

Study 81-0037

Title: An Open-Label, Single-Dose, Mass Balance and Pharmacokinetic Study of Proquin™ 500 mg Tablets in Healthy Adult Volunteers Under Fed Conditions

Objective:

To characterize the disposition and pharmacokinetics of ciprofloxacin in healthy volunteers following a single dose of Proquin™ 500 mg tablets

Study Design: This was an open-label, Phase I, single-center, single dose study to evaluate the disposition and pharmacokinetics of ciprofloxacin in plasma, urine and feces following oral administration of 1 Proquin™ 500 mg tablet

Subjects:

Twelve healthy, non-smoking volunteers (4 males and 8 females) with mean age of 28 years (19 to 43 years), mean weight of 74.1 kg (49.3 to 93.9 kg), and mean height of 171 cm (152 to 185 cm).

Drug Dosing and Administration:

Following an overnight fast and 30 minutes after administration of a standard moderate fat content breakfast (~ 600 calories; 40% fat), a single oral dose 500 mg Proquin™ was administered with 240 mL water.

Fluid control:

Subjects were required to drink at least 200 mL of water approximately every 30 minutes from one hour prior to dosing. Subjects were required to drink approximately 240 mL of water at approximately 2, 3, and 4 hours after dosing. Water will be available at all times.

Concomitant medications/Dietary restrictions:

There were no concomitant medications administered prior to study treatment.

Pharmacokinetic Sampling:

- Blood samples were collected in blood collection test tubes containing EDTA at time 0 (pre-dose), 0.5, 1, 2, 3, 3.5, 4, 4.5, 5.5, 6, 7, 8, 9, 10, 12, 18, 24, 36, and 48 hours.
- Complete urine output were collected for the following intervals: Check-in to 0, 0 to 2, 2 to 4, 4 to 6, 6 to 8, 8 to 12, 12 to 16, 16 to 24, 24 to 36, 36 to 48, 48 to 72, and 72 to 96 hours.
- All stools were collected over the following intervals: Check-in to 0, 0 to 24, 24 to 48, 48 to 72, 72 to 96, 96 to 120, 120 to 144, and 144 to 168 hours.

Bioanalytical Methods:

Plasma concentrations of ciprofloxacin were determined using a validated HPLC method with fluorescence detection. HPLC analysis yielded linear results for ciprofloxacin standards over the range of 24.999 ng/mL to 6399.73 ng/mL \pm 10%.

Urine concentrations of ciprofloxacin and its metabolites, desethyleneciprofloxacin (M1), sulfociprofloxacin (M2), oxociprofloxacin (M3), and formylciprofloxacin (M4) were determined using a validated HPLC method with fluorescence detection. HPLC analysis yielded linear results for ciprofloxacin in the range of 1.5 μ g/mL to 15 μ g/mL \pm 10%. Similarly, assays for the metabolites, M1, M2, M3, and M4, were linear over the range of 0.5 to 5 μ g/mL \pm 10%.

Fecal concentrations of ciprofloxacin and its metabolites were determined using a liquid chromatography/mass spectrometry (LC/MS) method. The LC/MS analysis yielded linear results for ciprofloxacin in the range of 100 ng/mL to 1250 ng/mL. Similarly, assays for the metabolites, M1, M2, M3,

and M4, were linear over the range of 25 to 1250 ng/mL. Due to the nature of the analyte, the variability was larger.

Pharmacokinetic Analysis:

The primary PK endpoints consisted of the following parameters:

Plasma (for ciprofloxacin): AUC_{0-t} , $AUC_{0-\infty}$, C_{max} , T_{max} , $t_{1/2}$

Urine:

amount recovered in the urine ($TA_{e,urine}$ for ciprofloxacin and the metabolites M1, M2, M3, and M4, and the overall recovery of the administered dose in the urine (sum of the $TA_{e,urine}$ for ciprofloxacin and the metabolites)

Feces:

Total amounts [$A_{e,fececs(0-168)}$] recovered in the feces for ciprofloxacin and the metabolites, and the overall recovery of the administered dose in the feces [sum of $A_{e,fececs(0-168)}$]

Mean % Total Dose or Total Recovery: Sum of $TA_{e,urine}$ and $A_{e,fececs(0-168)}$ for ciprofloxacin and the metabolites

Safety Assessment:

- Physical exams, clinical laboratory tests and vital signs (taken at screening, check-in, and at the end of the study or at early termination)
- Adverse events (recorded throughout the study)
- EKG monitoring (at screening)

Results:

Plasma Pharmacokinetics

The mean ciprofloxacin plasma concentration-time profile is presented in Figure 23. The mean ciprofloxacin plasma pharmacokinetic parameters are presented in Table 64. The table excluded the plasma, urine and fecal concentration data on Subject 007 because of incomplete sampling and very low ciprofloxacin concentrations in the PK samples collected.

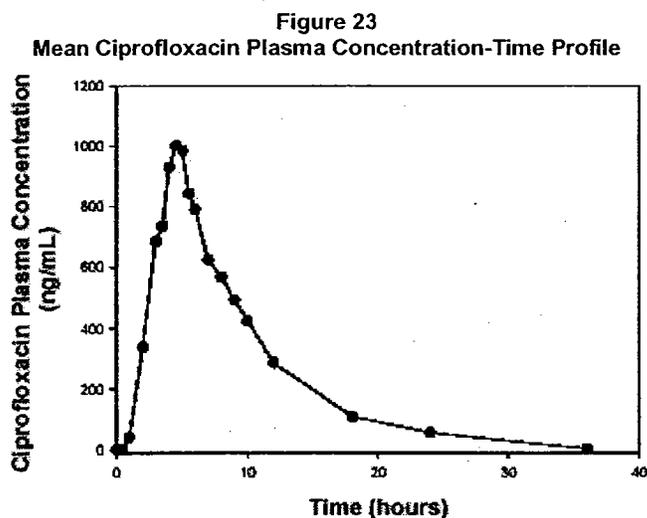


TABLE 65
Mean Plasma Ciprofloxacin Pharmacokinetic Parameters*

AUC _{0-t} (ng·h/mL) [†]	AUC _{∞t} (ng·h/mL) [†]	C _{max} (ng/mL) [†]	t _{max} (h) [‡]	t _{1/2} (h) [‡]
8624.6 (38.3%)	8984.5 (36.8%)	1307.0 (41.0%)	4.65 ± 1.29	4.93 ± 0.71

[†]Geometric mean (%CV)

[‡]Mean ± SD

*Excludes Subject 007

Urinary Pharmacokinetics

Mean cumulative amounts of ciprofloxacin, M1, M2 and M3 recovered in the urine are presented in Figures 24 and 25. The pharmacokinetic parameter results for M4 (formylciprofloxacin) in urine were not calculated in this study as all concentrations for this particular metabolite were below the limit of quantitation.

