose of ciprofloxacin and active metabolites excreted into the urine following a 3-day therapy with the two treatments.

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FIGURE 11  
Percentage of Dose versus Metabolite Fraction on Day 3,  
following the administration of 1x500 mg Proquin™ tablet once a day (Treatment A)  
and 1 x250 mg Cipro® tablet twice a day (Treatment B)



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c) What are the characteristics of drug distribution, i.e., protein binding?

At ciprofloxacin concentrations lower than 3  $\mu\text{M}$  ( $\approx C_{\text{max}}$  in healthy volunteers), the percentage of plasma protein binding of ciprofloxacin was  $\leq 37\%$ . At test concentrations exceeding 3  $\mu\text{M}$ , the percentage of plasma protein binding decreased. Thus, ciprofloxacin has a low potential to alter the pharmacokinetics of drugs that are highly protein-bound.

The mean and individual percentages of bound ciprofloxacin in human plasma at various test concentrations are given in the table below.

TABLE 25

Concentration ( $\mu\text{M}$ )	Percentage of Radioactivity				Standard Deviation
	Unbound		Bound		
	Individual	Mean	Individual	Mean	
0.9	7	70.9	3	29.1	5.7
3		63.4		36.6	1.2
9		73.5		26.5	2.5
30		90.1		9.93	6.37

d) Does the mass balance study suggest renal or hepatic as the major route of elimination?

Ciprofloxacin is eliminated by renal and non-renal routes. In this Mass Balance Study (Study 81-0037), about 85% of the administered dose was accounted for, i.e., 34% and 39% of the dose were excreted as unchanged ciprofloxacin in urine and feces, respectively, whereas 7% and 4% of the administered dose were excreted into the urine and the feces, respectively, as ciprofloxacin active metabolites. The total recovery, in urine and feces, of ciprofloxacin and the metabolites, M1, M2, M3, and M4, are summarized in Table 26. These urinary and fecal percentage recovery findings are consistent with that in the literature.

The renal clearance of ciprofloxacin was about 304 to 383 mL/min (18.24 to 23.5L/h) which suggests the involvement of renal tubular secretion and glomerular filtration as mechanisms or renal elimination.

**TABLE 26**  
**Mean % Recovery of Ciprofloxacin, M1, M2, M3, and M4**  
**Following a Single Dose of Proquin 500 mg (Excluding Subject 007)**

	Ciprofloxacin	M1	M2	M3	M4	Total
<b>Urine</b>	33.9%	0.61%	2.81%	3.29%	-	40.6
<b>Feces</b>	39.1%	0.54%	3.24%	0.37%	0.15%	43.4%
<b>Total</b>	73.0%	1.15%	6.05%	3.66%	0.15%	84.0%

The majority (95%) of urinary excretion for ciprofloxacin, M1, M2 and M3 occurred within 24 hours of dosing. The majority (>93%) of the fecal elimination of ciprofloxacin, M1, M2, M3, and M4 occurred by Day 5 following dosing. The longer time needed to excrete majority of the ciprofloxacin and its metabolites into the feces suggests the possible occurrence of biliary recycling or enterohepatic recirculation.

e) Based on PK parameters, what is the degree of linearity or nonlinearity in the dose-concentration relationship?

The sponsor did not conduct a formal study to investigate the dose-concentration relationship of ciprofloxacin from Proquin™. Table 26 below provides a cross-study comparison of the plasma PK parameters of ciprofloxacin following single dose administration of either Proquin™ 500 mg or 1000 mg, with a moderate-fat content meal. It appears from the dose-normalized AUC and Cmax data that the pharmacokinetics of ciprofloxacin (Proquin™) are linear at least from a 500 to 1000 mg, the clinical dose range. The Tmax was not affected by doubling the dosage.

**TABLE 26**  
**Cross-study comparison of Pharmacokinetic Parameters of a single dose of Proquin™:**  
**500 mg versus 1000 mg**

STUDY	PROQUIN DOSE (MG)	FAT CONTENT OF THE MEAL ADMINISTERED WITH PROQUIN™	FLUID CONTROL? (YES/NO)	C <sub>MAX</sub> <sup>a,b</sup> (NG/ML)	T <sub>MAX</sub> (H)	AUC <sub>0-24H</sub> <sup>a,b</sup> (NG*H/ML)
Drug Interaction with Omeprazole (81-0027)	1000	moderate	Y	1272	3.95	7723
Drug Interaction with Antacids 1 (81-0028)	1000	moderate	Y	1041	4.45	7405
Drug Interaction with Antacids 2 (81-0033)	1000	moderate	N	1206	4.10	7449
<b>AVERAGE of GEO MEANS</b>	<b>1000</b>			<b>1173</b>		<b>7526</b>
Drug Interaction with Coumadin (81-0035)	500	moderate	N	819	4.89	7242
IVIVC (81-0029)	500	moderate	N	1274	4.56	8336
<b>AVERAGE of GEO MEANS</b>	<b>500</b>			<b>1047</b>		<b>7789</b>

<sup>a</sup> Geometric mean; Dose-normalized to 500 mg

<sup>b</sup> For Drug Interaction Studies: The PK parameter values are for Proquin™ alone (without the other drug).

f) How do the PK parameters change with time following chronic dosing?

Based on the plasma PK data in Table 22, the accumulation of ciprofloxacin and its metabolites is minimal by the last day of therapy (Day 3) with Proquin™ 500mg OD. The Day 3-to-Day 1 accumulation ratios in terms of AUC<sub>0-24h</sub> and C<sub>max</sub> were 1.23 and 1.19, respectively. Based on a comparison of the Day 1 and Day 3 Max Rate of ciprofloxacin, M1, M2, and M3 excretion into the urine, the renal excretion of ciprofloxacin and its metabolites is fairly stable throughout the treatment period.

g) What is the inter- and intra-subject variability of PK parameters in volunteers and patients, and what are the major causes of variability?

In the clinical pharmacology studies, the reported % inter-subject CV (coefficient of variation) about the mean AUC or C<sub>max</sub> in healthy volunteers was around 30% when Proquin™ was given with a meal; the %CV was around 50% when Proquin™ was given under fasted conditions.

### C. Intrinsic Factors

1. What intrinsic factors (age, gender, race, weight, height, disease, genetic polymorphism, pregnancy, and organ dysfunction) influence exposure (PK usually) and/or response and what is the impact of any differences in exposure on efficacy or safety responses?

Age, gender, race, weight, and height were not shown to influence the steady-state plasma AUC<sub>0-24h</sub>, C<sub>max</sub>, and the elimination t<sub>1/2</sub> of ciprofloxacin from Proquin™ 500mg extended-release tablets. The table below summarizes the effects of these variables on Proquin™ (plasma and urinary) PK parameters in healthy volunteers given Proquin™ 500mg daily for 3 days. It can be observed that the steady-state C<sub>min</sub> of ciprofloxacin was statistically significantly higher (p=0.0049) in males than in females, although all other ciprofloxacin PK parameters considered in the ANOVA analysis of plasma PK parameters were not (Table 27A). However, this gender difference was not evident in terms of the cumulative amounts of ciprofloxacin excreted into the urine, as shown in Table 27B. Thus, these same intrinsic factors are not expected to influence the response to Proquin™ in the treatment of uncomplicated urinary tract infections. The clinical efficacy/safety studies enrolled female patients only, in accordance with the known higher relative prevalence rates of this type of infection in females.

TABLE 27A  
STATISTICAL COMPARISON OF CIPROFLOXACIN PLASMA PHARMACOKINETIC PARAMETERS  
IN HEALTHY VOLUNTEERS FOLLOWING PROQUIN™ 500MG QD X 3 DAYS (Study 81-0026)

INTRINSIC FACTOR	PHARMACOKINETIC PARAMETER				
	AUC <sub>0-24h</sub> (ng·h/mL)	C <sub>max</sub> (ng/mL)	T <sub>max</sub> (hours)	C <sub>min</sub> (ng/mL)	MRT (hours)
ANOVA (α = 0.05)					
<b>GENDER</b>					
Females (n=14)	7898 ± 2178	870 ± 269	5.9 ± 2.2	53.4 ± 18.1	9.0 ± 0.9
Males (n=13)	7913 ± 1782 (NS)	843 ± 222 (NS)	6.2 ± 3.1 (NS)	83.0 ± 30.7 (p=0.0049)	9.7 ± 1.4 (NS)
<b>RACE</b>					
Asians (n=5)	7800 ± 2427	883 ± 222	4.0 ± 1.4	62.0 ± 10.7	8.7 ± 0.8
Blacks (n=4)	8411 ± 2252	878 ± 342	7.3 ± 2.1	63.2 ± 20.3	9.7 ± 0.4
Caucasians (n=18)	7767 ± 1872 (NS)	845 ± 241 (NS)	6.4 ± 2.8 (NS)	70.3 ± 33.8 (NS)	9.4 ± 1.4 (NS)
Correlation Coefficients (r) from Linear Regression Analysis					
<b>AGE</b> (<65 years; 38.5 ± 10.3 years)	0.0008	0.015	0.0164	0.017	0.011
<b>BODY WEIGHT</b> (71.3 ± 11.3 kg)	0.0088	0.016	0.0226	0.1808	0.1252
<b>HEIGHT</b> (1.68 ± 0.10 m <sup>2</sup> )	0.124	0.1085	1 × 10 <sup>-6</sup>	0.0437	0.0412

**TABLE 27A**  
**STATISTICAL COMPARISON OF CIPROFLOXACIN URINARY EXCRETION**  
**IN HEALTHY VOLUNTEERS FOLLOWING PROQUIN™ 500MG QD X 3 DAYS (Study 81-0026)**

INTRINSIC FACTOR	CIPROFLOXACIN DOSE EXCRETED INTO THE URINE (%)	STATISTICAL SIGNIFICANCE BY ANOVA ( $\alpha=0.05$ ) OR CORRELATION COEFFICIENT ( $r^2$ ) BY LINEAR REGRESSION
GENDER Females (n=14) Males (n=13)	31.8 ± 9.3 34.1 ± 8.2	NS
RACE Asians (n=5) Blacks (n=4) Caucasians (n=18)	32.7 ± 8.6 25.5 ± 2.7 34.6 ± 9.0	NS
AGE (<65 years; 38.5 ± 10.3 years)		$R^2 = 0.0147$
BODY WEIGHT (71.3 ± 11.3 kg)		$R^2 = 0.0062$
HEIGHT (1.68 ± 0.10 m <sup>2</sup> )		$R^2 = 0.0013$

Subgroup analyses based on age group (<65 years and ≥65 years) and race (Caucasian and non-Caucasian) were performed for the primary efficacy parameter (the microbiological eradication rate at the Test-of-Cure Visit) for the efficacy population of the pivotal clinical trial (Study 81-0015). The differences in the rates of microbiological eradication at the Test-of-Cure Visit were similar between treatment groups in patients who were <65 years of age and in patients who were ≥65 years of age, as well as between treatment groups in Caucasian patients and in non-Caucasian patients in the efficacy population (Table 28).

It was noted that for patients who were in the Proquin™ treatment arm, Caucasians had a slightly higher microbiological eradication rate than non-Caucasians (94.4% versus 89.3%). This finding is consistent with the slightly higher percentage of the ciprofloxacin dose (% Dose) excreted in the urine of Caucasian subjects compared to non-Caucasian subjects who received Proquin™ 500mg OD x 3 days in Study 81-0026 (34.6% versus 29.5%; see Table 27B above). Unfortunately, all the subjects in Study 81-0026 were <65 years old which precludes a direct comparison with the efficacy findings in the age subgroups of Study 81-0015. However, a cross-study comparison suggest that the elderly patients given a single dose of Proquin™ 500mg (Study 81-0032), had a slightly lower percentage (by 11%) of the ciprofloxacin dose excreted into their urine although these elderly patients demonstrated a 20% higher ciprofloxacin AUC<sub>0-24</sub> compared to that that seen in younger healthy volunteers (Study 81-0028) which suggests a decreased renal clearance of ciprofloxacin in elderly patients. Furthermore, the slightly lower urinary ciprofloxacin concentrations in these elderly patients could help explain why the microbiological eradication rate in younger patients (<65 years) was slightly higher than in elderly patients (≥ 65 years) in the pivotal efficacy trial (93.5% versus 85.7%).

**TABLE 28**  
**Analysis of 1-Week Microbiological Eradication Rate at Test-of-Cure Visit:**  
**Efficacy Population, By Age Group and By Race Group (Study 81-0015)**

ONE-WEEK MICROBIOLOGICAL RESPONSE	TREATMENT GROUP			
	Proquin™		Cipro® IR	
BY AGE	<65 years	≥65 years	<65 years	≥65 years
n	269	14	237	20
Microbiological Eradication Rate (TMER)	93.8%	85.7%	89.2%	94.7%
95% CI of TMER	(90.86%, 96.74%)	(67.36%, 100.00%)	(85.21%, 93.19%)	(84.63%, 100.00%)
Percent Failures (%)	6.2%	14.3%	10.8%	5.3%

Treatment Difference (Proquin™ - Cipro® IR)	4.60%	-9.00%		
P value	(<0.0001)	(0.461)		
95% CI TMER	(-0.36%, 9.56%)	(-29.92%, 11.92%)		
<b>BY RACE</b>				
	<b>TREATMENT GROUP</b>			
	<b>Proquin™</b>		<b>Cipro® IR</b>	
	Caucasians	Non-Caucasians	Caucasians	Non-Caucasians
n	226	57	215	42
Microbiological Eradication Rate (TMER)	94.4%	89.3%	90.0%	88.1%
95% CI of TMER	(91.33%, 97.47%)	(81.20%, 97.40%)	(85.93%, 94.07%)	(78.31%, 97.89%)
Percentage Failures (%)	5.6%	10.7%	10.0%	11.9%
Treatment Difference (Proquin™ - Cipro® IR)	4.40%	1.20%		
P value	(<0.001)	(0.041)		
95% CI TMER	(-0.69%, 9.49%)	(-11.51%, 13.91%)		

2. Based upon what is known about exposure-response relationships and their variability, and the groups studied, healthy volunteers vs. patients vs. specific populations (examples shown below), what dosage regimen adjustments, if any, are recommended for each of these groups? If dosage regimen adjustments are not based upon exposure-response relationships, describe the alternative basis for the recommendation.

#### *Elderly*

For elderly patients, dosage adjustment is not needed. Following a 500mg dose of Proquin™, ciprofloxacin AUC<sub>0-t</sub> and C<sub>max</sub> values in elderly subjects were found to be slightly higher (by 20 and 24%, respectively) compared to those in younger subjects enrolled in reference PK studies with a comparable protocol design. Both the mean/median T<sub>max</sub> values and the elimination half-lives of elderly subjects were comparable to those in the younger subjects of the reference study. However, the percentage of the ciprofloxacin dose excreted into the urine was lower (by about 11%) in elderly subjects than in younger subjects.

#### *Pediatric patients*

No dosage recommendations.

The clinical trials included only female adult patients because uncomplicated urinary tract infections (uUTIs) are not prevalent in children or in male adults. The occurrence of UTI or cystitis in a child is almost always caused by anatomic or congenital abnormalities, a neurogenic bladder, and/or diabetes mellitus. Thus, a pediatric waiver was requested by the sponsor. The conduct of future pharmacokinetic studies involving pediatric patients is thus a remote possibility.

#### *Gender*

Dosage adjustment based on gender is not needed. Although there was no dedicated study to evaluate the influence of gender on ciprofloxacin pharmacokinetics in subjects who took Proquin™, a comparative analysis of female and male healthy volunteers enrolled in the steady-state PK study (Study 81-0026) suggested that there were no gender-dependent statistically significant PK differences that would warrant dosage adjustment based on gender.

#### *Race*

Dosage adjustments based on race are not needed. Although there was no dedicated study to evaluate the influence of race on ciprofloxacin pharmacokinetics in subjects who took Proquin™, a comparative analysis of healthy Asians, Blacks and Caucasians enrolled in the steady-state PK study (Study 81-0026) suggested that there were no race-dependent statistically significant plasma and urinary PK differences that would warrant dosage adjustment based on race.

#### *Renal impairment*

From the findings of the study involving subjects with normal renal function, mild and moderate renal impairment, dosage adjustment is not needed in patients with mild to moderate renal impairment. The systemic exposures (as AUC<sub>0-t</sub>) of ciprofloxacin in subjects with mild and moderate renal impairment were 42% and 54% higher, respectively, compared to subjects with normal renal function. The total ciprofloxacin clearance values for those with normal renal function, those with mild renal impairment and those with moderate renal impairment were 56, 41 and 39 mL/min, respectively.