FIGURE 24
Mean Ciprofloxacin Cumulative Amount Recovered in Urine
Following the Administration of Proquin™ 500 mg

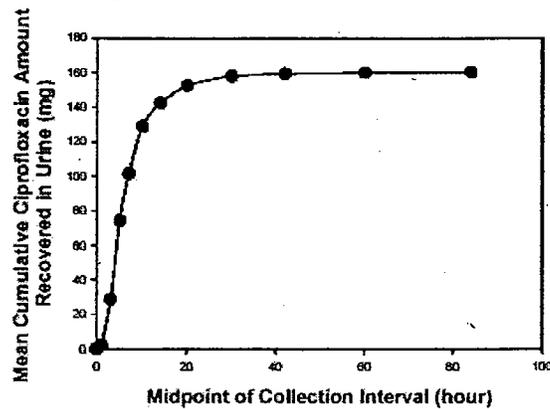
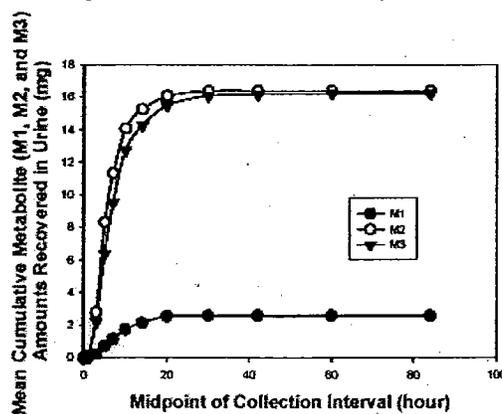


FIGURE 25
Mean M1, M2, and M3 Cumulative Amounts Recovered in Urine
Following the Administration of Proquin™ 500 mg



The mean urinary pharmacokinetic parameters for ciprofloxacin, M1, M2, and M3 are summarized in Table 65.

TABLE 65
Mean Urinary Pharmacokinetic Parameters for Ciprofloxacin, M1, M2, and M3
(Excluding Subject 007)

Pharmacokinetic Parameter	Ciprofloxacin	M1	M2	M3
TAc (mg)	167.5 (15.7%) [†] 169,4 ± 26,7 [‡]	2,74 (20.9%) [†] 2,80 ± 0,58 [‡]	16,9 (26.8%) [†] 17,5 ± 4,68 [‡]	16,7 (24.0%) [†] 17,1 ± 4,12 [‡]
Max Rate (mg/h) [‡]	25,4 ± 5,61	0,294 ± 0,07	3,09 ± 0,91	2,25 ± 0,67
T _{max} Rate _{urine} (h) [†]	5,00 ± 0,89	5,73 ± 1,01	5,0 ± 0,89	5,55 ± 0,93
CL _r /F (L/h) [‡]	20,7 ± 5,80	NC	NC	NC
%Dose (% CV)	33,9 (15,7%)	0,61 (20,9%)	2,81 (26,8%)	3,29 (24,0%)

[†]Geometric mean (%CV)

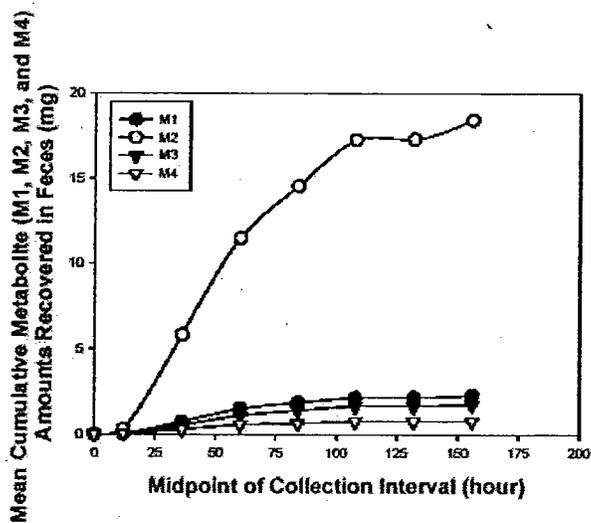
[‡]Mean ± SD

NC – not calculated

Fecal Pharmacokinetics

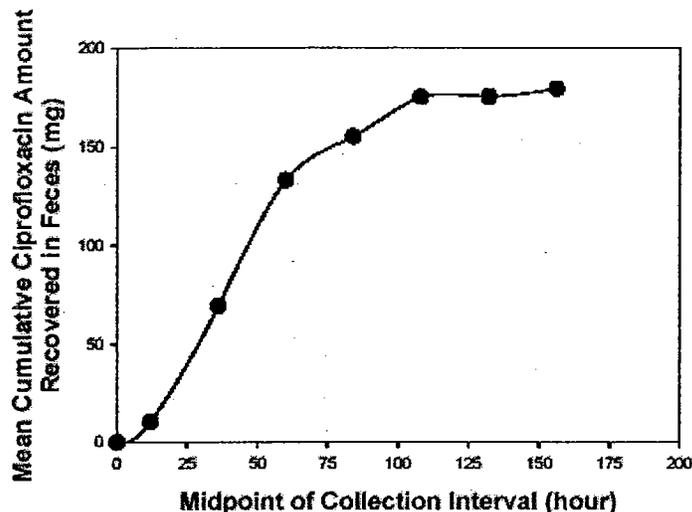
Mean cumulative amounts of ciprofloxacin, M1, M2, M3, and M4 recovered in the feces are presented in Figures 26 and Figure 27.

FIGURE 26
Mean Ciprofloxacin Cumulative Amount Recovered in Feces
Following the Administration of Proquin™ 500 mg



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FIGURE 27
Mean M1, M2, M3, and M4 Cumulative Amounts Recovered in
Feces Following the Administration of Proquin™ 500 mg



The mean fecal pharmacokinetics results are summarized in Table 66.

TABLE 66
Mean Fecal Pharmacokinetic Parameters for Ciprofloxacin and its
Metabolites (M1, M2, M3, and M4)
(Excluding Subject 007)

	Ciprofloxacin	m1	m2	m3	m4
$A_{e\text{feces}}$ (mg)	184.0 (32.1%) [†] 195.5 ± 62.7 [‡]	2.43 (19.6%) [†] 2.47 ± 0.48 [‡]	19.8 (17.3%) [†] 20.1 ± 3.48 [‡]	1.85 (25.1%) [†] 1.90 ± 0.48 [‡]	0.75 (39.0%) [†] 0.83 ± 0.33 [‡]
Max Rate _{feces} (mg/hr) [‡]	4.64 ± 2.81	0.06 ± 0.031	0.48 ± 0.24	0.05 ± 0.02	0.02 ± 0.01
T _{max} Rate _{feces} (hr) [‡]	64.4 ± 39.9	70.9 ± 34.6	70.9 ± 36.2	70.9 ± 36.2	66.5 ± 37.3
%Dose _{feces} (%CV)	39.1 (32.1%)	0.54 (19.5%)	3.24 (17.3%)	0.37 (25.2%)	0.15 (39.0%)

[†]Geometric mean (%CV)

[‡]Mean ± SD

The total recovery, in urine and feces, of ciprofloxacin and the metabolites, M1, M2, M3, and M4, are summarized in Table 67.

TABLE 67
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
Urine	33.9%	0.61%	2.81%	3.29%	-	40.6
Feces	39.1%	0.54%	3.24%	0.37%	0.15%	43.4%
Total	73.0%	1.15%	6.05%	3.66%	0.15%	84.0%

Safety Results:

- Of the 12 subjects in this study, 3 subjects (25%) experienced a total of 10 treatment-emergent AEs. Seven (7) of the 10 AEs were mild in severity and 3 were moderate. The Investigator considered 1 AE of mild nausea to be possibly related to the study treatment, and the remaining AEs to be either remotely related or unrelated.
- No serious AEs occurred in this study.
- No subject discontinued the study due to an AE, and all AEs in this study resolved.

REVIEWER'S COMMENTS

1. In this Mass Balance Study, about **85%** of the administered dose was accounted for, i.e., 34% and 39% of the dose was excreted as unchanged ciprofloxacin in urine and feces, respectively, whereas 7% and 4% of the administered dose was excreted into the urine and the feces, respectively, as ciprofloxacin metabolites.
2. Since none of the subjects in the study population were smokers (Smoking is a CYP1A2 inducer; ciprofloxacin is a CYP1A2 substrate), these ciprofloxacin disposition findings apply to the general population of non-smokers, with mean age of 28 years old (19 to 43 years old) who were predominantly (82%) Caucasians (the remainder were Blacks). Seven of the 11 subjects evaluated for ciprofloxacin PK were females.
3. 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.
4. M2 (sulfociprofloxacin) is the major metabolite of ciprofloxacin appearing in both the urine and the feces; M3 (oxociprofloxacin) is also a major urinary metabolite.

**APPEARS THIS WAY
ON ORIGINAL**

Study 84-0001

In Vitro Protein Binding of Ciprofloxacin in Human Plasma

Objective

To evaluate the extent of protein binding of ciprofloxacin in human plasma *in vitro*.

Materials

Test System

Pooled plasma with anticoagulant (Na heparin) was derived from human males who did not take any medications during the 7 days prior to blood collection. The pH of the plasma was adjusted, if needed, to approximately pH 7.4 with hydrochloric acid.

Buffer solution

A 0.1 M sodium-potassium phosphate buffer (pH 7.4) was used to prepare stock solutions and working solutions of ciprofloxacin.

Methodology

Fortification of Matrices

The appropriate fortification solution (ciprofloxacin 0.9, 3, 9, or 30 μM) was added to the matrix and the contents of the vial were mixed. The matrix was then incubated at approximately 37°C for approximately 15 minutes.

Ultrafiltration

The fortified matrix was centrifuged (37°C, 2,000 xg) using an ultrafiltration device (with MW cut-off 30,000 Da) to separate the unbound drug from the plasma-bound drug. The ultrafiltrate was weighed and analyzed for ciprofloxacin using LC/MS/MS. All protein binding determinations were done in triplicate.

Nonspecific binding

A fortified buffer (ciprofloxacin 30 μM) was centrifuged as stated above. The difference in concentration between the filtered and the initial unfiltered fortified buffer was the amount of nonspecific binding.

Calculations

Percentage of nonspecific binding = $100 * (C_{\text{matrix}} - C_{\text{ultrafiltrate}}) / C_{\text{matrix}}$

Protein Binding = $100 * (C_{\text{ultrafiltrate}} / C_{\text{matrix}})$

Results and Discussion

- Based on stability data after 15-minute incubation at 37°C, ciprofloxacin was considered to be sufficiently stable in plasma and buffer under the conditions of the study.
- Nonspecific binding of ciprofloxacin to the ultrafilter was 3.71% at 30 μM .
- The mean and individual percentages of bound ciprofloxacin in human plasma at various test concentrations are given in the table below.

TABLE 68

Concentration (μM)	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

- The plasma protein binding of ciprofloxacin in human plasma is low (<50%) and does not appear to be concentration dependent between 0.9 and 9 μM . Protein binding of ciprofloxacin may decrease between 9 and 30 μM .

Reviewer's comment:

At ciprofloxacin 3 μM ($\approx C_{\text{max}}$ in healthy volunteers), the percentage of plasma protein binding of ciprofloxacin was about 37%. At >3 μM ciprofloxacin concentrations, the magnitude of plasma protein binding is expected to decrease. Thus, ciprofloxacin has a low potential to alter the pharmacokinetics of drugs that are highly protein bound is low.