Based on literature information, the 2-fold increase in ciprofloxacin t<sub>1/2</sub> is similar to the 1.7-fold and 1.66-fold increase in t<sub>1/2</sub> observed in subjects in Study 81-0036 with mild renal impairment and moderate renal impairment, respectively. Based on labeling information available for CIPRO® immediate release and modified-release dosage forms, patients with severe renal impairment (those with creatinine clearance <30 mL/min) should receive up to 500 mg q24 h for the treatment of uUTI and patients with ESRD should receive a ciprofloxacin dose of 500 mg q18h. Thus, although no studies were conducted to evaluate ciprofloxacin PK in subjects with severe renal impairment following a Proquin™ 500mg dose, it is assumed that the same dosing recommendation applies to Proquin™ 500mg because the total exposure (both AUC and C<sub>max</sub>) from Proquin™ is similar, if not slightly lower than that achieved from CIPRO® IR.

#### *Hepatic impairment*

The sponsor of Proquin™ did not conduct a clinical study to evaluate ciprofloxacin pharmacokinetics in patients with hepatic impairment. Labeling information available for other ciprofloxacin dosage forms indicates that dosage adjustment is not required in patients with stable chronic cirrhosis, as well as that ciprofloxacin pharmacokinetics in patients with acute hepatic insufficiency have not been fully elucidated.

#### *Pregnancy and Lactation*

No recommendations. Based on labeling information available for other dosage forms of ciprofloxacin, ciprofloxacin is excreted in breast milk, as well as that the safety of ciprofloxacin use in pregnant women had not been established.

*What pharmacogenetics information is there in the application and is it important or not?*

There was no pharmacogenetics information in this NDA submission.

#### **D. Extrinsic Factors**

1. *What extrinsic factors (drugs, herbal products, diet, smoking, and alcohol use) influence dose-exposure and/or response and what is the impact of any differences in exposure on response?*

The effect of smoking (a CYP1A2 inducer) on the pharmacokinetics of ciprofloxacin from Proquin™ was not investigated. Only non-smoking subjects were included in the clinical pharmacology studies conducted by the sponsor of Proquin™.

2. *Drug-Drug Interactions*

- a) *Is the drug a substrate of CYP enzymes?*

Prototyping studies were not conducted by the sponsor to identify which CYP450 enzymes are responsible for the metabolism of ciprofloxacin to at least four less active metabolites, namely oxociprofloxacin (M1), sulfociprofloxacin (M2), desethyleneciprofloxacin(M3), and formylciprofloxacin (M4), which are all excreted to a similar extent in the urine and feces.

- b) *Is there an in-vitro basis to suspect in vivo drug-drug interactions? Are there any in-vivo drug-drug interaction studies that indicate the exposure alone and/or exposure-response relationships are different when drugs are co-administered? Is the drug an inhibitor and/or an inducer of CYP enzymes?*

### Inhibition of CYP450 –Mediated Metabolism

The findings of the *in vitro* drug interaction study (Study 84-002) conducted by the sponsor indicated that ciprofloxacin, at test concentrations ranging from 0.3 to 90  $\mu\text{M}$ , had no significant inhibitory effect on the activities of CYP3A4, CYP2C19, and CYP2D6. Table 29 presents the values for percent activity remaining relative to the negative control in each CYP-isoenzyme-specific assay at each concentration of ciprofloxacin. The study did not include positive controls of CYP450 inhibition.

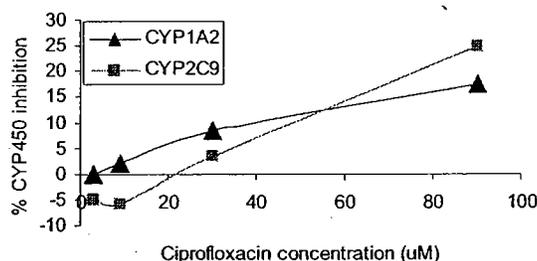
At 90  $\mu\text{M}$  (approximately 36x the plasma  $C_{\text{max}}$  in healthy volunteers), the resulting decrease in the metabolism of probe substrates for CYP1A2 and CYP2C9 were only 18% and 25%, respectively. However, concentration-related increases in CYP1A2- and CYP2C9-mediated metabolism were observed *in vitro* (Figure 12).

**TABLE 29**  
Effect of ciprofloxacin on CYP450 activity

CYP450 enzyme	Probe substrate (concentration)	Metabolite assayed	Percent of activity remaining*						
			Ciprofloxacin concentration ( $\mu\text{M}$ )						
			0	0.3	0.9	3	9	30	90
CYP1A2	Phenacetin (100 $\mu\text{M}$ )	acetaminophen	NA	103	100	101	97.9	91.7	82.5
CYP2C9	Diclofenac (10 $\mu\text{M}$ )	4'-hydroxydiclofenac	NA	95.5	105	97.8	106	96.5	75.3
CYP2C19	S-Mephenytoin (50 $\mu\text{M}$ )	4'-hydroxymephenytoin	NA	106	105	107	104	107	115
CYP2D6	Bufuralol (10 $\mu\text{M}$ )	1'-hydroxybufuralol	NA	105	105	103	101	109	120
CYP3A4	Testosterone (50 $\mu\text{M}$ )	6 $\beta$ -hydroxytestosterone	NA	99.1	99.0	101	95.6	101	98.6
	Midazolam (5 $\mu\text{M}$ )	1'-hydroxymidazolam	NA	93.4	95.2	102	107	102	102

NA- not applicable  
\* average of triplicate values

**FIGURE 12**  
Relationship between ciprofloxacin concentration and Inhibitory Effects of ciprofloxacin on CYP1A2 and CYP2C9 metabolic activities



It is important to note that in the literature, the potential of ciprofloxacin to decrease the clearance of CYP1A2 substrates (e.g., theophylline, caffeine, tizanidine) in humans have been demonstrated. The findings of pharmacokinetic studies suggest that ciprofloxacin inhibits hepatic demethylation (but not hydroxylation) of theophylline and such effect is dependent on the level of CYP1A2 expression in the individual subjects. *In vitro*, ciprofloxacin was able to inhibit the demethylation of theophylline or caffeine (as the probe CYP1A2 substrate) significantly (at least by 70%) only at high test concentrations (500, 1000 and 2000  $\mu\text{g/mL}$ ) but not at lower test concentrations (10 and 100  $\mu\text{M}$ ; Sarkar et al., 1990; Fuhr et al, 1992 ). Thus, it is not known whether ciprofloxacin achieves hepatocyte concentrations that are much higher than that achieved in systemic circulation, thereby allowing ciprofloxacin to cause substantial inhibition of the hepatic metabolism of CYP1A2 substrates *in vivo*. If this were true, a maximum inhibitory effect on the metabolism of the CYP1A2 substrate drug would be achieved when the other drug is co-administered around the time of peak ciprofloxacin concentrations. This was the case in the tizanidine drug interaction study that showed that when given 1 hour after ciprofloxacin [ $T_{\text{max}}$  0.5 to 1 hour], tizanidine AUC increased by 10-fold and  $C_{\text{max}}$  by 7-fold (Granfors et al., 2004).

Based on the observed poor relationship between *in vitro* and *in vivo* metabolic inhibitory effects of ciprofloxacin on CYP1A2 enzyme activity, the potential of ciprofloxacin to inhibit the metabolism of drugs that are CYP2C9 substrates cannot be ruled out at this time. In connection with this, it is important to note that although there is conflicting data in the literature, there have been reports of the potential of ciprofloxacin to enhance the pharmacodynamic effects of warfarin (a CYP2C9/CYP3A4 substrate), especially in elderly patients under long-term anticoagulant therapy and being treated with ciprofloxacin for infection.

#### Induction of CYP450-Mediated Metabolism

In Study 84-0003, the sponsor evaluated the CYP450 induction potential of ciprofloxacin using primary cultures of human hepatocytes. Table 30 summarizes the fold-induction data on CYP1A2, CYP2C9 and CYP3A enzyme activities by ciprofloxacin (0.45  $\mu$ M to 45  $\mu$ M), as well as by the positive inducer controls. Ciprofloxacin (at concentrations of 0.45 to 45  $\mu$ M) did not induce CYP2C or CYP3A activities of primary cultures of human hepatocytes. At 45  $\mu$ M (approximately equivalent to 18x the  $C_{max,ss}$  in healthy volunteers who received Proquin™ 500 mg OD for 3 days), ciprofloxacin showed a weak induction effect on CYP1A2. Because the effect was <40% of that produced by the positive inducer control (omeprazole 30  $\mu$ M), ciprofloxacin is not projected to cause *in vivo* induction of the metabolism of CYP1A2 substrates. To date, the literature provides no evidence of such interactions precipitated by ciprofloxacin *in vitro* or *in vivo*.

**TABLE 30**  
**Fold-induction on CYP1A2, CYP2C9 and CYP3A enzyme activities**  
**by ciprofloxacin (0.45  $\mu$ M to 45  $\mu$ M), in comparison with the positive inducer controls**

CYP1A2	0.5% v/v DMSO	Omeprazole (30 $\mu$ M)	Ciprofloxacin		
			0.45 $\mu$ M	4.5 $\mu$ M	45 $\mu$ M
mean	0	12.90	0.90	1.33	1.80
sd	0	7.72	0.10	0.25	0.46
CYP2C9	0.5% v/v DMSO	Rifampin (50 $\mu$ M)	Ciprofloxacin		
			4.5 $\mu$ M	4.5 $\mu$ M	4.5 $\mu$ M
mean	0	4.10	1.00	1.20	1.00
sd	0	0.80	0.36	0.46	0.30
CYP3A	0.5% v/v DMSO	Rifampin (50 $\mu$ M)	Ciprofloxacin		
			4.5 $\mu$ M	4.5 $\mu$ M	4.5 $\mu$ M
mean	0	3.43	1.13	1.20	1.17
sd	0	1.33	0.31	0.44	0.15

#### c) Is there a known mechanistic basis for pharmacodynamic drug-drug interactions?

There is conflicting evidence in the literature regarding the potential of ciprofloxacin to affect the pharmacokinetics and pharmacodynamics of warfarin. The two-way, single dose drug interaction study conducted by the sponsor (Study 81-0035) failed to show any influence on the exposures of ciprofloxacin and the R- and S- enantiomers of warfarin, as well as the PD of warfarin. Likewise, prospective single-dose and multiple dose PK and PK/PD studies in healthy volunteers or patients on short-term or long-term coagulation therapy with warfarin have failed to corroborate adverse event reports and some literature evidence of a PD-based drug interaction between ciprofloxacin and warfarin (e.g., case reports). Several reviews have advocated alternative mechanisms; the hypoprothrombinemic effect observed in patients taking warfarin and ciprofloxacin may not be due to ciprofloxacin-mediated inhibition of warfarin metabolism. According to at least 3 publications, infection or fever may increase PT in anticoagulated patients, possibly via inhibition of hepatic metabolism by interferon. An alternative explanation for the

interaction between warfarin and various antibiotics is that some antibiotics like ciprofloxacin have the ability to destroy intestinal flora that synthesize vitamin K and the resulting decrease in the activity level of vitamin K is responsible for enhancing warfarin's anticoagulant effect.

Based on case reports submitted to the FDA, totaling 66 from 1987 to 1997, the drug interaction may occur 2—16 days following the addition of quinolone therapy to a patient receiving warfarin therapy. The mean time to coagulopathy was 5.5 days. Such interactions occurred mostly in elderly patients with several medical problems leading some to attribute the alterations in warfarin PD on risk factors (e.g., fever, infection, congestive heart failure, thyroid disease, polypharmacy). Thus, as is the case with other fluoroquinolones, Proquin™ should be administered with caution in patients receiving coumarin anticoagulant therapy and prothrombin time and international normalized ratio (INR) should be monitored very closely.

### E. General Biopharmaceutics

1. *What is the relative bioavailability of the proposed to-be-marketed formulation to the formulation used in the pivotal clinical trial?*

The same formulation (different lot number) used in the clinical pharmacology studies reviewed was used in the pivotal clinical efficacy trials. The lot number and the assay potency (% of label claim, if available) of Proquin™ and Cipro® immediate-release oral formulations used in these clinical studies are presented in the following table:

TABLE 31

STUDY	PROQUIN™		CIPRO® 250 mg	
	Lot Number	Assay Potency	Lot Number	Assay Potency
81-0025 Single-dose PK	HT3602		54002PR	NA
81-0026 Multiple-dose PK	HT3602		54002PR	NA
81-0005 Efficacy/Safety	010036		OLDV	NA
81-0015 Efficacy/Safety	HT360R, HT361R, HT362R		2500C7X	NA

NA-not available

2. *What is the effect of food on the bioavailability (BA) of ciprofloxacin from Proquin™?*

A high-fat meal increased the systemic and urinary bioavailability of ciprofloxacin and metabolites from orally administered Proquin™ 500 mg. Table 32 compares the pharmacokinetic parameters for ciprofloxacin in the plasma and Tables 33A to 33D compares PK parameters in the urine under fasted versus fed conditions. The ciprofloxacin AUC was higher by 170% and the cumulative urinary excretion of the unchanged drug was higher by 154% (with smaller variability) when given with a high-fat meal compared to when given under fasted conditions. Both the ciprofloxacin mean T<sub>max</sub> in the plasma and the mean T<sub>max,rate</sub> in the urine were longer (by 2.2 hours and by 2.7 hours, respectively), under fed conditions.

TABLE 32  
Pharmacokinetic Parameters for Ciprofloxacin in Plasma

Pharmacokinetic Parameter	Ciprofloxacin GR™ 500 mg Tablets – fasted (Test) (n=27) Geometric mean (%CV)	Ciprofloxacin GR™ 500 mg Tablets - fed (Reference) (n=27) Geometric mean (%CV)	p-value
AUC <sub>0-8</sub> (ng·hr/mL) §	2687.3 (51.7)	7246.0 (24.6)	< 0.0001 <sup>†</sup>
AUC <sub>0-12</sub> (ng·hr/mL) §	2961.9 (48.0)	7587.8 (24.2)	< 0.0001 <sup>†</sup>
C <sub>max</sub> (ng/mL) §	482.8 (50.8)	1064.0 (36.1)	< 0.0001 <sup>†</sup>
T <sub>max</sub> (hr) §	2.30 ± 0.74 <sup>†</sup> 2.50*	4.49 ± 2.32 <sup>†</sup> 4.00*	0.0002
t <sub>1/2</sub> (hr) §	5.07 ± 1.61 <sup>†</sup>	4.89 ± 1.10 <sup>†</sup>	0.448

\* Median values

† Mean ± SD

‡ The p-value is from ANOVA on ln-transformed data

TABLE 33A  
Summary of Pharmacokinetic Results for Ciprofloxacin in Urine

Pharmacokinetic Parameter	Ciprofloxacin GR™ 500 mg Tablets – fasted (Test) (n=27) mean ± SD	Ciprofloxacin GR™ 500 mg Tablets - fed (Reference) (n=27) mean ± SD	p-value
T <sub>max</sub> Rate (hr) §	3.44 ± 1.50	6.15 ± 2.73	< 0.0001
Max Rate (mg/hr) §	13.99 ± 7.97	29.46 ± 12.20	< 0.0001
Ae (mg) §	69.5 (52.9) <sup>†</sup>	176.4 (20.2) <sup>†</sup>	< 0.0001
CL <sub>r</sub> (L/hr) §	24.12 ± 5.57	23.97 ± 6.05	0.922
%Dose §	16.02 ± 8.48	36.07 ± 7.29	< 0.0001

† Geometric mean (%CV)

TABLE 33B  
Summary of Pharmacokinetic Results for Desethyleneciprofloxacin (M1) in Urine

Pharmacokinetic Parameter	Ciprofloxacin GR™ 500 mg Tablets – fasted (Test) (n=27) mean ± SD	Ciprofloxacin GR™ 500 mg Tablets - fed (Reference) (n=27) mean ± SD	p-value
T <sub>max</sub> Rate (hr) §	4.41 ± 1.99	7.30 ± 3.01	< 0.0001
Max Rate (mg/hr) §	0.18 ± 0.08	0.29 ± 0.10	< 0.0001
Ae (mg) §	0.9 (59.6) <sup>†</sup>	2.2 (30.7) <sup>†</sup>	< 0.0001
%Dose §	0.23 ± 0.14	0.51 ± 0.16	< 0.0001

† Geometric mean (%CV)

TABLE 33C  
Summary of Pharmacokinetic Results for Sulfociprofloxacin (M2) in Urine

Pharmacokinetic Parameter	Ciprofloxacin GR™ 500 mg Tablets – fasted (Test) (n=27) mean ± SD	Ciprofloxacin GR™ 500 mg Tablets - fed (Reference) (n=27) mean ± SD	p-value
T <sub>max</sub> Rate (hr) §	3.74 ± 1.85	6.07 ± 2.84	0.0002
Max Rate (mg/hr) §	1.46 ± 1.10	3.06 ± 1.40	< 0.0001
Ae (mg) §	5.5 (66.5) <sup>†</sup>	15.5 (38.3) <sup>†</sup>	< 0.0001
%Dose §	1.11 ± 0.74	2.70 ± 1.03	< 0.0001

† Geometric mean (%CV)

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TABLE 33D  
Summary of Pharmacokinetic Results for Oxociprofloxacin (M3) in Urine

Pharmacokinetic Parameter	Ciprofloxacin GR <sup>TM</sup> 500 mg Tablets – fasted (Test) (n=27) mean ± SD	Ciprofloxacin GR <sup>TM</sup> 500 mg Tablets – fed (Reference) (n=27) mean ± SD	p-value
T <sub>max</sub> Rate (hr) §	3.89 ± 1.78	6.37 ± 2.71	<0.0001
Max Rate (mg/hr) §	1.38 ± 0.68	2.51 ± 1.07	<0.0001
Ae (mg) §	7.1 (50.5) <sup>†</sup>	16.3 (27.2) <sup>†</sup>	<0.0001
% Dose §	1.55 ± 0.78	3.27 ± 0.89	<0.0001

<sup>†</sup>Geometric mean (%CV)

3. Was a fed BE study conducted? What dosing recommendation should be made, if any, regarding administration of the Proquin<sup>TM</sup> in relation to meals or meal types? How do the inconsistencies in the fat content of the co-administered meal and the use of a fluid control measure in the clinical pharmacology studies and clinical trials influence the findings?