**APPEARS THIS WAY
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Study 84-0002**Inhibitory Potential of Ciprofloxacin Towards Human Hepatic Microsomal Cytochrome P450 Isoenzymes****Objective:**

To determine the potential of ciprofloxacin to inhibit the major human cytochrome P450 (CYP) isoenzymes (CYP1A2, CYP2C9, CYP2C19, CYP2D6, and CYP3A4).

Study Design:

This *in vitro* study used pooled human hepatic microsomes from fifteen individuals to test the potential of ciprofloxacin to inhibit the metabolism of test substrates at concentrations that give half the maximum reaction velocity (K_m) for human hepatic microsomes in the assay. Assays were performed in the absence and presence of ciprofloxacin (0.3 to 9.0 μM).

Methodology:

The probe substrate in assay buffer was incubated with microsomal protein (0.1 to 0.5 mg/mL) and NADPH (1 mM), in the absence or presence of ciprofloxacin. Incubation was carried out in 96-well tube plates at 37°C. The reaction was terminated after 3 to 60 minutes depending on the assay, by the addition of a specific organic solvent solution. Samples were centrifuged and the resulting supernatant was analyzed using LC/MS/MS for the metabolite of interest.

Results and Discussion:

Table 69 presents the values for percent activity remaining relative to the negative control in each CYP-isoenzyme-specific assay at each concentration of ciprofloxacin.

TABLE 69
Effect of ciprofloxacin on CYP450 activity

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

NA- not applicable

* average of triplicate values

As seen from Table 69 above, 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. Consequently, IC_{50} values were not calculated. At 90 μM , there was minor inhibition observed for CYP1A2 and CYP2C19.

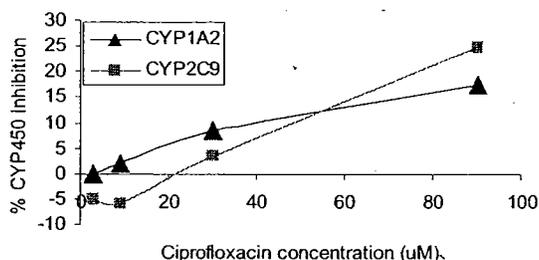
Sponsor's conclusion:

Ciprofloxacin at plasma concentrations up to 90 μM in human subjects would not be expected to cause inhibitory drug-drug interactions with concomitantly administered medications that are substrates of CYP1A2, CYP2C9, CYP2C19, CYP2D6, and/or CYP3A4.

Reviewer's comments:

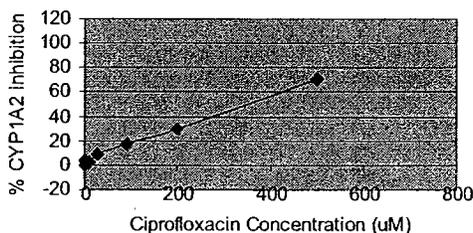
1. All the probe substrates in this *in vitro* metabolic inhibition study were acceptable and the concentrations at which they were used were within or close to the acceptable concentration range, as specified in the draft Guidance for *in vitro/in vivo* drug interaction studies.
2. The microsomal protein concentration (< 1 mg/mL) used in the study is acceptable.
3. The plasma $C_{max,ss}$ of ciprofloxacin from Proquin™ 500 mg QD in healthy volunteers is about 820 ng/mL (range: — ng/mL). At the maximum test concentration (90 μ M) used in the *in vitro* metabolic inhibition study, ciprofloxacin was able to decrease the activities of CYP1A2 and CYP2C9 by 18% and 25%, respectively. Because these inhibitory effects occurred at a test concentration of about $\approx 36x$ the $C_{max,ss}$ of ciprofloxacin from Proquin™, the applicant did not consider any of such decreases in enzyme activity of potential clinical relevance. In addition, there was no apparent inhibitory effect on all five of the tested CYP450 isoforms at ciprofloxacin 3 μ M ($\approx C_{max,ss}$).
4. However, since positive inhibitor controls were not included in the study, it would be difficult to validate the negative test results for ciprofloxacin. This same *in vitro* study should have shown that the chosen positive inhibitor controls were able to produce at least an 80% inhibition of CYP450 enzyme activity.
5. Nevertheless, it was evident that ciprofloxacin had a concentration-dependent increase in inhibitory activity against CYP1A2 and CYP2C9, as seen in the Figure 28 below.

FIGURE 28



6. In two separate published studies (Fuhr et al., 1992; Granfors et al., 2004) that evaluated the CYP1A2 inhibitory potential of ciprofloxacin, 200 μ M and 500 μ M concentrations were able to produce 30% and 70% inhibition of CYP1A2 metabolic activity. When these literature data were used to extend the CYP1A2 inhibitory profile of ciprofloxacin in the present study, the linear concentration-dependent inhibitory activity of ciprofloxacin was verified (see Figure 29 below).

FIGURE 29



7. 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 μ M) but not at lower test

concentrations (10 and 100 μM ; Sarkar et al., 1990; Fuhr et al, 1992). Thus, it is speculated here that ciprofloxacin achieves concentrations within the locale of CYP1A2 enzymes 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_{max} 0.5 to 1 hour], tizanidine AUC increased by 10-fold and C_{max} by 7-fold (Granfors et al., 2004).

8. 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 anticoagulant effects of warfarin (a CYP2C9/CYP3A4 substrate), especially in elderly patients with infection and under long-term anticoagulant therapy.

Reviewer's Labeling Recommendation:

Because the *in vitro* metabolic inhibition study conducted did not use positive inhibitor controls, the lack of significant CYP450 metabolic inhibitory activity by ciprofloxacin at concentrations of up to 9 μM ($\approx 3 \times C_{\text{max,ss}}$) could not be validated. The potential of ciprofloxacin to inhibit the enzyme activity of CYP1A2 and CYP2C9 could not be excluded. Despite the overall negative *in vitro* CYP450 inhibitory findings of the study conducted, the label should mention the potential of ciprofloxacin to decrease the clearance of specific drugs that are known CYP1A2 substrates (e.g., theophylline) for which there has been sufficient clinical evidence of a drug interaction. It is not known whether ciprofloxacin achieves hepatocyte concentrations that are much higher than the maximal plasma concentrations tested in the *in vitro* study.