Yes, the bioequivalence studies and all other clinical pharmacology studies comparing Proquin<sup>TM</sup> 500 mg OD to Cipro® 250 mg BID were conducted under fed conditions (with high-fat or moderate-fat meal; with or without fluid control). In the clinical efficacy/safety trials, patients with uncomplicated UTI were instructed to take the medication and placebo tablets twice daily, either after dinner or after breakfast.

Overall, when given with a high-fat meal, Proquin<sup>TM</sup> 500 mg OD was bioequivalent to Cipro® IR 250 mg BID, in terms of systemic exposure (AUC but not C<sub>max</sub>) and cumulative urinary excretion of ciprofloxacin and major metabolites.

In the clinical pharmacology studies, there was inconsistency as to the fat-content of the meal and the use of a fluid control measure wherein 100 mL or 200mL drinking water was taken every hour or every 2 hours until 24 hours post-dose. There were no formal studies conducted to evaluate the potential of the fat content of the meal and/or the fluid control measure to influence the PK of ciprofloxacin. The reviewer conducted a cross-study comparison of ciprofloxacin PK parameters (AUC<sub>0-24h</sub>, C<sub>max</sub>, and T<sub>max</sub>), taking into consideration the fat-content of the co-administered meal and the presence/absence of the fluid control measure (Table 34).

With a moderate-fat meal, the oral bioavailability of Proquin<sup>TM</sup> is expected to be slightly lower than when given with a high-fat meal, i.e., with a moderate-fat meal (IVVC Study; 81-0029), the AUC<sub>0-24h</sub> of Proquin<sup>TM</sup> 500mg tablet was about 89% of the AUC<sub>0-24h</sub> of Cipro® 500mg immediate release tablet on Day 1 whereas when given with a high-fat meal, it was about 92% and 98% of Cipro® 250mg BID on Day 1 and Day 3 of dosing, respectively. However, it appears from the non-inferiority findings of the clinical trial that any such differences in the oral bioavailability of Proquin<sup>TM</sup> (as a consequence of differences in fat content of meals taken concomitantly with the Proquin<sup>TM</sup>) would have not been clinically significant. Although the C<sub>max</sub> of the reference (immediate-release) Cipro® treatment would have been slightly reduced by its co-administration with food in the trial, according to the label of Cipro®, the over-all absorption would have not been significantly altered.

Assuming there were no other significant experimental sources of variation among these studies, it can be concluded, especially from a comparison of the two antacid drug interaction studies conducted, that there was no trend or significant difference observed in the C<sub>max</sub>, T<sub>max</sub>, and AUC<sub>0-24h</sub> of ciprofloxacin from Proquin<sup>TM</sup> that could be strongly attributed to the influence of fluid control or lack thereof.

TABLE 34

Study	Fat content of the meal administered with Proquin™	Fluid control? (Yes/No)	Cmax <sup>a,b</sup> (ng/mL)	Tmax (h)	AUC <sub>0-24h</sub> <sup>a,b</sup> (ng*h/mL)
Drug Interaction with Omeprazole (81-0027)	moderate	Y	1272	3.95	7723
Drug Interaction with Antacids 1 (81-0028)	moderate	Y	1041	4.45	7405
Drug Interaction with Antacids 2 (81-0033)	moderate	N	1206	4.10	7449
Drug Interaction with Coumadin (81-0035)	moderate	N	819	4.89	7242
IVIVC (81-0029)	moderate	N	1274	4.56	8336

<sup>a</sup> Geometric mean; Dose-normalized to 500 mg

<sup>b</sup> For Drug Interaction Studies: The PK parameter values are for Proquin™ alone (without the other drug).

4. How do the dissolution conditions and specifications assure *in vivo* performance and quality of the product?

Establishment of a Level A IVIVC

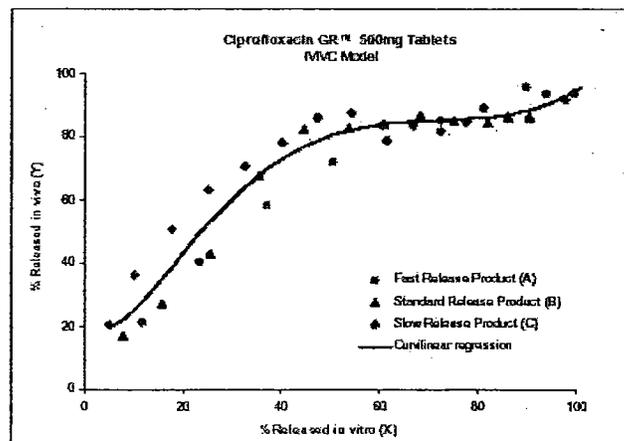
Using a numerical deconvolution method, the *in vivo* release kinetics of ciprofloxacin from the tested formulations (Fast-release, Standard-release, and Slow-release) was calculated from their plasma concentration levels obtained from healthy volunteers in Study 81-0029. The percentages released *in vivo* were plotted against percent released *in vitro* for the same time points from the three test formulations (Figure 13; data summarized in Table 35). The resulting polynomial function describing the correlation of % released *in vitro* (X) and % released *in vivo* (Y) was obtained:

Regression equation:

$R^2 = 0.94$

FIGURE 13

Correlation between percent released *in vivo* (Y-axis) and percent released *in vitro* (X-axis)



**TABLE 35**  
**In-Vitro and In-Vivo Drug Release Data used in IVIVC Model**



*Setting Biorelevant In-vitro Release Specifications from the Level A IVIVC Model*  
 Based on the established Level A In-Vitro - In-Vivo Correlation (IVIVC), the following *in vitro* release specifications were proposed for Proquin™ extended release ciprofloxacin dosage form. These *in vitro* drug release specifications are acceptable.

**TABLE 36**  
***In vitro* release specifications for Proquin™ 500mg Tablets**

Time (h)	Lower limit (%)	Upper limit (%)
2	/	/
4	/	/
7	/	/

USP dissolution apparatus I (basket, 100 rpm, 37°C)  
 Medium: 900 mL 0.1N hydrochloric acid

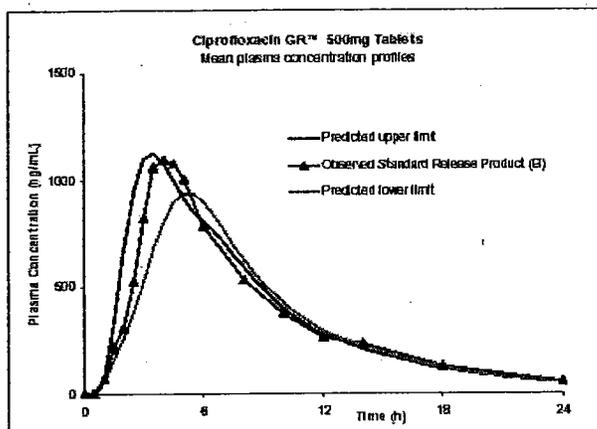
The *in vitro* release profiles of the theoretical side batches are plotted in Figure 14 together with the profile of the biobatch (Standard Release Product) tested *in vivo*.

**FIGURE 14**  
*In vitro* release product specifications, constructed profiles of side batches (upper and lower limits) and measured Proquin™ 500mg Tablets (Standard Release Product) tested *in vivo*



The simulated plasma concentration profiles for these theoretical side batches are compared with the plasma concentrations observed *in vivo* in Figure 15.

FIGURE 15  
Predicted plasma profiles for side batches (upper and lower limits)  
compared with plasma concentrations of Proquin™ 500mg  
Tablets (Standard Release Product) observed *in vivo*



The calculated bioequivalence parameters for these side batches are summarized in the table below. The resulting ratios between predicted and observed values, defined as relative bioavailability, meet the acceptable bioequivalence range criteria. Based on these values, the theoretical side batches are bioequivalent to Proquin™ standard-release tablets.

TABLE 37

PK-parameters	Relative bioavailability (%)				
	Predicted UL	Predicted LL	Observed Standard (B)	UL/Standard	LL/Standard
C <sub>max</sub> (ng/mL)	1125.516	936.521	1032.319	103.0	85.7
AUC <sub>(0-24h)</sub> (ng.h/mL)	8876.28	7993.95	8355.32	108.2	95.7

## F. Analytical Section

1. How are the active moieties identified and measured in the plasma and urine in the clinical pharmacology and biopharmaceutics studies? Which metabolites have been selected for analysis and why?

A validated HPLC assay method with fluorescence detection was employed for the analysis of ciprofloxacin in plasma samples, and of ciprofloxacin and its four major metabolites, desethyleneciprofloxacin (M1), sulfociprofloxacin (M2), oxociprofloxacin (M3), and fomylciprofloxacin (M4) in urine samples.

2. What bioanalytical methods are used to assess concentrations?

The validated method C25-01a was used to analyze the plasma samples; C26-00a was used for the urine samples. The following table provides a description of the assay conditions.

TABLE 38

Sample Preparation and Assay conditions	C25-01a	C26-00a
Sample Preparation		
Assay	Reversed-phase HPLC	Reversed-phase HPLC
HPLC Column		
Mobile phase		
Flow rate		
Injection volume		
Internal standard		
Detector		

- a) *What is the range of the standard curves? How do these ranges relate to the requirements for clinical studies? What curve fitting techniques were used?*

The assay method was valid in the range of 24.999 ng/mL to 6399.730 ng/mL  $\pm$  10% for ciprofloxacin in human plasma; the average  $r^2$  for 5 standard curves was 0.9996. In human urine, the assay method was valid from 1.500 mcg/mL to 15.001 mcg/mL for ciprofloxacin, and 0.500 mcg/mL to 5.000 mcg/mL for the metabolites. At almost all urine (and plasma?) sampling time points, the formylciprofloxacin (M4) was below the limit of quantification (BLQ).

- b) *What are the lower and upper limits of quantification (LLOQ/ULOQ)?*

The lower limit of quantification (LLOQ) for ciprofloxacin was 24.986 ng/mL and 1.5 mcg/mL in plasma and urine samples, respectively. The LLOQ for all the metabolites in the urine were 0.5 mcg/mL.

- c) *What is the accuracy, precision and selectivity at these limits?*

**Intra-Batch Accuracy and Precision.** The mean for each quality control level and the LLOQ had a relative error from the theoretical ranging from 0.9% to 1.8% and coefficient of variation ranging from 1.4% to 5.4%.

**Inter-Batch Accuracy and Precision.** The percent coefficient of variation for each QC sample and the LLOQ for five consecutive assay runs was determined with values ranging from 1.8% to 4.6%. The relative error of the mean ranged from 0.3% to 2.4%.

**Selectivity.** None of the 7 individual sources of human plasma samples (potassium EDTA as anticoagulant) showed significant interfering peaks at the retention time of ciprofloxacin or the internal standard. In addition, common Over-the-Counter (OTC) drugs and Oral Contraceptives (OC) tested did not present any interfering peaks with ciprofloxacin and the internal standard.

- d) *What is the absolute recovery of ciprofloxacin from the plasma samples?*

The overall recovery for ciprofloxacin was 83.1% with a mean CV of 3.3%.

- e) *What is the sample stability under the conditions used in the study?*

*Freeze-thaw Stability.* Ciprofloxacin at  $-25^{\circ}\text{C} \pm 10^{\circ}\text{C}$  and  $-70^{\circ}\text{C} \pm 10^{\circ}\text{C}$  in human plasma was stable for three freeze-thaw cycles.

*In-Process Stability.* Ciprofloxacin showed no loss of response within four hours at room temperature.

*Autosampler Stability.* Ciprofloxacin was stable in extracted samples for up to approximately 95 hours at room temperature.

*Long-term Stability.* Ciprofloxacin in human plasma at  $-25^{\circ}\text{C} \pm 10^{\circ}\text{C}$  and  $-70^{\circ}\text{C} \pm 10^{\circ}\text{C}$  will be determined with QC samples at QC High and QC Low levels (Data not available at the time of NDA submission).

e) *What is the QC sample plan?*

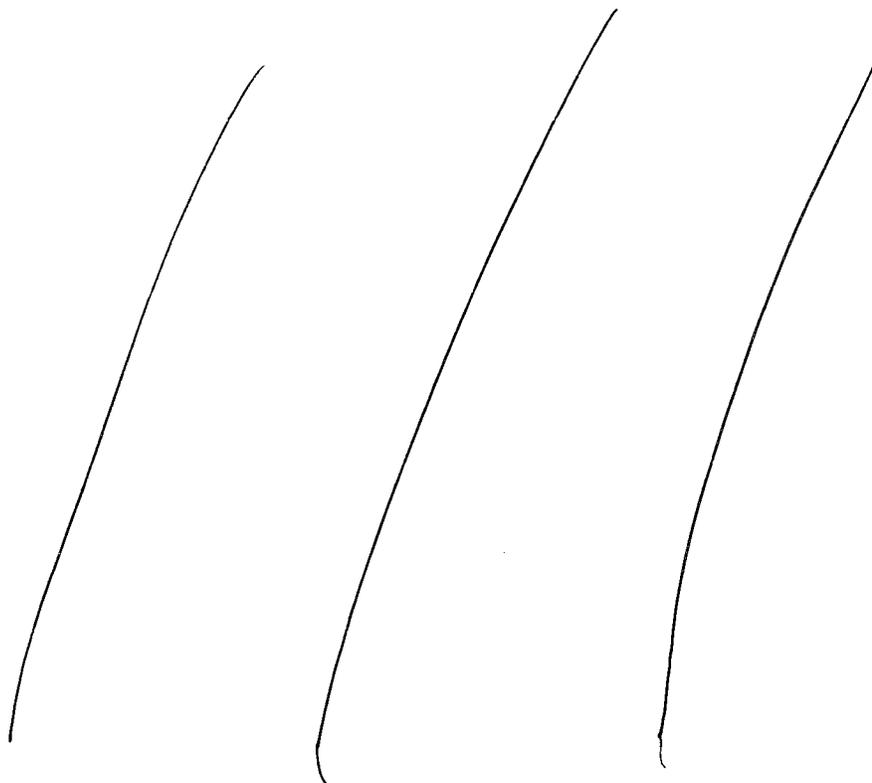
The assay was validated against three quality control samples that were freshly prepared. The concentrations of the ciprofloxacin in plasma QC Low, QC Med, and QC High were, 74.9997, 1199.96, and 4799.8ng/mL. The concentrations of the QC samples in urine are tabulated below:

ID	Ciprofloxacin	M1	M2	M3	M4
QC High	12.001	4.000	4.000	4.000	4.000
QC Med	3.750	1.250	1.250	1.250	1.250
QC Low	3.000	1.000	1.000	1.000	1.000

#### **IV. Labeling Recommendations**

The reviewer's recommended labeling changes were interspersed in the proposed package insert below. Deleted text appears with a strikethrough. Added text is marked with a double underscore.

#### **V. Appendices**



34 Page(s) Withheld

       Trade Secret / Confidential

✓ Draft Labeling

       Deliberative Process

## B. Individual Study Reviews

### Study 81-0025

#### A Two-Way Crossover, Open-Label, Single-Dose, Fed, Bioavailability Study To Compare Proquin™ 500 mg (qd) Tablets with Cipro® 250 mg (bid) Tablets in Healthy Non-Smoking Male and Female Subjects

##### **Objective:**

To assess the relative bioavailability of ciprofloxacin from Proquin™ (Gastric Retentive) 500 mg Tablets (single dose) versus Cipro® immediate-release 250 mg Tablets (twice daily x 2 doses)

##### **Study population:**

Twenty-eight normal, non-smoking male/female (1:1) subjects with mean age of 35 (20 to 52 years) were enrolled in the study. The mean weight was 71 kg (58 to 92 kg). There were 19 Caucasians, 2 Asians, and 7 Blacks. All but one of these subjects completed the study.

##### **Dosing and Administration:**

Following a fast of at least 4 hours, one of the following treatments were received with 240 mL of water per treatment period, 30 minutes after the start of a standardized, approximately 1000 calorie, high-fat (~50%) content meal. The wash-out period between treatments was 6 days.

Treatment A: Ciprofloxacin 500 mg Tablet (Lot #: HT3602; potency —, of label claim), once daily after dinner

Treatment B: CIPRO® 250 mg Tablet (Lot #: 54002PR) twice daily after breakfast and dinner

**Fluid control measure:** Water (100 mL) was administered at each of the following time points: 2.0, 3.0, 4.0, 5.0, 6.0, 7.0, 8.0, 9.0, 10.0, 12.0 (Treatment A only), 14.0, 16.0, 18.0, 20.0, 22.0, and 24.0 hours post-drug administration. After 24 hours post-dose, water will be permitted *ad libitum*.

##### **Pharmacokinetic sampling:**

**Blood** samples will be collected based on the following schedule:

Treatment A: 0.0 (pre-dose), 0.5, 1.0, 1.5, 2.0, 3.0, 3.5, 4.0, 4.5, 5.0, 6.0, 9.0, 12.0, 14.0, 18.0, 24.0 and 36.0 hours post-drug administration.

Treatment B: 0.0 (pre-dose), 0.5, 1.0, 1.5, 2.0, 2.5, 3.0, 3.5, 4.0, 5.0, 6.0, 9.0, 12.0 (pre-dose), 12.5, 13.0, 13.5, 14.0, 14.5, 15.0, 15.5, 16.0, 17.0, 18.0, 21.0, 24.0, 30.0, and 36.0 hours post-drug administration.

**Urine** (at least 20 mL per time interval) will be collected as follows:

##### Treatments A and B:

Pre-dose (complete void and collect), 0.0-2.0, 2.0-4.0, 4.0-6.0, 6.0-8.0, 8.0-10.0, 10.0-12.0, 12.0-14.0, 14.0-16.0, 16.0-18.0, 18.0-24.0, 24.0-36.0 hours first post-dose.

##### **Criteria for evaluation:**

###### Pharmacokinetics

The following pharmacokinetic parameters for ciprofloxacin were calculated by standard non compartmental methods from **plasma** profiles:

- Area under the concentration-time curve from time zero to the time of dosing interval ( $AUC_T$ )
- maximum plasma concentration after dosing ( $C_{max}$ ),
- concentration at the end of a dosing interval during multiple dosing ( $C_{min}$ )
- average plasma concentration in a dosing interval during multiple dosing ( $C_{ave}$ )
- time to reach peak plasma concentration ( $T_{max}$ )
- plasma half-life ( $t_{1/2}$ )

The following pharmacokinetic parameters for ciprofloxacin, desethylene ciprofloxacin (M1), sulfociprofloxacin (M2), oxociprofloxacin (M3), and formylciprofloxacin (M4) were calculated by standard non-compartmental methods from **urine** profiles:

- amount excreted in urine (Ae)
- maximum observed excretion rate (Max Rate)
- midpoint of collection interval associated with the maximum observed excretion rate ( $T_{\max}$  Rate).
- fractions of total dose recovered in urine (% Dose)
- Renal clearance (Cl<sub>r</sub>) - for ciprofloxacin only

#### Safety

- Adverse events
- Vital signs
- ECGs
- Laboratory parameters
- Physical examinations

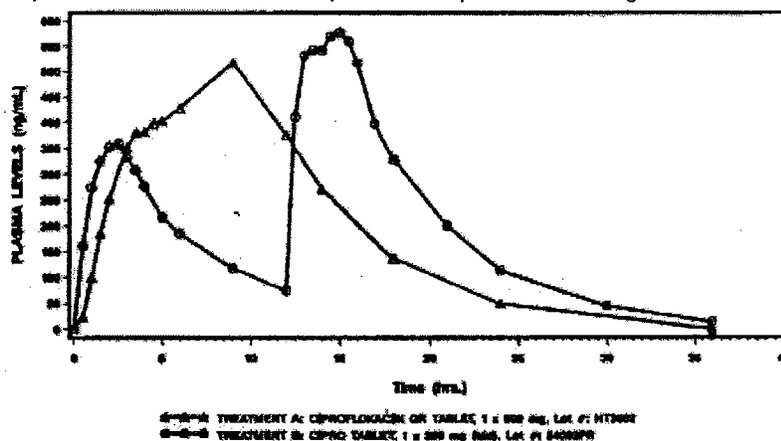
#### Statistical Analysis:

- ANOVA was performed on ln transformed AUC<sub>0-t</sub>, AUC<sub>0-inf</sub> and C<sub>max</sub>, and untransformed T<sub>max</sub> and t<sub>1/2</sub>, at a level of significance of 0.05.
- The ratio of geometric means and the 90% geometric confidence interval (90% C.I.) were calculated based on the difference in the Least Squares Means of the plasma AUC<sub>0-t</sub>, AUC<sub>0-inf</sub> and C<sub>max</sub> between the test and reference treatments.
- ANOVA was performed on Ae, %Dose, Max Rate, and T<sub>max,rate</sub> at a level of significance of 0.05.

#### Results and Discussion:

##### Pharmacokinetics

Mean ciprofloxacin plasma concentration time profiles are presented in Figure 16.



The following tables summarize the plasma and urine pharmacokinetic parameters of ciprofloxacin and three of its active metabolites. The total systemic exposure of ciprofloxacin from the two treatments were similar in terms of AUC<sub>0-t</sub> and AUC<sub>0-inf</sub> with 90% confidence intervals of 91.98% and 93.78, respectively.

The T<sub>max</sub> of ciprofloxacin from a single dose of PROQUIN™ is longer than from the first or second dose of Cipro IR (9 hours versus 2.5 hours). The C<sub>max</sub> of PROQUIN™ 500 mg is 46.5% higher than the first C<sub>max</sub> of Cipro IR 250 mg but 24.2% lower than the C<sub>max</sub> of the second dose of Cipro IR. The plasma elimination half-life was different between the two treatments.

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TABLE 40  
Summary of Plasma Pharmacokinetic Parameters of Ciprofloxacin

Pharmacokinetic Parameter	Ciprofloxacin GR <sup>TM</sup> 500 mg Tablets (single dose) (A) (n=27) Geometric mean (%CV)	Cipro <sup>®</sup> 250 mg Tablets (twice daily x 2 doses) (B) (n=27) Geometric mean (%CV)	p-value
AUC <sub>0-36</sub> (ug-hr/mL) †	6236.7 (29.1)	6792.7 (24.7)	0.063 <sup>‡</sup>
AUC <sub>0-inf</sub> (ng-hr/mL) †	6535.5 (28.5) <sup>*</sup>	7047.3 (23.7)	0.161 <sup>‡</sup>
C <sub>max</sub> (ng/mL) †	C <sub>max</sub> : 691.6 (31.0)	C <sub>max</sub> : 471.2 (27.8)	<0.0001 <sup>‡</sup>
		C <sub>max</sub> : 912.8 (25.7)	0.0002 <sup>‡</sup>
T <sub>max</sub> (hr) †	T <sub>max</sub> : 7.04 ± 3.31 <sup>†</sup> 9.00 <sup>*</sup>	T <sub>max</sub> : 2.13 ± 0.98 <sup>†</sup> 2.50 <sup>*</sup>	<0.0001
		T <sub>max</sub> : 14.00 ± 1.19 <sup>†</sup> 13.50 <sup>*</sup>	<0.0001
t <sub>1/2</sub> (hr) †	4.49 ± 0.83 <sup>†*</sup>	4.60 ± 0.93 <sup>†</sup>	0.242

\* Median values  
† Mean ± SD  
‡ The p-value is from ANOVA on ln-transformed data  
\* n=26

TABLE 41

Parameter	Ciprofloxacin GR <sup>TM</sup> 500 mg Tablets (single dose) (A) vs. Cipro <sup>®</sup> 250 mg Tablets (twice daily x 2 doses) (B)		
	90% C.I.	Ratio of Means (A/B)	Intra-Subject CV
AUC <sub>0-36</sub>	85.47% to 98.98%	91.98%	15.77%
AUC <sub>0-inf</sub>	86.91% to 101.19%	93.78%	16.03%
C <sub>max</sub> vs. C <sub>max</sub>	131.17% to 163.50%	146.44%	23.68%
C <sub>max</sub> vs. C <sub>max</sub>	68.10% to 84.44%	75.83%	23.11%

The ciprofloxacin 0 - 36 hour urinary recovery was significantly lower (by ~10%, p=0.0416) from PROQUIN<sup>TM</sup> 500 mg QD than from Cipro IR 250 mg BID. The renal clearance of ciprofloxacin was not different between the two treatments.

TABLE 42  
Summary of Urinary Pharmacokinetic Parameters of Ciprofloxacin

Pharmacokinetic Parameter	Ciprofloxacin GR <sup>TM</sup> 500 mg Tablets (single dose) (A) (n=27) mean ± SD	Cipro <sup>®</sup> 250 mg Tablets (twice daily x 2 doses) (B) (n=27) mean ± SD	p-value
T <sub>max, urine</sub> (hr) †	T <sub>max, urine</sub> : 7.82 ± 3.97	T <sub>max, urine</sub> : 3.74 ± 0.36	<0.0001
		T <sub>max, urine</sub> : 15.44 ± 0.29	<0.0001
Max Rate (mg/hr) †	Max Rate <sub>0</sub> : 17.82 ± 4.76	Max Rate <sub>1</sub> : 10.99 ± 0.61	<0.0001
		Max Rate <sub>2</sub> : 20.33 ± 1.13	0.046
A <sub>e</sub> (mg) †	131.8 (21.2) <sup>†</sup>	146.5 (18.1) <sup>†</sup>	0.042
CL (L/hr) †	21.81 ± 5.34	25.99 ± 17.84	0.397
%Dose †	26.94 ± 5.71	29.82 ± 5.39	0.042

† Geometric mean (%CV)  
‡ Manually rounded from values obtained in Appendix 3

Similar urinary excretion profiles between the two treatments were observed for metabolites M1, M2, and M3 (desethyleneciprofloxacin, sulfociprofloxacin, and oxociprofloxacin, respectively). The pharmacokinetic parameters for the three metabolites are shown in the following tables. Insufficient PK data for the 4<sup>th</sup> metabolite precluded the calculation of PK parameters for this metabolite.

TABLE 43A  
Pharmacokinetic Parameters of desethyleneciprofloxacin (M1) in Urine

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Pharmacokinetic Parameter	Ciprofloxacin GR™ 500 mg Tablets (single dose) (A) (n=27) (mean ± SD)	Cipro® 250 mg Tablets (twice daily x 2 doses) (B) (n=27) (mean ± SD)	p-value
T <sub>max, total</sub> (hr) ‡	T <sub>max, total</sub> : 8.78 ± 4.27	T <sub>max, total</sub> : 4.70 ± 1.90 T <sub>max, total</sub> : 16.64 ± 1.40	<0.0001 <0.0001
Max Rate (mg/hr) ‡	Max Rate: 0.28 ± 0.07	Max Rate1: 0.18 ± 0.06 Max Rate2: 0.27 ± 0.09	<0.0001 0.618
Ae (mg) ‡	2.3 (37.9) <sup>§</sup>	2.4 (29.2) <sup>§</sup>	0.950
%Dose ‡	0.53 ± 0.20	0.53 ± 0.16	0.950

<sup>§</sup> Geometric mean (%CV)  
‡ Manually rounded from values obtained in Appendix 3

**TABLE 43B**  
Pharmacokinetic Parameters of Sulfociprofloxacin (M2) in Urine

Pharmacokinetic Parameter	Ciprofloxacin GR™ 500 mg Tablets (single dose) (A) (n=27) (mean ± SD)	Cipro® 250 mg Tablets (twice daily x 2 doses) (B) (n=26) (mean ± SD)	p-value
T <sub>max, total</sub> (hr) ‡	T <sub>max, total</sub> : 7.44 ± 3.78	T <sub>max, total</sub> : 4.08 ± 1.90 T <sub>max, total</sub> : 15.46 ± 1.53	0.002 <0.0001
Max Rate (mg/hr) ‡	Max Rate: 2.21 ± 0.82	Max Rate1: 1.25 ± 0.63 Max Rate2: 2.43 ± 1.08	0.0001 0.437
Ae (mg) ‡	13.5 (29.8) <sup>§</sup>	14.5 (31.8) <sup>§</sup>	0.432
%Dose ‡	2.28 ± 0.68	2.45 ± 0.76 <sup>§</sup>	0.432

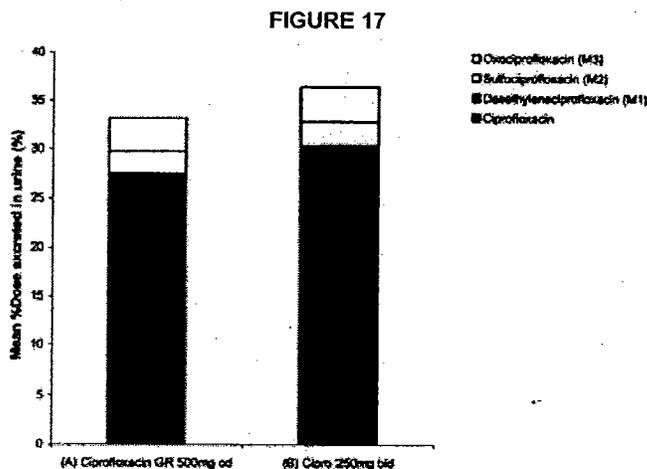
<sup>§</sup> Geometric mean (%CV)  
<sup>§</sup> n = 26  
‡ Manually rounded from values obtained in Appendix 3

**TABLE 43C**  
Pharmacokinetic Parameters of Oxociprofloxacin (M3) in Urine

Pharmacokinetic Parameter	Ciprofloxacin GR™ 500 mg Tablets (single dose) (A) (n=27) (mean ± SD)	Cipro® 250 mg Tablets (twice daily x 2 doses) (B) (n=27) (mean ± SD)	p-value
T <sub>max, total</sub> (hr) ‡	T <sub>max, total</sub> : 8.04 ± 4.01	T <sub>max, total</sub> : 3.96 ± 1.16 T <sub>max, total</sub> : 15.67 ± 1.47	<0.0001 <0.0001
Max Rate (mg/hr) ‡	Max Rate: 2.30 ± 0.98	Max Rate1: 1.53 ± 0.73 Max Rate2: 2.31 ± 1.04	0.601 0.947
Ae (mg) ‡	16.6 (36.4) <sup>§</sup>	18.0 (31.6) <sup>§</sup>	0.289
%Dose ‡	3.40 ± 1.24	3.62 ± 1.14	0.289

<sup>§</sup> Geometric mean (%CV)  
‡ Manually rounded from values obtained in Appendix 3

Figure 17 shows a comparison of the two treatments in terms of the total percentage of the dose excreted in the urine (as parent + metabolites).



### Safety

In Treatment A (Proquin™ 500 mg tablets QD), two subjects experienced a total of 3 adverse events. In Treatment B (Cipro 250 mg tablets BID), five subjects experienced a total of 14 adverse events.