**APPEARS THIS WAY
ON ORIGINAL**

Study 84-0003**Evaluation of CYP450 Induction Potential of Ciprofloxacin Using Primary Cultures of Human Hepatocytes****Objective:**

- To measure the extent of induction of specific CYP450 marker enzymes (CYP1A, CYP2C, CYP3A) by ciprofloxacin using human hepatocytes
- To compare the effects of ciprofloxacin with standard prototypical inducers

Study Design:**Methodology:**

Human hepatocytes were incubated for 48 hours with ciprofloxacin (0.45, 4.5, and 45 μM) and omeprazole or rifampicin as prototypical inducers of CYP1A, CYP2C, and CYP3A isoforms. Selective substrates were introduced and the effects of ciprofloxacin and the prototypical inducers were quantified.

Results:

The demographics for the three human liver donors are presented in Table 70. The medical and drug histories of these patients did not indicate that their livers were unsuitable for use in induction studies.

TABLE 70
Donor demographics

Donor number	Sex	Age	Race	Medical history*	Drug history*	Cell viability (%)†
1	Female	76	Cauc	None provided	None	83
2	Male	45	Cauc	Sigmoid colon adenocarcinoma Sigmoid colectomy	None	93
3	Female	65	Cauc	Hypertension	Beclomethasone Enalapril Fexofenadine Bendrofluzide Loperamide	77

Cauc: Caucasians

*based on information made available to UKHTB Ltd. Not necessarily exhaustive/complete

†measured on receipt at Covance by trypan blue exclusion

Table 71 summarizes the fold-induction data on CYP1A2, CYP2C9 and CYP3A enzyme activities by ciprofloxacin (0.45 μM to 45 μM), as well as by the positive inducer controls. There was a weak induction effect by ciprofloxacin at 45 μM (approximately 18x the expected $C_{\text{max,ss}}$ of ciprofloxacin from a 3-day treatment with Proquin™ 500 mg tablets QD, the recommended treatment regimen for uncomplicated urinary tract infection).

TABLE 71
CYP1A2 Fold-induction

Donor	0.5% v/v DMSO	Omeprazole (30 μM)	Cipro (0.45 μM)	Cipro (4.5 μM)	Cipro (45 μM)
1	/	/	/	/	/
2	/	/	/	/	/
3	/	/	/	/	/
mean	0	12.90	0.90	1.33	1.80
sd	0	7.72	0.10	0.25	0.46

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CYP2C9 Fold - induction

Donor	0.5% v/v DMSO	Rifampin (50 μ M)	Cipro (0.45 μ M)	Cipro (4.5 μ M)	Cipro (45 μ M)
1	/	/	/	/	/
2	/	/	/	/	/
3	/	/	/	/	/
mean	0	4.10	1.00	1.20	1.00
.sd	0	0.80	0.36	0.46	0.30

CYP3A Fold-induction

Donor	0.5% v/v DMSO	Rifampin (50 μ M)	Cipro (0.45 μ M)	Cipro (4.5 μ M)	Cipro (45 μ M)
1	/	/	/	/	/
2	/	/	/	/	/
3	/	/	/	/	/
mean	0	3.43	1.13	1.20	1.17
sd	0	1.33	0.31	0.44	0.15

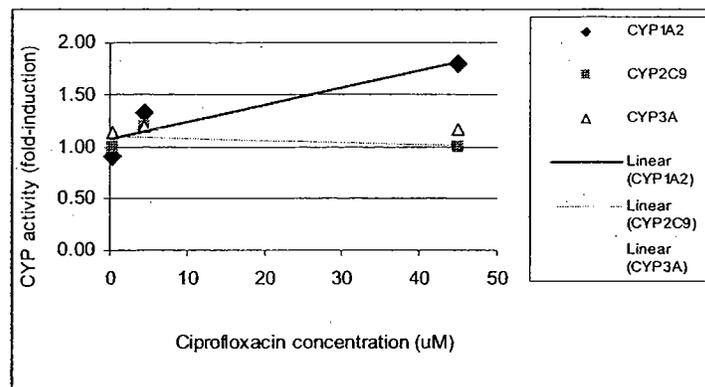
Conclusions:

- Ciprofloxacin (at concentrations of 0.45 to 45 μ M) did not induce CYP2C or CYP3A activities of primary cultures of human hepatocytes.
- Ciprofloxacin (at 45 μ M) showed a weak induction effect on CYP1A2.

Reviewer's comments:

1. The positive inducer controls and test concentrations used in this *in vitro* study are acceptable. At the chosen test concentrations, all these positive inducer controls were able to demonstrate a >2-fold induction in CYP isoforms activity in hepatocytes from all three donor livers.
2. The test drug (ciprofloxacin) concentrations were within an acceptable range that included a concentration (45 μ M) that was at least 1 order of magnitude greater than the expected $C_{max,ss}$ of ciprofloxacin from ProquinTM.
3. That up to 45 μ M ciprofloxacin ($\approx 18x C_{max,ss}$) did not induce the activities of these two enzymes *in vitro* suggest that the potential for *in vivo* induction of the metabolism of drugs that are CYP3A or CYP2C substrates is low.
4. The lack of (>2-fold) induction effect on both CYP3A and CYP2C9 by ciprofloxacin indirectly supports the notion that these two CYP450 isoforms are co-inducible.
5. The findings that 45 μ M ciprofloxacin produced almost a 2-fold induction of CYP1A2 metabolism and that ciprofloxacin produced a dose-dependent increase in CYP1A2 induction effect (see Figure 29 below) are probably not clinically significant. Because the fold-induction effect of ciprofloxacin (up to 45 μ M) *in vitro* is <40% that produced by omeprazole 30 μ M, an *in vivo* CYP1A2 induction study for ciprofloxacin is not warranted.

FIGURE 29



6. At this time, there is no literature evidence that ciprofloxacin has a CYP1A2 induction effect *in vitro* or *in vivo* in humans.