### Reviewer's comments:

1. As expected, the Tmax of ciprofloxacin from the reference treatment (Cipro® 250 mg BID) was prolonged (2.5 hours versus 0.5 to 1.0 hours) in this study because it was given with a meal. Based on the label of immediate release ciprofloxacin (Cipro®), food is not expected to substantially affect the extent of ciprofloxacin absorption.
2. That the Tmax of ciprofloxacin from PROQUIN™ 500 mg QD is even longer than 2.5 hours, i.e., 9.0 hours, suggests that there was something inherent in this formulation or dosage form that slowed down drug release and/or drug absorption.
3. The exact mechanism (be it gastric retention or some other mechanism) involved in the prolonged Tmax of ciprofloxacin was not elucidated for PROQUIN™ but the sponsor had previously conducted similar such studies for another gastric-retentive dosage form they themselves developed (metformin). The inactive ingredients of Proquin™ are similar to that of Glumetza® (Metformin) 500mg extended-release tablets for which pharmacoscintigraphic studies appeared to demonstrate a gastric-retentive mechanism.
4. When both were given with a high-fat meal, Proquin™ 500mg QD was found to be bioequivalent to Cipro® 250mg BID in terms of AUC<sub>0-24h</sub>. The Cmax of Proquin™ 500mg QD was 50% of the sum of Cmax values from the two doses of Cipro® 250mg BID.
5. Therefore, based on comparative single-dose PK exposure data, a substantial meal is needed for Proquin™ 500mg QD to be considered bioequivalent to Cipro® 250mg BID/fed. The label of Cipro® 250 mg states that the extent of absorption of ciprofloxacin is not affected by food so that it is assumed that this relationship will remain regardless of whether the reference treatment was given with or without a meal.
6. That a . . . meal is needed to achieve therapeutic ciprofloxacin concentrations from Proquin™ should be mentioned in the . . .
7. The table below compares the dose-dependent plasma PK parameters of ciprofloxacin from various dosage forms, i.e., Proquin™ versus Cipro® in this study, and Cipro XR® versus Cipro® (data from Cipro XR® package insert). Assuming there was no significant inter-study food effects on the systemic oral bioavailability of the reference Cipro® treatment, the percentage of reference ciprofloxacin AUC<sub>0-24h</sub> from Proquin™ 500mg QD/fed was arithmetically smaller than that from Cipro XR® 500mg QD/fasted. As seen in the table, Cipro XR® 500mg QD/fasted is more similar to Cipro® 250mg BID/fasted than Proquin™ 500mg QD/fed is to Cipro® 250mg BID (fasted or fed) in terms Tmax and daily total Cmax.

**TABLE 44**  
Day 1 Plasma Pharmacokinetic Parameters of Proquin™ versus Cipro® XR,  
Relative to the Reference Cipro® IR Treatment

Dosage Form	Fasted/Fed	Tmax (hr)	Cmax (ng/mL)	% of Cmax <sup>b</sup> Cipro® 250 mg BID (Fed or Fasted)	AUC <sub>0-24h</sub> (ng*h/mL)	% of AUC <sub>0-24h</sub> of Cipro® 250 mg BID (Fed or Fasted)
Proquin™ 500 mg QD	Fed (with high-fat meal)	7.0 (mean) 9.0 (median)	692	50% of Cipro® 250 mg BID (Fed)	6237	91.8% of Cipro® 250 mg BID (Fed)

Cipro® 250 mg BID <sup>a</sup>	Fed (with high-fat meal)	2.0 (mean) 2.5 (median)	1384 <sup>b</sup>		6793	
Cipro XR 500 mg QD <sup>a</sup>	Fasted	1.5 (median)	1590 ± 430	139% of Cipro® 250 mg BID (Fasted)	7970 ± 1870	96.6% of Cipro® 250 mg BID (Fasted)
Cipro® 250 mg BID <sup>a</sup>	Fasted	1.0 (median)	1140 ± 230 <sup>b</sup>		8250 ± 2150	

<sup>a</sup> values from Cipro XR® Package Insert

<sup>b</sup> C<sub>max,1</sub> + C<sub>max,2</sub>

8. The table below compares the cumulative amounts of ciprofloxacin excreted into the urine during a 24-hour dosing interval from Proquin™ under fed conditions against immediate-release and modified release dosage forms of Cipro® under fasted conditions. Assuming there was no significant inter-study food effects on the urinary bioavailability of the reference Cipro® treatment, the % of reference cumulative amount of ciprofloxacin excreted into the urine over a 24-hour period from Proquin™ 500mg QD/fed was arithmetically greater than that from Cipro XR® 500mg QD/fasted, a trend in contrast with that found from plasma concentrations profiles.

TABLE 45

Dosage Form	Fed/Fasted	Cumulative amount excreted into urine during a 24-hour interval (A <sub>e, 0-24h</sub> ) (mg)	% of Reference Cipro® 250 mg BID (Fed or Fasted)
Proquin™ 500 mg QD	Fed (with high-fat meal)	134.7 ± 28.6	90.6% of Cipro® 250 mg BID (Fed)
Cipro® 250 mg BID <sup>a</sup>	Fed (with high-fat meal)	149.0 ± 26.9	
Cipro XR 500 mg QD <sup>a</sup>	Fasted	168.2 ± 46.10	84.8% of Cipro® 250 mg BID (Fasted)
Cipro® 250 mg BID <sup>a</sup>	Fasted	197.9 ± 157.4	

<sup>a</sup> values from Cipro XR® NDA Submission

9. In the PK studies conducted for Cipro XR® by its own sponsor, the urinary ciprofloxacin concentrations were always substantially (at least 100x) above the reported MIC<sub>90</sub> (=0.03 mcg/mL) of *E. coli* isolates. In the case of Proquin™ 500mg QD, the mean urinary ciprofloxacin concentration values obtained in the single-dose PK study were at least 165x and 49x the MIC<sub>90</sub> values (0.016 mcg/mL and 0.045 mcg/mL) for *E. coli* isolates strain 1 and strain 4, respectively. In this same study, the reference Cipro® 250mg BID treatment afforded mean urinary ciprofloxacin concentrations that were at least 254x and 77x higher than the MIC<sub>90</sub> values of *E. coli* strain 1 and strain 4, respectively. Therefore, assuming there were no significant inter-study differences and the MIC<sub>90</sub> of *E. coli* isolates were exactly the same for both studies, the lowest (urinary ciprofloxacin concentrations-to-MIC<sub>90</sub>) ratios achieved from Proquin™ 500mg QD would be somewhat lower than the lowest PK/PD ratios from the reference treatment (Cipro® 250mg BID) but comparable to the lowest PK/PD ratios reported for Cipro XR® 500mg QD.
10. Based on the PK/PD study report submitted by the sponsor, the plasma ciprofloxacin AUC<sub>0-24h</sub>-to-MIC<sub>90</sub> ratios for *E. coli* strain 1 and strain 2 for Proquin™ 500mg QD were 405.6 and 144.2, respectively, and for Cipro® 250mg BID, 401.0 and 142.6, respectively. However, using geometric mean AUC<sub>0-24h</sub> values presented in the final report for Study 81-0025 (single dose, comparative PK study), the reviewer calculated the following AUC/MIC ratios for the two strains of *E. coli* based on the actual AUC data submitted for Study 81-0025. It can be seen from the table below that the AUC/MIC ratios for *E. coli* were greater than 125.

TABLE 46

Treatment	AUC <sub>0-24h</sub> (Day 1) ng*h/mL	AUC/MIC <sub>90</sub>	
		<i>E. coli</i> strain 1 (MIC <sub>90</sub> =0.016 mcg/mL)	<i>E. coli</i> strain 2 (MIC <sub>90</sub> =0.045 mcg/mL)
Proquin™ 500mg QD	6236.7	389.8	138.6
Cipro® 250mg BID	6792.7	424.6	151.0
% of Cipro® 250mg BID	92%		

11. Based on the PK/PD study report submitted by the sponsor, the plasma ciprofloxacin C<sub>max</sub>-to-MIC<sub>90</sub> ratios for *E. coli* strain 1 and strain 2 for Proquin™ 500mg QD were 45 and 16, respectively, and for Cipro® 250mg BID, 59 and 21, respectively. The C<sub>max</sub> values used were the average of individual C<sub>max</sub> values and were not taken from the mean plasma concentration profiles. However, the reviewer used the geometric mean C<sub>max</sub> values presented in the final report for Study 81-0025 (single dose, comparative PK study), to calculate the C<sub>max</sub>/MIC ratios for the two strains of *E. coli*. It can be seen from the table below that the C<sub>max</sub>/MIC<sub>90</sub> ratios for *E. coli* were greater than equal to 10.

TABLE 47

Treatment	C <sub>max</sub> (Day 1) ng*h/mL	C <sub>max</sub> /MIC <sub>90</sub>	
		<i>E. coli</i> strain 1 (MIC <sub>90</sub> =0.016 mcg/mL)	<i>E. coli</i> strain 2 (MIC <sub>90</sub> =0.045 mcg/mL)
Proquin™ 500mg QD	C <sub>max,0</sub> = 692	43	15
Cipro® 250mg BID	C <sub>max,1</sub> = 471 C <sub>max,2</sub> = 913	29 57	10 20
% of Cipro® 250mg BID (sum of 2 doses)	50%		

**APPEARS THIS WAY  
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**Study 81-0026****A Two-Way Crossover, Open-Label, Fed, Steady-State Bioavailability Study of Proquin™ 500 mg (qd) Tablets versus Cipro® 250 mg (bid) Tablets in Healthy Non-Smoking Male and Female Subjects****Objective:**

To assess the relative bioavailability of ciprofloxacin from Proquin™ (Gastric Retentive) 500 mg Tablets (single dose) versus Cipro® 250 mg Tablets (twice daily) under steady state conditions

**Study population:**

Twenty eight (28) normal, healthy non-smoking male/female (1:1) subjects with mean age of 38 (23 to 61) years old and mean weight of 71 (50 to 92) kg were enrolled in the study. Majority (68%) were Caucasians; the remainder were Asians (18%) and Blacks (14%). All but one of the enrolled subjects completed the study.

**Dosing and Administration:**

Following a fast of at least 4 hours, one of the following treatments were received with 240 mL of water per treatment period, 30 minutes after the start of a standardized, approximately 1000 calorie, high-fat (~50%) content meal for three consecutive days. The wash-out period between treatments was about 7 days.

**Treatment A:** Ciprofloxacin 500 mg Tablet (Lot #: HT3602; potency — of label claim), once daily after dinner

**Treatment B:** CIPRO® 250 mg Tablet (Lot #: 54002PR) twice daily after breakfast and dinner

**Fluid control measure:**

**Day 1, Day 2 and Day 3 Treatments A and B:** For all treatments, 100 mL (at ambient temperature) water was administered according to the following schedule: 2.0, 3.0, 4.0, 5.0, 6.0, 7.0, 9.0, 10.0, 12.0 (only Treatment A), 14.0, 16.0, 18.0, 20.0 and 22.0 hours post 0.0 hour dose.

**Pharmacokinetic Sampling:**

**Blood** samples will be collected based on the following schedule:

**(Day 1) Treatments A and B:** (pre-dose)

**(Day 2) Treatments A and B:** 0.0 (pre-dose)

**(Day 3)**

**Treatment A:** 0.0 (pre-dose), 0.5, 1.0, 1.5, 2.0, 3.0, 3.5, 4.0, 4.5, 5.0, 6.0, 9.0, 12.0, 14.0, 18.0 and 24.0 post-drug administration.

**Treatment B:** 0.0 (pre-dose), 0.5, 1.0, 1.5, 2.0, 2.5, 3.0, 3.5, 4.0, 5.0, 6.0, 9.0, 12.0, 12.5, 13.0, 13.5, 14.0, 14.5, 15.0, 15.5, 16.0, 17.0, 18.0, 21.0 and 24.0 post-drug administration.

**Urine** (at least 20 mL per time interval) will be collected from all subjects during the course of the study on Days 1 through 3 as follows:

**(Day 1) Treatments A and B:**

Pre-dose (complete void and collect), 0.0-2.0, 2.0-4.0, 4.0-6.0, 6.0-8.0, 8.0-10.0, 10.0-12.0, 12.0-14.0, 14.0-16.0, 16.0-18.0 and 18.0-24.0 hours post-dose.

**(Day 2) Treatment A and B:**

Pre-dose (complete void and collect), 0.0-8.0, 8.0-16.0 and 16-24 hours post-dose.

**(Day 3) Treatments A and B:**

Pre-dose (complete void and collect), 0.0-2.0, 2.0-4.0, 4.0-6.0, 6.0-8.0, 8.0-10.0, 10.0-12.0, 12.0-14.0, 14.0-16.0, 16.0-18.0 and 18.0-24.0 hours post-dose.

**Criteria for evaluation:**

Pharmacokinetics

The following pharmacokinetic parameters for ciprofloxacin were calculated by standard non-compartmental methods from **plasma** profiles:

- Area under the concentration-time curve from time zero to the time of dosing interval ( $AUC_T$ )
- maximum plasma concentration after dosing ( $C_{max}$ ),
- concentration at the end of a dosing interval during multiple dosing ( $C_{min}$ )
- average plasma concentration in a dosing interval during multiple dosing ( $C_{ave}$ )
- time to reach peak plasma concentration ( $T_{max}$ ),
- degree of concentration swing at steady state (% Swing),
- degree of concentration fluctuation at steady state (% fluctuation)
- mean residence time (MRT).

The following pharmacokinetic parameters for ciprofloxacin, desethyleneciprofloxacin (M1), sulfociprofloxacin (M2), oxociprofloxacin (M3), and formylciprofloxacin (M4) were calculated by standard non-compartmental methods from **urine** profiles:

- amount excreted in urine ( $A_e$ )
- maximum observed excretion rate (Max Rate)
- midpoint of collection interval associated with the maximum observed excretion rate ( $T_{max}$  Rate).
- fractions of total dose recovered in urine (% Dose)
- Renal clearance (Cl<sub>r</sub>) - for ciprofloxacin only

#### Safety

- Adverse events
- Vital signs
- ECGs
- Laboratory parameters
- Physical examinations

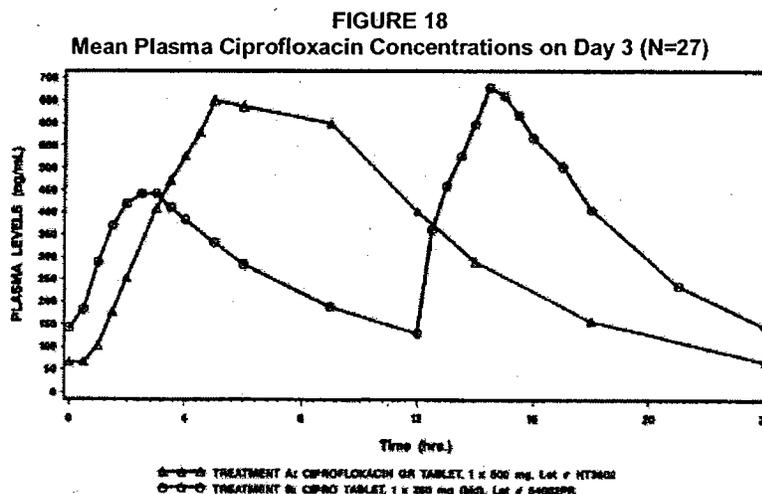
#### **Statistical Analysis:**

The ratio of geometric means and the 90% geometric confidence interval (90% C.I.) were calculated based on the difference in the Least Squares Means of the plasma AUC, and  $C_{max}$ , as well as urine  $A_e$  and Cl<sub>r</sub>, between the test and reference formulations.

#### **Results and Discussion:**

##### Pharmacokinetics

Mean ciprofloxacin plasma concentration time profiles are presented in Figure 18.



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A summary of statistical analyses of ciprofloxacin PK parameters comparing the two treatments follow.

TABLE 48

SUMMARY OF PHARMACOKINETIC RESULTS FOR CIPROFLOXACIN IN PLASMA (DAY 3)

Pharmacokinetic Parameters	Ciprofloxacin GR™ 500 mg Tablets (qd) (A) n = 27	CIPRO® 250 mg Tablets (bid) (B) n = 27	p-value
	Geometric Mean (%CV)	Geometric Mean (%CV)	
AUC <sub>0-24</sub> (ng·hr/mL) §	7667.6 (24.8)	7834.6 (15.9)	0.509 <sup>†</sup>
C <sub>max</sub> (ng/mL) §	C <sub>max</sub> : 824.1 (28.4)	C <sub>max1</sub> : 568.1 (24.7)	<0.0001 <sup>†</sup>
		C <sub>max2</sub> : 934.1 (27.2)	0.021 <sup>†</sup>
C <sub>min</sub> (ng/mL)	62.59 (42.449)	139.28 (29.391)	<0.0001 <sup>†</sup>
T <sub>max</sub> (hr) §	T <sub>max</sub> : 6.06 ± 2.63 <sup>†</sup> 5.00 <sup>*</sup>	T <sub>max1</sub> : 2.52 ± 1.20 <sup>†</sup> 2.02 <sup>*</sup>	ND
		T <sub>max2</sub> : 14.46 ± 1.42 <sup>†</sup> 14.50 <sup>*</sup>	ND
Degree of Fluctuation (%)	240.4 ± 44.1 <sup>†</sup>	250.4 ± 69.6 <sup>†</sup>	0.506
C <sub>avg</sub> (ng/mL)	329.4 ± 81.6 <sup>†</sup>	330.5 ± 52.5 <sup>†</sup>	0.509
Degree of Swing (%)	1322.9 ± 586.1 <sup>†</sup>	627.5 ± 295.0 <sup>†</sup>	ND
MRT (hr)	9.29 ± 1.18 <sup>†</sup>	11.93 ± 0.57 <sup>†</sup>	<0.0001

<sup>†</sup> Arithmetic mean ± SD; <sup>†</sup> The p-value is from ANOVA on ln-transformed data; ND: Not Determined  
<sup>\*</sup> Median values; § Manually rounded from values obtained in Appendix 3

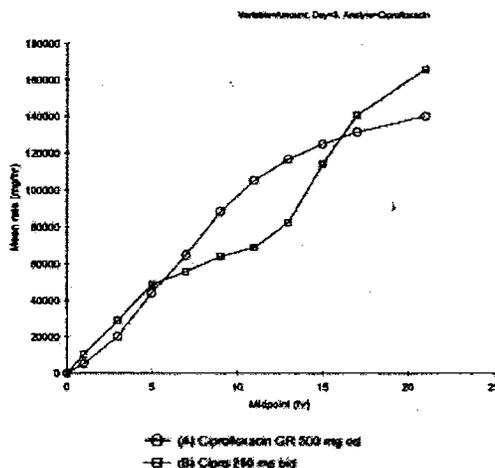
TABLE 49

Pharmacokinetic Parameters	Ciprofloxacin GR™ 500 mg Tablets (qd) (A) vs. CIPRO® 250 mg Tablets (bid) (B)		
	90% Confidence Interval	Ratio of Means	Intra-Subject CV
AUC <sub>0-24</sub>	92.21% to 103.60%	97.74%	12.52%
C <sub>max1</sub> vs. C <sub>max2</sub>	130.67% to 160.20%	144.69%	21.89%
C <sub>min1</sub> vs. C <sub>min2</sub>	80.77% to 96.23%	88.17%	18.82%
C <sub>avg</sub>	40.39% to 49.75%	44.82%	22.40%

Mean cumulative amounts of ciprofloxacin excreted in the urine on Day 3 following PROQUIN™™ 500 mg QD and Cipro® 250 mg BID are shown in Figure 19. The mean percent of the dose excreted on Day 3 as parent drug and metabolites is compared between the two treatments on Figure 20. The mean pharmacokinetic parameters for ciprofloxacin, M1, M2, and M3 in urine are summarized in Tables 50 and 51A.

FIGURE 19

Mean Ciprofloxacin Cumulative Amount Excreted in Urine on Day 3 following the administration of 1 x 500 mg Proquin™ tablet (Lot # HT3602) once a day (Treatment A) and 1 x 250 mg Ciprofloxacin Cipro® tablet (Lot # 54002PR) twice a day (Treatment B) (N=27)



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FIGURE 20  
Percentage of Dose versus Metabolite Fraction on Day 3  
following the administration of 1x500 mg Proquin™ tablet  
(Lot # HT3602) once a day (Treatment A) and 1 x250 mg Ciprofloxacin  
Cipro® tablet (Lot # 54002PR) twice a day (Treatment B)

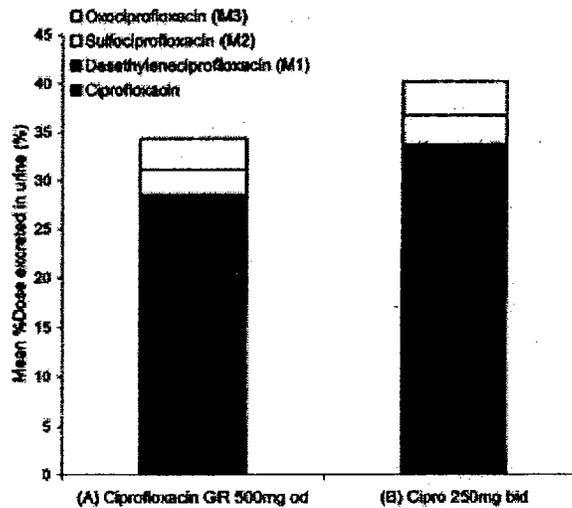


TABLE 50

## SUMMARY OF PHARMACOKINETIC RESULTS FOR CIPROFLOXACIN IN URINE:

Pharmacokinetic Parameters	<i>Ciprofloxacin GR™ 500 mg Tablets (qd) (A)</i> n = 27 Mean ± SD	<i>CIPRO® 250 mg Tablets (bid) (B)</i> n = 27 Mean ± SD	p-values§
<b>Day 1</b>			
T <sub>Max Rate</sub> (hr)	T <sub>Max Rate</sub> : 8.19 ± 3.00	T <sub>Max Rate</sub> : 3.30 ± 2.20 T <sub>Max Rate</sub> : 15.26 ± 1.61	<0.0001 <0.0001
Max Rate (mg/hr)	Max Rate0: 20.35 ± 9.29	Max Rate1: 13.70 ± 12.94 Max Rate2: 21.08 ± 7.05	0.031 0.61§
Ae (mg)	134.4 (30.4) <sup>†</sup>	149.3 (22.4) <sup>†</sup>	0.187
% Dose	28.34 ± 8.63	30.50 ± 6.82	0.187
<b>Day 2</b>			
T <sub>Max Rate</sub> (hr)	8.85 ± 4.89	16.74 ± 4.70	<0.0001
Max Rate (mg/hr)	9.94 ± 3.85	12.06 ± 4.71	0.049
Ae (mg)	133.0 (32.6) <sup>†</sup>	160.0 (24.7) <sup>†</sup>	0.010
% Dose	27.98 ± 9.12	33.43 ± 8.24	0.010
<b>Day 3</b>			
T <sub>Max Rate</sub> (hr)	T <sub>Max Rate</sub> : 7.22 ± 2.62	T <sub>Max Rate</sub> : 4.19 ± 1.39 T <sub>Max Rate</sub> : 15.37 ± 1.47	<0.0001 <0.0001
Max Rate (mg/hr)	Max Rate0: 19.54 ± 8.32	Max Rate1: 14.12 ± 4.86 Max Rate2: 20.57 ± 5.49	0.001 0.450
Ae (mg)	131.8 (31.7) <sup>†</sup>	164.1 (14.4) <sup>†</sup>	0.0003
Cl <sub>r</sub> (L/hr)	18.24 ± 5.68	21.30 ± 4.19	0.0002
% Dose	27.97 ± 8.87	33.13 ± 4.77	0.0003

<sup>†</sup> Geometric mean (%CV); § Manually rounded from values obtained in Appendix 3

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TABLE 51A  
Pharmacokinetic parameters for Desethyleneciprofloxacin (M1) in Urine

Pharmacokinetic Parameter	Ciprofloxacin GR <sup>TM</sup> 500 mg Tablets (qd)(A) (n=27) (mean ±SD)	CIPRO <sup>®</sup> 250 mg Tablets (bid)(B) (n=27) (mean ±SD)	p-value§
<b>Day 1</b>			
T <sub>Max Rate</sub> (hr)	T <sub>Max Rate</sub> : 10.04 ± 3.01	T <sub>Max Rate</sub> 1: 4.48 ± 3.17 T <sub>Max Rate</sub> 2: 16.15 ± 2.54	<0.0001 <0.0001
Max Rate (mg/hr)	Max Rate0: 0.25 ± 0.11	Max Rate1: 0.15 ± 0.13 Max Rate2: 0.22 ± 0.08	0.001 0.220
Ae (mg)	2.0 (35.8) <sup>†</sup>	1.8 (30.5) <sup>†</sup>	0.132
% Dose	0.46 ± 0.17	0.40 ± 0.12	0.132
<b>Day 2</b>			
T <sub>Max Rate</sub> (hr)	13.44 ± 6.80	18.96 ± 4.09	0.003
Max Rate (mg/hr)	0.18 ± 0.06	0.20 ± 0.06	0.239
Ae (mg)	2.5 (27.1) <sup>†</sup>	2.8 (19.1) <sup>†</sup>	0.234
% Dose	0.57 ± 0.16	0.61 ± 0.12	0.234
<b>Day 3</b>			
T <sub>Max Rate</sub> (hr)	T <sub>Max Rate</sub> : 8.11 ± 2.74	T <sub>Max Rate</sub> 1: 4.63 ± 1.36 T <sub>Max Rate</sub> 2: 16.56 ± 1.95	<0.0001 <0.0001
Max Rate (mg/hr)	Max Rate0: 0.30 ± 0.10	Max Rate1: 0.22 ± 0.10 Max Rate2: 0.25 ± 0.08	0.004 0.047
Ae (mg)	2.5 (30.7) <sup>†</sup>	2.7 (23.1) <sup>†</sup>	0.523
% Dose	0.58 ± 0.18	0.60 ± 0.14	0.523

<sup>†</sup> Geometric mean (%CV); § Manually rounded from values obtained in Appendix 3

TABLE 51B  
Pharmacokinetic Parameters Sulfociprofloxacin (M2) in Urine

Pharmacokinetic Parameter	Ciprofloxacin GR <sup>TM</sup> 500 mg Tablets (qd)(A) (n=27) (mean ±SD)	CIPRO <sup>®</sup> 250 mg Tablets (bid)(B) (n=27) (mean ±SD)	p-value§
<b>Day 1</b>			
T <sub>Max Rate</sub> (hr)	T <sub>Max Rate</sub> : 8.33 ± 2.94	T <sub>Max Rate</sub> 1: 3.44 ± 2.10 T <sub>Max Rate</sub> 2: 15.44 ± 1.28	<0.0001 <0.0001
Max Rate (mg/hr)	Max Rate0: 2.57 ± 1.25	Max Rate1: 1.73 ± 2.01 Max Rate2: 2.55 ± 1.42	0.038 0.967
Ae (mg)	14.5 (41.5) <sup>†</sup>	15.3 (44.8) <sup>†</sup>	0.559
% Dose	2.59 ± 1.06	2.70 ± 1.21	0.559
<b>Day 2</b>			
T <sub>Max Rate</sub> (hr)	9.30 ± 4.35	16.33 ± 4.61	<0.0001
Max Rate (mg/hr)	1.24 ± 0.60	1.35 ± 0.65	0.383
Ae (mg)	14.6 (46.4) <sup>†</sup>	16.3 (38.8) <sup>†</sup>	0.383
% Dose	2.67 ± 1.24	2.85 ± 1.11	0.413
<b>Day 3</b>			
T <sub>Max Rate</sub> (hr)	T <sub>Max Rate</sub> : 7.52 ± 2.52	T <sub>Max Rate</sub> 1: 4.11 ± 1.28 T <sub>Max Rate</sub> 2: 15.52 ± 1.53	<0.0001 <0.0001
Max Rate (mg/hr)	Max Rate0: 2.55 ± 1.01	Max Rate1: 1.59 ± 0.82 Max Rate2: 2.59 ± 1.21	0.0002 0.816
Ae (mg)	14.1 (44.0) <sup>†</sup>	16.5 (39.9) <sup>†</sup>	0.077
% Dose	2.55 ± 1.12	2.89 ± 1.15	0.077

<sup>†</sup> Geometric mean (%CV); § Manually rounded from values obtained in Appendix 3

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TABLE 51C  
Pharmacokinetic Parameters for Oxociprojloxacin (M3) in Urine

Pharmacokinetic Parameter	Ciprofloxacin GR™ 500 mg Tablets (qd)(A) (n=27) (mean ±SD)	CIPRO® 250 mg Tablets (bid)(B) (n=27) (mean ±SD)	p-value‡
<b>Day 1</b>			
T <sub>Max Rate</sub> (hr)	T <sub>Max Rate</sub> : 8.56 ± 2.79	T <sub>Max Rate</sub> 1: 3.74 ± 2.36 T <sub>Max Rate</sub> 2: 15.96 ± 1.48	<0.0001 <0.0001
Max Rate (mg/hr)	Max Rate0: 2.05 ± 1.02	Max Rate1: 1.43 ± 1.33 Max Rate2: 1.95 ± 0.84	0.037 0.674
Ae (mg)	14.1 (38.0) <sup>†</sup>	14.8 (30.2) <sup>†</sup>	0.833
% Dose	2.91 ± 1.11	2.95 ± 0.89	0.833
<b>Day 2</b>			
T <sub>Max Rate</sub> (hr)	10.96 ± 5.63	17.81 ± 3.67	<0.0001
Max Rate (mg/hr)	1.19 ± 0.48	1.26 ± 0.51	0.545
Ae (mg)	15.7 (33.3) <sup>†</sup>	17.2 (26.6) <sup>†</sup>	0.337
% Dose	3.20 ± 1.07	3.43 ± 0.91	0.337
<b>Day 3</b>			
T <sub>Max Rate</sub> (hr)	T <sub>Max Rate</sub> : 7.37 ± 2.66	T <sub>Max Rate</sub> 1: 4.19 ± 1.27 T <sub>Max Rate</sub> 2: 15.74 ± 1.38	<0.0001 <0.0001
Max Rate (mg/hr)	Max Rate0: 2.31 ± 0.88	Max Rate1: 1.61 ± 0.65 Max Rate2: 2.04 ± 0.72	0.002 0.140
Ae (mg)	15.9 (33.9) <sup>†</sup>	18.1 (21.9) <sup>†</sup>	0.182
% Dose	3.25 ± 1.10	3.35 ± 0.78	0.182

<sup>†</sup> Geometric mean (%CV); § Manually rounded from values obtained in Appendix 3

#### Safety

- During Treatment A (Ciprofloxacin-GR), 6 subjects experienced a total of 11 AEs and during Treatment B (Cipro®), 10 subjects experienced a total of 16 AEs, all mild in severity.
- There was a single incident of nausea that was associated with the immediate release (Cipro®) treatment.

#### Reviewer's comments:

1. Proquin™ 500 mg QD was found to be systemically bioequivalent to Cipro® 250 mg BID, in terms of ciprofloxacin AUC<sub>0-24h</sub> when both were given under fed conditions as a 3-day treatment. Therefore, based on comparative steady-state PK exposure data, as well as single dose PK exposure data, a substantial meal is needed for Proquin™ 500mg QD to be considered bioequivalent to Cipro® 250mg BID/fed. The label of Cipro® 250 mg states that the extent of absorption of ciprofloxacin is not affected by food so that it is assumed that this relationship will remain regardless of whether the reference treatment was given with or without a meal.
2. Based on the statistical analysis findings, the C<sub>max,ss</sub> of ciprofloxacin from Proquin™ 500 mg QD is 45% higher (p<0.0001) than the C<sub>max,ss</sub> from the morning dose of Cipro® 250 mg BID but 12% lower (p=0.021) than the C<sub>max,ss</sub> from the afternoon dose of Cipro® 250 mg BID on the third day of treatment. The C<sub>max,ss</sub> of Proquin™ 500mg QD was about 45% lower than the sum of C<sub>max,ss</sub> values from the two doses of Cipro® 250mg BID. This profile of Proquin™ 500mg QD showing a lower daily peak ciprofloxacin plasma concentration compared to the total C<sub>max</sub> derived from two doses of Cipro™ 250mg BID makes Proquin™ distinct from Cipro XR® 500mg QD which shows a daily C<sub>max</sub> value comparable to the total C<sub>max</sub> from two doses of immediate release Cipro® 250mg. The clinical significance of these C<sub>max</sub> differences between the two dosage forms (especially in the context of AE profile differences) is not known.

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3. The  $C_{min,ss}$  was 55% lower ( $p < 0.0001$ ) from the Proquin™ 3-day treatment than the Cipro® treatment. The mean residence time (MRT) of ciprofloxacin in the body was longer by 2.5 hours following Cipro® 250 mg BID. For reference: The  $C_{min}$  of Cipro XR® was found to be 35% lower than the  $C_{min}$  of Cipro IR®.
4. During the 3-day dosing period, the %Dose,  $A_e$ , and CL<sub>r</sub> of ciprofloxacin were consistently slightly higher (by 8 to 20%) from Cipro® 250 mg BID than from Proquin™ 500 mg QD but the difference was significant ( $p < 0.05$ ) only on Days 2 and 3.
5. Consistent with plasma  $T_{max}$ , the  $T_{max,rate}$  of ciprofloxacin from Proquin™ 500 mg in the urine on Days 1 through 3 was longer than the first  $T_{max,rate}$  of Cipro® 250 mg.
6. According to the label of Cipro® tablets, when given with food, the  $T_{max}$  of ciprofloxacin is prolonged to 2 hours (versus 1 hour, without food) but the AUC is not substantially affected. Such was the observed plasma  $T_{max}$  (~2 hours post-dose) of ciprofloxacin from Cipro® tablet in this study.
7. The table below compares the steady-state dose-dependent plasma PK parameters of ciprofloxacin from various dosage forms, i.e., Proquin™ versus Cipro® in this study, and Cipro XR® versus Cipro® (data from Cipro XR® NDA submission). Assuming there was no significant inter-study food effects on the systemic oral bioavailability of the reference Cipro® treatment, the percentage of reference ciprofloxacin  $AUC_{0-24h}$  from Proquin™ 500mg QD/fed was comparable to that from Cipro XR® 500mg QD/fasted at steady state conditions. As seen from Table 52 below, Cipro XR® 500mg QD/fasted produced a higher total daily  $C_{max}$  than Cipro® 250mg BID/fasted whereas Proquin™ 500mg QD/fed produced a lower total daily  $C_{max}$  relative Cipro® 250mg BID (fed). The  $T_{max}$  of Cipro® XR is very similar to the  $T_{max}$  of Cipro® immediate release tablets under the same fasted/fed condition.