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Study 81-0035**A Three-way, Crossover, Open-Label, Single-Dose, Fed, Pharmacokinetic/Pharmacodynamic Study of the Interaction Between Proquin™ 500 mg Tablets and Coumadin® 7.5 mg Tablets in Normal Healthy Non-Smoking Male Subjects****Objectives:****Primary-**

To assess the single dose pharmacokinetic and pharmacodynamic interaction between Proquin™ 500 mg tablets and warfarin (Coumadin®) 7.5 mg tablets under fed conditions. A single dose study was conducted because the effect on absorption of either drug was to be evaluated.

Secondary-

To assess the safety and tolerability of the Proquin™ 500 mg tablet when co-administered with the Coumadin® 7.5 mg tablet under fed conditions

Study Design:

A randomized, three-way, crossover open-label, single-dose, fed design

Study Population:

All 18 enrolled healthy, non-smoking male subjects with mean age of 36 years (22 to 51 years) completed the study. The mean weight was 80 kg (64 to 104 kg); the mean height was 1.74 m (1.65 to 1.88 m). There were 11 Caucasians, 5 Asians, and 2 Blacks.

Dosing and Administration:

Following a fast of at least 6 hours, subjects were fed a standardized, approximately 500-600 calorie moderate-fat content meal (consumed within 30 minutes). At 0.0 hour, one of the following treatments was received with 240 mL of water. There was a 2-week wash-out period in between treatments.

Treatment A: 1-Proquin™ 500 mg tablet (Lot No. HT3602; potency — , of label claim)
1-Coumadin® 7.5 mg tablet

Treatment B: 1-Coumadin® 7.5 mg tablet

Treatment C: 1-Proquin™ 500 mg tablet

Dietary and Fluid control:

- Water will be provided *ad libitum* until 1 hour pre-dose and after 1 hour post-dose. The study drug will be administered 30 minutes after the start of the moderate fat content meal, with 240 mL of ambient temperature water.
- No food will be allowed for at least 4 hours post-dose. Standardized meals and drinks will be provided at designated times.
- Beverages with grapefruit, caffeine, xanthine, or with calcium fortification, and dairy products (except butter) will not be allowed.
- This study did not institute a fluid control technique (100 mL water every hour or every 2 hours after the Proquin™ dose) used in earlier PK studies.

Blood Sample Collection: Sixteen blood samples (10 mL each) will be drawn in each study period according to the following schedule:

0 (predose), 0.5, 6, 12, 24, 36, 48, 72, 96, and 120 hours post-drug administration

Analytical Methods:

A validated HPLC method was used to quantify ciprofloxacin. LC/MS/MS was used to quantify S-warfarin and R-warfarin.

Pharmacokinetics:

Plasma pharmacokinetic analysis will be conducted using a non-compartmental analysis. Parameters AUC_{0-t} , AUC_{0-inf} , C_{max} , T_{max} , and $t_{1/2}$, CL/F , and Vd/F will be calculated for ciprofloxacin, S-warfarin, and R-warfarin.

Pharmacodynamics:

- PT (baseline-corrected maximum prothrombin time, time to maximum prothrombin time, and area under the prothrombin time-versus time curve (AUCPT)) and
- aPTT (area under the activated partial thromboplastin time-versus time curve (AUCaPTT))

Results and Discussion:Pharmacokinetics

TABLE 72
Pharmacokinetic Parameters of Ciprofloxacin

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 [†]
AUC_{0-t} (ng·hr/mL)	7519.1 (26.9) ^{‡§}	7241.6 (23.6) ^{‡§}	0.344 [‡]
AUC_{0-inf} (ng·hr/mL)	7926.8 (25.8) ^{‡§}	7616.0 (23.3) ^{‡§}	0.291 [‡]
C_{max} (ng/mL)	862.7 (20.9) ^{‡§}	818.7 (19.9) ^{‡§}	0.382 [‡]
T_{max} (hr)	4.50 ± 0.98 [‡]	4.89 ± 1.94 [‡]	0.420
$t_{1/2}$ (hr)	5.02 ± 0.70 [‡]	5.07 ± 0.84 [‡]	0.803
CL/F (mL/min)	1072.59 ± 206.15 [‡]	1120.67 ± 253.81 [‡]	0.297
Vd/F (L)	461.56 ± 91.82 [‡]	486.63 ± 115.35 [‡]	0.211

[†] Geometric mean (%CV)

[‡] Mean ± SD

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

[§] Manually rounded from values obtained in Appendix 3

TABLE 73A
Pharmacokinetic Parameters of R-Warfarin

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 [†]
AUC_{0-t} (ng·hr/mL)	18875.1 (17.5) ^{‡§}	18638.8 (20.1) ^{‡§}	0.554 [‡]
AUC_{0-inf} (ng·hr/mL)	23935.1 (25.6) ^{‡§}	23311.5 (23.5) ^{‡§}	0.178 [‡]
C_{max} (ng/mL)	312.1 (17.7) ^{‡§}	316.4 (18.2) ^{‡§}	0.630 [‡]
T_{max} (hr)	6.75 ± 5.05 [‡]	5.89 ± 2.45 [‡]	0.497 [‡]
$t_{1/2}$ (hr)	52.56 ± 12.48 ^{‡*}	50.10 ± 9.23 [‡]	0.029 [‡]
CL/F (mL/min)	5.37 ± 1.28 [‡]	5.50 ± 1.33 [‡]	0.111 [‡]
Vd/F (L)	23.54 ± 4.13 ^{‡*}	23.22 ± 4.04 [‡]	0.733 [‡]

[†] Geometric mean (%CV)

[‡] Mean ± SD

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

^{*} n = 17

[§] Manually rounded from values obtained in Appendix 3

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TABLE 73B
Pharmacokinetic Parameters of S-Warfarin