**TABLE 52**  
Steady State Plasma Pharmacokinetic Parameters of Proquin™ versus Cipro® XR,  
Relative to the Reference Cipro® IR Treatment

Dosage Form	Fasted/Fed	$T_{max,ss}$ (hr)	$C_{max,ss}$ (ng/mL)	% of $C_{max,ss}$ <sup>b</sup> Cipro® 250 mg BID (Fed or Fasted)	$AUC_{0-24h, ss}$ (ng*h/mL)	% of $AUC_{0-24h, ss}$ of Cipro® 250 mg BID (Fed or Fasted)
Proquin™ 500 mg QD	Fed (with high-fat meal)	6.1 (mean) 5.0 (median)	824 (28.4)	55% of Cipro® 250 mg BID (Fed)	7667.6 (24.8)	98% of Cipro® 250 mg BID (Fed)
Cipro® 250 mg BID <sup>a</sup>	Fed (with high-fat meal)	2.5 (mean) 2.0 (median)	1502.2		7834.6 (15.9)	
Cipro XR 500 mg QD <sup>a</sup>	Fasted	1.5 (median)	$1.5 \pm 1.29^{b,c}$	134% of Cipro® 250 mg BID (Fasted)	$7.77 \pm 1.26^d$	97% of Cipro® 250 mg BID (Fasted)
Cipro® 250 mg BID <sup>a</sup>	Fasted	1.0 (median)	$1.12 \pm 1.22^{b,c}$		$7.99 \pm 1.30^d$	

<sup>a</sup> values from Cipro XR® Package Insert

<sup>b</sup>  $C_{max,1} + C_{max,2}$

<sup>c</sup> mg/L

<sup>d</sup> mg\*h/L

8. Based on the exposure-response relationship known for Cipro XR®, efficacy in the treatment of uncomplicated urinary tract infections (uUTI) depends upon antimicrobial concentrations in the urine rather than in the serum. Based on the %Dose (as parent + 3 metabolites) excreted into the urine on Day 1 and Day 3 of therapy, Cipro® 250 mg BID produces a consistently slightly (9% and 11%) higher urinary concentration of the active moieties of ciprofloxacin than Proquin™ OD. A comparison of the 24-hour cumulative amounts of ciprofloxacin excreted into the urine ( $A_{e,24h}$ ) and the corresponding urinary volumes obtained following the two treatments are summarized in Table 53.

TABLE 53

Treatment	Day	Ae <sub>24h</sub> (mg) (mean ± SD)	Volume of urine excreted in 24h (mL) (mean ± SD)	Mean pH (mean ± SD)
C-GR 500mg tablets (once daily)	1	141.7 ± 43.1	2127 ± 673	6.5 ± 0.4
	3	139.8 ± 44.3	2121 ± 509	6.8 ± 0.4
C-IR 250mg tablets (twice daily)	1	152.5 ± 34.1	2069 ± 576	6.5 ± 0.4
	3	165.7 ± 23.9	2311 ± 504	6.5 ± 0.4

9. Table 54 below compares the cumulative amounts of ciprofloxacin excreted into the urine during a 24-hour dosing interval from Proquin™ once daily under fed conditions against immediate-release and modified release dosage forms of Cipro® under fasted conditions. At steady state conditions, the relative cumulative amounts of ciprofloxacin excreted into the urine over a 24-hour period (expressed as % of Cipro® 250 mg BID) from Proquin™ 500mg QD appeared to be lower compared to that from Cipro XR® 500mg QD/fasted. However, this apparent time-dependent decrease in the ciprofloxacin Ae<sub>0-24-h</sub> of Proquin™ was actually due to an increase in the urinary excretion from the reference treatment over the 3-day dosing period; the Ae of Proquin™ was stable throughout the 3-day period.

TABLE 54

Dosage Form	Fed/Fasted	Cumulative amount of unchanged drug excreted into urine during a 24-hour interval (Ae <sub>0-24-h</sub> ) (mg)	% of Reference Cipro® 250 mg BID (Fed or Fasted)
Proquin™ 500 mg QD	Fed (with high-fat meal)	Day 1: 134.7 (28.6) Day 3: 131.8 (31.7)	Day 1: 90.6% Day 3: 80% of Cipro® 250 mg BID (Fed)
Cipro® 250 mg BID <sup>a</sup>	Fed (with high-fat meal)	Day 1: 149.0 (26.9) Day 3: 164.1 (14.4)	
Cipro XR 500 mg QD <sup>a</sup>	Fasted	Day 1: 168.2 ± 46.10 Day 5: 180 ± 36.5	Day 1: 84.8% Day 5: 105% of Cipro® 250 mg BID (Fasted)
Cipro® 250 mg BID <sup>a</sup>	Fasted	Day 1: 197.9 ± 157.4 Day 5: 171 ± 32.1	

<sup>a</sup> values from Cipro XR® NDA Submission

10. A review of the individual urine concentrations (ug/mL) of ciprofloxacin from PROQUIN™ QD and Cipro IR BID over a 3-day treatment period indicates that there was a 3-fold greater number of patients with urine samples during the 0-2 hour interval of Day 1 therapy that were below the limit of quantification (BLQ = 1.5 mcg/mL) in subjects who took PROQUIN™ than those who took Cipro IR. The average of the individual urine ciprofloxacin concentrations was about 6-fold higher from Ciprofloxacin immediate release than from Proquin extended release tablet. On all other time intervals on Days 1 and at all time intervals on Days 2 and 3, urine ciprofloxacin concentrations were always above 1 mcg/mL (the proposed MIC of susceptible pathogens). Table 55 presents the average individual urine ciprofloxacin concentrations at various time intervals on Day 1 and Day 3. It can be seen from these data that the average mean urine concentrations were always at least 10-fold greater than the MIC = 1 mcg/mL of susceptible pathogens at all times during the 3-day treatment interval. Based on the findings of the efficacy/safety trial conducted by the sponsor of PROQUIN™ 500 mg tablets, it appears that the observed difference in mean urinary drug concentrations during the 1<sup>st</sup> 2 hours of the 1<sup>st</sup> day of therapy may not be clinically relevant in terms of bacterial eradication (86.7% versus 84% at the Test-of-Cure Visit for PROQUIN™ and Cipro IR, respectively). However, it is not known whether such difference had a bearing on resistance development, i.e., on the observation that the recurrence rate was 40% higher in PROQUIN™-treated patients than in Cipro IR-treated patients (13.1% versus 9.4%).

TABLE 55

		Proquin XR 500 mg QD		Cipro 250 mg BID		Cipro/Proquin Ratio	
		Mean	Range		Range		
Day 1	0.0-2.0	11.814		69.664		5.90	
	2.0-4.0	136.775		124.214			0.91
	4.0-6.0	177.976		115.516			0.65
	6.0-8.0	96.06		50.512			0.53
	8.0-10.0	99.042		34.694			0.35
	10.0-12.0	136.225		30.732			0.23
	12.0-14.0	95.516		124.761			1.31
	14.0-16.0	43.041		283.753			6.59
	16.0-18.0	55.987		150.568			2.69
	18.0-22.0	46.216		61.502			1.33
	22.0-24.0	34.794		47.495			1.37
	mean	84.86		99.40			85.37
	sd	51.34		73.78			
Day 3	0.0-2.0	27.103		68.616		2.53	
	2.0-4.0	102.177		158.572			1.55
	4.0-6.0	209.923		103.756			0.49
	6.0-8.0	116.455		45.966			0.39
	8.0-10.0	89.714		23.633			0.26
	10.0-12.0	99.137		33.671			0.34
	12.0-14.0	103.645		115.897			1.12
	14.0-16.0	65.528		312.996			4.78
	16.0-18.0	45.429		176.412			3.88
	18.0-24.0	24.743		44.749			1.81
	mean	88.39		108.43			81.52
	sd	54.03		89.06			

11. The urinary ciprofloxacin concentration fluctuation index, (Max-Min)/Mean, was smaller from the Proquin 500 mg QD treatment than from Cipro 250 mg BID treatment. The same finding was observed in plasma. The clinical relevance of this difference is not known.
12. Table 56 below summarizes the ratios of PK/PD parameters from the ciprofloxacin exposure parameters on Day 3 of Proquin™ 500mg once-daily therapy and the MIC<sub>90</sub> values of 8 strains of pathogens commonly isolated in uncomplicated urinary tract infections (uUTI). It can be seen from the table below that the AUC/MIC ratios were greater than 100 and the C<sub>max</sub>/MIC ratios were greater than 10 for the following microbial strains: *E. coli* strain 1, *E. coli* strain 4, *K. pneumoniae*, and *P. mirabilis*. For the same microorganisms, the C<sub>min</sub>/MIC values were at least equal to 1. In these same subjects, ciprofloxacin concentrations were higher in the urine than in plasma. Thus, the 3-day regimen of Proquin™ 500mg once daily is expected to be effective in the treatment of uUTI caused by susceptible microbes.

TABLE 56  
Ratios for Ciprofloxacin AUC/MIC, C<sub>max</sub>/MIC and C<sub>min</sub>/MIC  
Following a 3-Day Regimen of Proquin™ 500 mg Once Daily

ORGANISM	MIC <sub>90</sub> (mcg/mL)	Ciprofloxacin AUC <sub>0-24h</sub> (7905 ng <sup>h</sup> /mL)	Ciprofloxacin C <sub>max</sub> (857 ng/mL)	Ciprofloxacin C <sub>min</sub> (67.7 ng/mL)	Ciprofloxacin C <sub>unif(0-24h)</sub> (65.91 mcg/mL)

<i>E. coli</i> ATCC 25922 (strain 1)	0.016	494	54	4	4119
<i>E. faecalis</i> ATCC 29212 (strain 2)	1	8	1	0.1	65.91
<i>S. aureus</i> ATCC 29213 (strain 3)	0.5	16	2	0.1	131.8
<i>E. coli</i> N9688 (strain 4)	0.045	176	19	2	1465
<i>K. pneumoniae</i> N9189 (strain 5)	0.016	494	54	4	4119
<i>E. faecalis</i> ST12.296 (strain 6)	>32	<0.25	<0.03	<0.002	<2.06
<i>S. saprophyticus</i> , SP8822 (strain 7)	0.5	16	2	0.1	131.8
<i>P. mirabilis</i> N9287 (strain 8)	0.045	176	19	2	1465

13. Tables 57A and B below compares the PK/PD ratios of the two 3-day treatment regimens, i.e., Proquin™ 500mg OD versus Cipro® 250mg BID. As expected, the C<sub>min</sub>/MIC ratios obtained for the BID regimen was about 2-fold higher than that following a once-daily regimen. However, it is not known whether this difference in C<sub>min</sub>/MIC ratios between the two treatments has a clinical significance (particularly in terms of relapse/recurrence/ resistance). However, it was noted that in the pivotal clinical trial that the recurrence rate was 40% higher in the Proquin™-treated patients than in the Cipro®-treated patients (13.1% versus 9.4%). Regardless of the C<sub>max</sub> (after the AM or the PM dose) of Cipro® 250 mg BID, the C<sub>max</sub>/MIC ratios were always above 10 for the same 4 microbial strains for which Proquin™ was found to produce adequate ciprofloxacin systemic exposure. The AUC/MIC ratios of the two treatments were similar.

TABLE 57A  
Ratios for Ciprofloxacin AUC/MIC, C<sub>max</sub>/MIC and C<sub>min</sub>/MIC  
Following a 3-Day Regimen of Proquin™ 500 mg Once Daily versus Cipro® 250 mg BID

ORGANISM	MIC <sub>90</sub> (mcg/mL)	Ciprofloxacin AUC <sub>0-24h</sub>		Ciprofloxacin C <sub>max</sub>		Ciprofloxacin C <sub>min</sub>	
		Proquin™ 500mg OD	Cipro® 250mg BID	Proquin™ 500mg OD	Cipro® 250mg BID <sup>1</sup>	Proquin™ 500mg OD	Cipro® 250mg BID
<i>E. coli</i> ATCC 25922 (strain 1)	0.016	494	496	54	37 61	4	9
<i>E. faecalis</i> ATCC 29212 (strain 2)	1	8	8	1	1 1	0.1	0.15
<i>S. aureus</i> ATCC 29213 (strain 3)	0.5	16	16	2	1 2	0.1	0.29
<i>E. coli</i> N9688 (strain 4)	0.045	176	176	19	13 22	2	3
<i>K. pneumoniae</i> N9189 (strain 5)	0.016	494	496	54	37 61	4	9
<i>E. faecalis</i>							

ST12,296176 (strain 6)	>32	<0.25	<0.25	<0.03	<0.02 <0.03	<0.002	<0.005
<i>S. saprophyticus</i> , SP8822 (strain 7)	0.5	16	16	2	1 2	0.1	0.29
<i>P. mirabilis</i> N9287 (strain 8)	0.045	176	176	19	13 22	2	3

two Cmax values for BID regimen

**TABLE 57B**  
Ratios for Ciprofloxacin average 24-hour urinary concentrations ( $C_{urine, 0-24h}$ )  
Following a 3-Day Regimen of Proquin™ 500 mg Once Daily versus Cipro® 250 mg BID

ORGANISM	MIC <sub>90</sub> (mcg/mL)	Ciprofloxacin $C_{urine, 0-24h}$	
		Proquin™ 500mg OD	Cipro® 250mg BID
<i>E. coli</i> ATCC 25922 (strain 1)	0.016	65.91	71.70
<i>E. faecalis</i> ATCC 29212 (strain 2)	1	4119.4	4481
<i>S. aureus</i> ATCC 29213 (strain 3)	0.5	66	72
<i>E. coli</i> N9688 (strain 4)	0.045	134	142
<i>K. pneumoniae</i> N9189 (strain 5)	0.016	1465	1593
<i>E. faecalis</i> ST12,296176 (strain 6)	>32	4119	4481
<i>S. saprophyticus</i> , SP8822 (strain 7)	0.5	<2.1	<2.2
<i>P. mirabilis</i> N9287 (strain 8)	0.045	1465	1593

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14. All three metabolites that were found in the urine possess antimicrobial activity, albeit much lesser than that of the parent compound. The mean cumulative amounts excreted over a 24-hour interval ( $A_{e0-24h}$ ) and the %Dose of the parent drug and the metabolites M1, M2, and M3 from Proquin™ QD are compared to those from Cipro® 250 mg BID over a 3-day treatment period in Table 58 below.

**TABLE 58**  
Urinary Excretion of Ciprofloxacin and Metabolites During the 3-Day Dosing Period:  
Proquin™ 500 mg OD versus Cipro® 250 mg BID

DAY	PK PARAMETER	ANALYTES	TREATMENTS		% of Cipro® 250 mg BID
			Cipro® 250 mg BID	Proquin 500 mg OD	
Day 1	% Dose	Cipro	30.50	28.34	93
		Cipro + M1 + M2 + M3	36.55	34.39	94
	$A_{e(0-24h)}$ , mg	Cipro	149.3	134.4	90

		Cipro + M1 + M2 + M3	181.2	165	91
Day 2	% Dose	Cipro	33.43	27.98	84
		Cipro + M1 + M2 + M3	40.32	34.42	85
	Ae <sub>(0-24h)</sub> , mg	Cipro	160	133	83
		Cipro + M1 + M2 + M3	196.3	165.8	85
Day 3	% Dose	Cipro	33.13	27.97	84
		Cipro + M1 + M2 + M3	40.17	34.35	86
	Ae <sub>(0-24h)</sub> , mg	Cipro	164.17	131.8	80
		Cipro + M1 + M2 + M3	201.4	164.3	82
AVERAGE for 3 DAYS	% Dose	Cipro	32.4	28.1	87
		Cipro + M1 + M2 + M3	39.0	34.4	88
	Ae <sub>(0-24h)</sub> , mg	Cipro	157.8	133.1	84
		Cipro + M1 + M2 + M3	193.0	165.0	86

**APPEARS THIS WAY  
ON ORIGINAL**

**Study 81-0024****A Two-Way Crossover, Open-Label, Fed, Single-Dose, Comparative, Pharmacokinetic Study of Proquin™ 500 mg (qd) Tablets in Healthy Non-Smoking Male and Female Subjects Under Fasting and Fed State****Objective:**

To assess the effect of food on the pharmacokinetic profile of ciprofloxacin from Proquin™ (Gastric Retentive) 500 mg Tablets

**Study population:**

Twenty-eight healthy non-smoking subjects (17 males, 11 females) with a mean age of 34 years (18 to 70 years) were enrolled in the study. The subjects' mean height was 1.72 m (1.54 to 1.91 m) and the mean weight was 75 kg (49 to 99 kg). The subject's mean BMI was 25.3 kg/m<sup>2</sup> (20.7 to 29.9 kg/m<sup>2</sup>). The subjects consisted of 21 Caucasians, one Asian and six Blacks. Twenty-seven completed the study and were eligible for PK evaluation.