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 ^d
AUC ₀₋₄ (ng-hr/mL)	11742.9 (20.6) ^{†‡}	11894.1 (20.3) ^{†‡}	0.539 ^d
AUC _{0-inf} (ng-hr/mL)	13361.1 (22.7) ^{†‡}	13512.9 (22.5) ^{†‡}	0.667 ^d
C _{max} (ng/mL)	287.3 (20.2) ^{†‡}	291.9 (21.5) ^{†‡}	0.555 ^d
T _{max} (hr)	4.03 ± 1.12 [†]	4.53 ± 2.16 [†]	0.315
t _{1/2} (hr)	39.28 ± 5.89 [†]	39.03 ± 5.31 [†]	0.842
CL/F (mL/min)	9.55 ± 1.88 [†]	9.44 ± 1.88 [†]	0.663
Vd/F (L)	32.10 ± 6.39 [†]	31.48 ± 5.78 [†]	0.386

[†] Geometric mean (%CV)

[‡] Mean ± SD

^d The p-value is from ANOVA on ln-transformed data

[†] Manually rounded from values obtained in Appendix 3

TABLE 74A
Relative Bioavailability Analysis of Treatment A Versus Treatment C for Ciprofloxacin

Parameter	90% C.I.	Ratio of Means	Intra-Subject CV
AUC ₀₋₄	97.06% to 111.07%	103.83%	11.54%
AUC _{0-inf}	97.62% to 110.98%	104.08%	10.98%
C _{max}	95.16% to 116.70%	105.38%	17.46%

TABLE 74B
Relative Bioavailability Analysis of Treatment A versus Treatment B for R-Warfarin

Parameter	90% C.I.	Ratio of Means	Intra-Subject CV
AUC ₀₋₄	95.25% to 102.32%	98.72%	6.12%
AUC _{0-inf}	94.49% to 103.46%	98.87%	7.76%
C _{max}	93.98% to 103.07%	98.42%	7.90%

TABLE 74C
Relative Bioavailability Analysis of Treatment A versus Treatment B for S-Warfarin

Parameter	90% C.I.	Ratio of Means	Intra-Subject CV
AUC ₀₋₄	95.25% to 102.32%	98.72%	6.12%
AUC _{0-inf}	94.49% to 103.46%	98.87%	7.76%
C _{max}	93.98% to 103.07%	98.42%	7.90%

Pharmacodynamics

TABLE 75
Pharmacodynamic Parameters of Warfarin

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 _{max} PT (hr) [§]	29.0 ± 25.6	30.1 ± 31.9	0.872
PT _{max} (sec) [§]	12.6 ± 0.9	12.4 ± 0.8	0.079
AUCPT (hr*sec) [†]	1428.9 ± 71.2	1419.0 ± 70.6	0.142
AUCaPTT (hr*sec) [†]	3439.2 ± 204.0	3406.3 ± 210.4	0.180

[†] Manually rounded from values obtained in Appendix 3

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Safety

There were three treatment-emergent AEs in the study. The frequency of AEs were 0, 2 (from 2 subjects), and 1 from Treatment A, B, and C, respectively. No serious AEs were reported.

Sponsor's Conclusions:

- Warfarin did not inhibit the absorption of ciprofloxacin when Proquin™ 500 mg tablets and Coumadin® 7.5 mg Tablet were co-administered as a single dose in the presence of food.
- The co-administration of 1-Proquin™ 500 mg tablet had no significant effect on the absorption and metabolism of either R- or S-warfarin, as well as the prothrombin time and activated thromboplastin time, from a single dose of Coumadin® 7.5 mg Tablet under fed condition.

Reviewer's comments:

1. In the *in vitro* CYP450 inhibition study conducted, up to 90 µM ciprofloxacin concentration (equivalent to about 40x the C_{max} of ciprofloxacin from Proquin™ in healthy volunteers), only 25% of CYP2C9 inhibition was seen. However, as was observed for CYP1A2, there was a concentration-dependent increase in CYP2C9 inhibition by ciprofloxacin.
2. Most drug interaction studies in the literature involving immediate-release ciprofloxacin and warfarin were multiple-dose studies. However, since Cipro® (immediate-release) and Proquin™ have similar systemic exposures, and because Proquin™ will be recommended to be taken with a meal and has a gastro-retentive drug release profile (unlike Cipro®), a single-dose study design was chosen by the sponsor with the aim of determining whether there is an early or absorptive phase interaction between the 2 drugs of interest.
3. The findings suggest that *single dose* co-administration of warfarin and ciprofloxacin does not result in changes in the C_{max} and AUC of ciprofloxacin, and the two enantiomers of warfarin. This finding is in agreement with the findings of single dose studies of other fluoroquinolones that also failed to show a drug interaction (Rocci et al 1990; Toon et al 1987; Liao et al, 1996). However, there was a slight but statistically significant increase in the elimination half-life of R-warfarin.
4. Several *multiple-dose* drug interaction studies in the literature have shown that ciprofloxacin and other fluoroquinolones could cause increases in warfarin's hypoprothrombinemic effect. Prospective multiple-dose studies involving subjects on anticoagulant therapy have failed to corroborate this finding but it should be noted that the study population in these studies were not receiving ciprofloxacin for treatment of infection. The following table summarizes PK and PD findings of two such published drug interaction studies.

TABLE 76

Authors (year)	Dosing and Administration	Study Population	PK and PD Findings
Israel et al., 1996	Ciprofloxacin 750 mg PO BID x 12 days	<u>Volunteers</u> receiving chronic warfarin therapy (n=36)	*Day 12 concentrations of : - S-warfarin did not change; - R-warfarin increased significantly (1.15x of placebo); - clotting factors II and VII decreased Day 12, mean PT ratio increased slightly (1.032 x of placebo) but no patient had bleeding or change in PT that required alteration in warfarin or ciprofloxacin therapy
Bianco et al, 1992	Ciprofloxacin 500 mg PO BID or placebo x 10 days	<u>Volunteers</u> stabilized on warfarin (n=16)	No significant increase in INR or bleeding events

5. It is thus possible that the hypoprothrombinemic effect observed in patients taking warfarin and ciprofloxacin is not due solely or mainly 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 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.

6. 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.
7. Serum levels of warfarin tend to be lower when administered with food but the extent of exposure is not affected. The effect of the moderate-fat content meal on the observed C_{max} of warfarin in this study is not known.