**Dosing and Administration:**

Following a fast of at least 10 hours, one of the following treatments per treatment period was received with 240 mL of water. The wash-out period between treatments was about 7 days.

**Treatment A:** Ciprofloxacin 500 mg Tablet (Lot #: HT3602; potency- — of label claim)

**Treatment B:** Treatment A, 30 minutes after the start of a standardized, approximately 1000 calorie, high-fat (~50%) content meal

**Fluid control measure:**

Servings of 100 mL water were provided every one or two hours according to scheduled time periods until 24 hours post-ciprofloxacin dose.

**Pharmacokinetic sampling:**

**Blood** samples were collected on the following times:

0.0 (pre-dose), 0.5, 1.0, 1.5, 2.0, 2.5, 3.0, 3.5, 4.0, 4.5, 5.0, 6.0, 8.0, 8.0, 10.0, 12.0, 14.0, 14.0, 18.0, 24.0, and 36.0 hours post-drug administration.

**Urine** samples will collected at the following time intervals:

Prior to dosing (complete void and collect), 0.0-2.0, 2.0-4.0, 4.0-6.0, 6.0-8.0, 8.0-10.0, 10.0-12.0, 12.0-16.0, 16.0-24.0, and 24.0-36.0 hours post-dose.

**Criteria for evaluation:****Pharmacokinetics**

The following pharmacokinetic parameters for ciprofloxacin were calculated by standard non compartmental methods from **plasma** profiles:

- Area under the concentration-time curve from time zero to the time of last measurable concentration ( $AUC_{0-t}$ )
- Area under the concentration-time curve from time zero to infinity ( $AUC_{0-inf}$ )
- maximum plasma concentration after dosing ( $C_{max}$ ),
- time to reach peak plasma concentration ( $T_{max}$ ),
- plasma half-life ( $t_{1/2}$ )

The following pharmacokinetic parameters for ciprofloxacin and its metabolites were calculated by standard non-compartmental methods from **urine** profiles:

- amount excreted in urine ( $A_e$ )
- maximum observed excretion rate (Max Rate)
- midpoint of collection interval associated with the maximum observed excretion rate ( $T_{max}$  Rate).
- fractions of total dose recovered in urine (% Dose)

- Renal clearance (Cl<sub>r</sub>) - for ciprofloxacin only

#### Safety

- Adverse events
- Vital signs
- ECGs
- Laboratory parameters
- Physical examinations

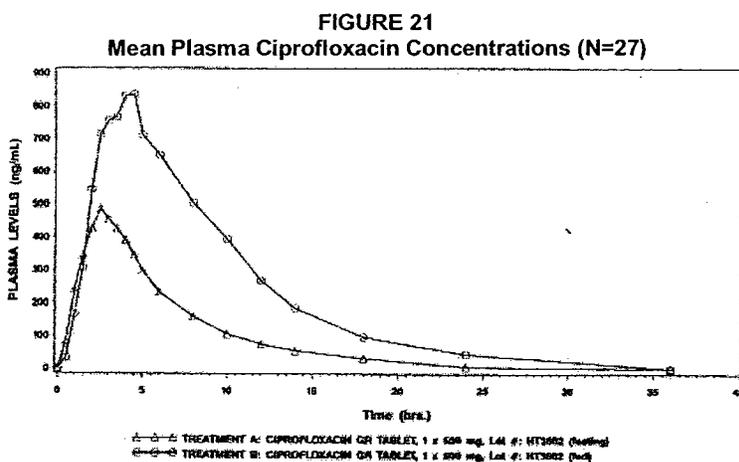
#### Statistical Analysis:

- ANOVA was performed on ln-transformed AUC<sub>0-t</sub>, AUC<sub>0-inf</sub>, and C<sub>max</sub> and on untransformed T<sub>max</sub> and T<sub>1/2</sub> at α=0.05. The ratio of geometric means and the 90% geometric confidence interval (90% C.I.) were calculated based on the difference in the Least Squares Means of the ln-transformed plasma AUC, and C<sub>max</sub>, between test and reference treatments.
- ANOVA was performed on A<sub>e</sub>, Cl<sub>r</sub>, %Dose, Max Rate and T<sub>max</sub> Rate at α=0.05.

#### Results and Discussion:

##### Pharmacokinetics

Mean ciprofloxacin plasma concentration time profiles are presented in Figure 21.



A summary of statistical analyses of ciprofloxacin plasma PK parameters under fasted and fed conditions follow.

**TABLE 59**  
**Summary of Pharmacokinetic Results for Ciprofloxacin in Plasma**

Pharmacokinetic Parameter	Ciprofloxacin GR <sup>TM</sup> 500 mg Tablets - fasted (Test) (n=27) Geometric mean (%CV)	Ciprofloxacin GR <sup>TM</sup> 500 mg Tablets - fed (Reference) (n=27) Geometric mean (%CV)	p-value
AUC <sub>0-t</sub> (ng·hr/mL) ‡	2687.3 (51.7)	7246.0 (24.6)	<0.0001 <sup>†</sup>
AUC <sub>0-inf</sub> (ng·hr/mL) ‡	2961.9 (48.0)	7587.8 (24.2)	<0.0001 <sup>†</sup>
C <sub>max</sub> (ng/mL) ‡	482.8 (50.8)	1064.0 (36.1)	<0.0001 <sup>†</sup>
T <sub>max</sub> (hr) §	2.30 ± 0.74 <sup>‡</sup>	4.49 ± 2.32 <sup>‡</sup>	0.0002
t <sub>1/2</sub> (hr) §	5.07 ± 1.61 <sup>‡</sup>	4.89 ± 1.10 <sup>‡</sup>	0.448

<sup>‡</sup> Median values

<sup>§</sup> Mean ± SD

<sup>†</sup> The p-value is from ANOVA on ln-transformed data

<sup>‡</sup> Manually rounded from values obtained in Appendix 3

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TABLE 60

Parameter	Ciprofloxacin GR <sup>TM</sup> 500 mg Tablets - fasted (A) vs. Ciprofloxacin GR <sup>TM</sup> 500 mg Tablets - fed (B)		
	90% C.I.	Ratio of Means (A:B)	Intra-Subject CV
AUC <sub>0-24</sub>	30.75% to 44.24%	36.89%	39.08%
AUC <sub>0-inf</sub>	32.95% to 45.82%	38.85%	35.44%
C <sub>max</sub>	36.88% to 54.90%	45.00%	42.75%

Mean cumulative amounts of ciprofloxacin excreted in the urine following PROQUIN<sup>TM</sup> 500 mg QD under fasted and fed conditions are shown in Figure 22. The mean pharmacokinetic parameters for ciprofloxacin, M1, M2, and M3 in urine are summarized in Tables 61-62A-C. The urinary concentrations of M4 were not high enough to allow for calculation of its corresponding pharmacokinetic parameters.

FIGURE 22  
Cumulative amount of Ciprofloxacin excreted in urine

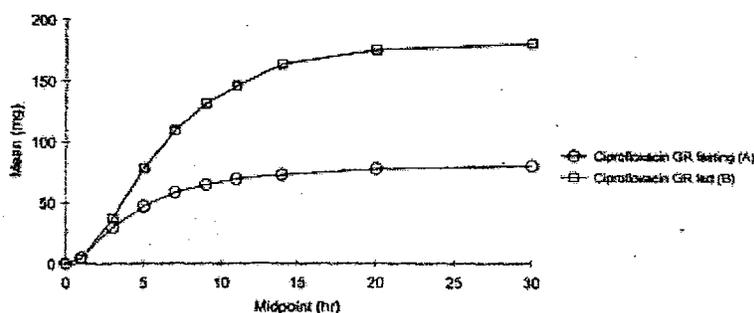


TABLE 61  
Summary of Pharmacokinetic Results for Ciprofloxacin in Urine

Pharmacokinetic Parameter	Ciprofloxacin GR <sup>TM</sup> 500 mg Tablets - fasted (Test) (n=27) mean ± SD	Ciprofloxacin GR <sup>TM</sup> 500 mg Tablets - fed (Reference) (n=27) mean ± SD	p-value
T <sub>max</sub> Rate (hr) §	3.44 ± 1.50	6.15 ± 2.73	< 0.0001
Max Rate (mg/hr) §	13.99 ± 7.97	29.46 ± 12.20	< 0.0001
Ae (mg) §	69.5 (52.9) <sup>†</sup>	176.4 (20.2) <sup>†</sup>	< 0.0001
Cl <sub>r</sub> (L/hr) §	24.12 ± 5.57	23.97 ± 6.05	0.922
% Dose §	16.02 ± 8.48	36.07 ± 7.29	< 0.0001

<sup>†</sup> Geometric mean

§ Manually rounded from values obtained in Appendix 3

TABLE 62A  
Summary of Pharmacokinetic Results for Desethyleneciprofloxacin (M1) in Urine

Pharmacokinetic Parameter	Ciprofloxacin GR <sup>TM</sup> 500 mg Tablets - fasted (Test) (n=27) mean ± SD	Ciprofloxacin GR <sup>TM</sup> 500 mg Tablets - fed (Reference) (n=27) mean ± SD	p-value
T <sub>max</sub> Rate (hr) §	4.41 ± 1.99	7.30 ± 3.01	< 0.0001
Max Rate (mg/hr) §	0.18 ± 0.08	0.29 ± 0.10	< 0.0001
Ae (mg) §	0.9 (59.6) <sup>†</sup>	2.2 (30.7) <sup>†</sup>	< 0.0001
% Dose §	0.23 ± 0.14	0.51 ± 0.16	< 0.0001

<sup>†</sup> Geometric mean (%CV)

§ Manually rounded from values obtained in Appendix 3

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TABLE 62B  
Summary of Pharmacokinetic Results for Sulfociprofloxacin (M2) in Urine

Pharmacokinetic Parameter	Ciprofloxacin GR™ 500 mg Tablets – fasted (Test) (n=27) mean ± SD	Ciprofloxacin GR™ 500 mg Tablets - fed (Reference) (n=27) mean ± SD	p-value
T <sub>max, Rate</sub> (hr) §	3.74 ± 1.85	6.07 ± 2.84	0.0002
Max Rate (mg/hr) §	1.46 ± 1.10	3.06 ± 1.40	< 0.0001
Ae (mg) §	5.5 (66.5) <sup>†</sup>	15.5 (38.3) <sup>†</sup>	< 0.0001
% Dose §	1.11 ± 0.74	2.70 ± 1.03	< 0.0001

<sup>†</sup> Geometric mean (%CV)

§ Manually rounded from values obtained in Appendix 3

TABLE 62C  
Summary of Pharmacokinetic Results for Oxociprofloxacin (M3) in Urine

Pharmacokinetic Parameter	Ciprofloxacin GR™ 500 mg Tablets – fasted (Test) (n=27) mean ± SD	Ciprofloxacin GR™ 500 mg Tablets - fed (Reference) (n=27) mean ± SD	p-value
T <sub>max, Rate</sub> (hr) §	3.89 ± 1.78	6.37 ± 2.71	< 0.0001
Max Rate (mg/hr) §	1.38 ± 0.68	2.51 ± 1.07	< 0.0001
Ae (mg) §	7.1 (50.5) <sup>†</sup>	16.3 (27.2) <sup>†</sup>	< 0.0001
% Dose §	1.55 ± 0.78	3.27 ± 0.89	< 0.0001

<sup>†</sup> Geometric mean (%CV)

§ Manually rounded from values obtained in Appendix 3

### Safety

- Five (5) subjects experienced a total of five (5) AEs in Treatment A (Proquin™ tablets, fasted) whereas three (3) subjects experienced a total of five (5) AEs in Treatment B (Proquin™ tablets, fed). All were considered mild in severity.

### Reviewer's comments:

1. Statistical analyses of data in this study suggest that the systemic and urinary (oral) bioavailability of ciprofloxacin and metabolites from Proquin™ 500mg QD were substantially higher (as ciprofloxacin AUC by 170%, and as cumulative urinary excretion of unchanged drug by 154%) and of smaller variability when given with a high-fat meal than when given under fasted conditions. Both the ciprofloxacin mean T<sub>max</sub> in the plasma and the ciprofloxacin mean T<sub>max, Rate</sub> in the urine were longer after Proquin™ (fed) than after Proquin™ (fasted) by 2.2 hours and by 2.7 hours, respectively.
2. The substantial increase in the oral bioavailability (AUC) of Proquin™ as a consequence of the co-administration with a high-fat meal does not appear to result in increases in adverse events or other safety concerns when compared to administration of Proquin™ under fasted conditions.
3. It should be noted here that in subsequent PK studies and in the therapeutic trials, Proquin™ was administered with a moderate-fat content meal, as was the reference Cipro® treatment. With a moderate-fat meal, the oral bioavailability of Proquin™ is expected to be slightly lower than when given with a high-fat meal, i.e., with a moderate-fat meal (IVVC Study; 81-0029), the AUC<sub>0-24h</sub> of Proquin™ 500mg tablet was about 89% of the AUC<sub>0-24h</sub> of Cipro® 500mg immediate release tablet on Day 1 whereas when given with a high-fat meal, it was about 92% and 98% of Cipro® 250mg BID on Day 1 and Day 3 of dosing, respectively. However, it appears from the non-inferiority findings of the clinical trial that any such differences in the oral bioavailability of

Proquin™ (as a consequence of differences in fat content of meals taken concomitantly with the Proquin™) would have not been clinically significant. Although the C<sub>max</sub> of the reference (immediate-release) Cipro® treatment would have been slightly reduced by its co-administration with food in the trial, according to the label of Cipro®, the over-all absorption would have not been significantly altered.

4. In PK studies conducted earlier by the sponsor, a fluid control technique was instituted, i.e., 100mL or 200mL of water was given after the Proquin™ dose every 1 or 2 hours until 24 hours post-dose, presumably to assist in the gastric-retentive mechanism of the dosage form. Such fluid control measure was not observed in later PK protocols and in the clinical efficacy/safety trials. The table below provides a comparison of the AUC<sub>0-24h</sub> values of Proquin™ 500mg QD with or without fluid control; all these studies co-administered the dosage form with a moderate-fat content meal. Assuming there were no significant experimental sources of variation among these studies, it can be concluded (especially from a comparison of the antacid drug interaction studies) that there was no trend or significant difference observed in the C<sub>max</sub>, T<sub>max</sub>, and AUC<sub>0-24h</sub> of ciprofloxacin from Proquin™ that could be strongly attributed to the influence of fluid control or lack thereof.

TABLE 63

Study	Fat content of the meal administered with Proquin™	Fluid control? (Yes/No)	C <sub>max</sub> <sup>a,b</sup> (ng/mL)	T <sub>max</sub> (h)	AUC <sub>0-24h</sub> <sup>a,b</sup> (ng*h/mL)
Drug Interaction with Omeprazole (81-0027)	moderate	Y	1272	3.95	7723
Drug Interaction with Antacids 1 (81-0028)	moderate	Y	1041	4.45	7405
Drug Interaction with Antacids 2 (81-0033)	moderate	N	1206	4.10	7449
Drug Interaction with Coumadin (81-0035)	moderate	N	819	4.89	7242
IVIVC (81-0029)	moderate	N	1274	4.56	8336
PK in Renally-Impaired (81-0036)	moderate	N	1363 <sup>c</sup>	3.25 <sup>c,d</sup>	8722 <sup>c</sup>

<sup>a</sup> Geometric mean; Dose-normalized to 500 mg

<sup>b</sup> For Drug Interaction Studies: The PK parameter values are for Proquin™ alone (without the other drug).

<sup>c</sup> For Renal Impairment Study: The PK parameter values are for the subjects with normal renal function.

<sup>d</sup> median

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