Reviewer's Labeling Recommendation:

The ability of a single-dose drug interaction study between warfarin and ciprofloxacin in healthy volunteers to detect *in vivo* PK and/or PD drug interaction in patients with infection and under long-term anticoagulation therapy is uncertain. Although the exact mechanism behind or role of ciprofloxacin in bleeding AE case reports received by FDA is not established to this time, the label of PROQUIN™® will state that as is the case with other fluoroquinolones, PROQUIN™® should be administered with caution in patients receiving coumarin anticoagulant therapy and as such, prothrombin time and international normalized ratio (INR) should be monitored very closely.

**APPEARS THIS WAY
ON ORIGINAL**

Study 81-0032**One-Way, Single-Dose, Fed, Pharmacokinetic Study of Proquin™ 500 mg Tablets In Normal Healthy Non-Smoking Male and Female Subjects Over 65 Years of Age****Objective:**

To determine the pharmacokinetics and safety of Proquin™ 500 mg tablets in elderly subjects

Study Design:

This is a one-way, single-dose study of patients under fed conditions.

Study Population:

Sixteen (16) normal, healthy, non-smoking elderly subjects (10 males, 6 females), with mean age of 69 years (65 to 80 years) were enrolled in this study. The mean weight was 72 kg (54 to 87 kg); the mean height was 1.65 m (1.49 to 1.81 m). There were 12 Caucasians, 2 Asians and 2 Blacks. All the subjects in this study had normal serum creatinine values (60-110 µM for males and 50-100 µM for females).

Dosage and Administration:

Following an overnight fast of at least 10 hours, one Proquin™ 500 mg tablet (Lot # HT3602) was taken by each patient with 240 mL of water, 30 minutes after the start of a standardized, approximately 500 to 600 calorie, moderate fat content meal.

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, 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 were drawn in the study at 0 (predose), 0.5, 1.0, 2.0, 3.0, 3.5, 4.0, 4.5, 5.0, 5.5, 6.0, 9.0, 12.0, 14.0, 18.0, 24.0, and 36.0 hours post-drug administration.

Urine samples were collected from all subjects during the following time intervals: prior to dosing (complete void and collection), 0-2.0, >2.0-4.0, >4.0-6.0, >6.0-8.0, >8.0-10.0, >10-12, >12-16, >16-24, >24-36 hours post-dose.

Analytical Procedure:

A validated HPLC assay was employed for the analysis of ciprofloxacin in plasma and urine samples. For plasma samples, the LLOQ was 24.999 ng/mL and for urine the LLOQ was 1.5 µg/mL.

Criteria for evaluation:**Pharmacokinetics**

The C_{max} and T_{max} were determined by visual inspection of the plasma concentration-time profiles. Using non-compartmental modeling, the following pharmacokinetic parameters were determined from the plasma profiles: Areas under the concentration-time curve from time zero to time of last measurable concentration, [AUC(0-t)], AUC(0-∞), and t_{1/2}; from urine profiles: the amount excreted in urine (A_e), renal clearance (CL_r), maximum observed excretion rate (Max Rate), midpoint of collection interval associated with the maximum observed excretion rate (T_{max} Rate), and the percent of dose excreted in urine (% Dose).

Safety

The incidence of adverse events were tabulated. Absolute values for vital signs, ECGs, laboratory parameters and physical examination were also documented and values outside the normal range were flagged. Abnormal shifts from baseline were tabulated.

Statistical Methods:

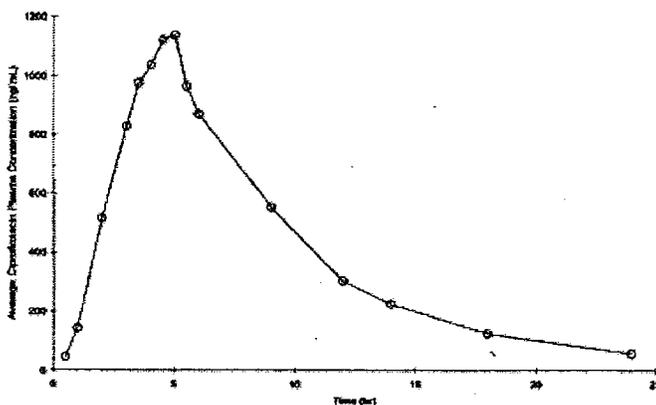
Descriptive statistics (e.g., mean, standard deviation, relative standard deviation, regression analyses) were performed for plasma concentrations and for all PK parameters.

Results and Discussion:Pharmacokinetics

Mean and individual ciprofloxacin plasma concentration-time profiles following ingestion of Proquin™ 500 mg tablets with a moderate fat content meal are presented in Figures 30 and 31. The semilogarithmic plot indicates that the pharmacokinetics of ciprofloxacin fits a 1-compartment model with first-order elimination from systemic circulation (Figure 32). The pharmacokinetic parameters for ciprofloxacin in plasma are summarized in the Table 77.

Figure 30

Mean plasma ciprofloxacin plasma concentration-time profile of subjects following a single dose of Proquin™ 500 mg tablets under fed conditions (Linear plot)

**Figure 31**

Individual plasma ciprofloxacin plasma concentration-time profile of subjects following a single dose of Proquin™ 500 mg tablets under fed conditions

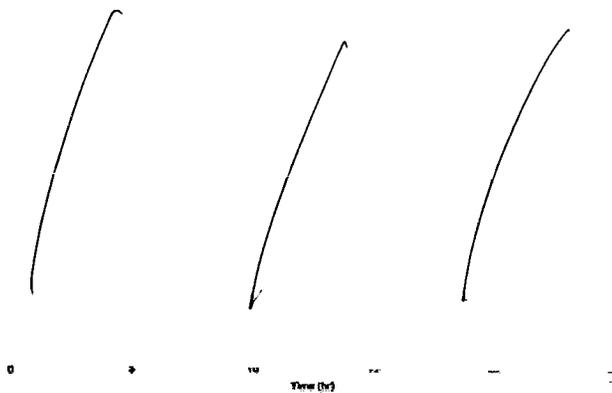


Figure 32
Mean plasma ciprofloxacin plasma concentration-time profile of subjects following a single dose of Proquin™ 500 mg tablets under fed conditions (Semi-logarithmic plot)

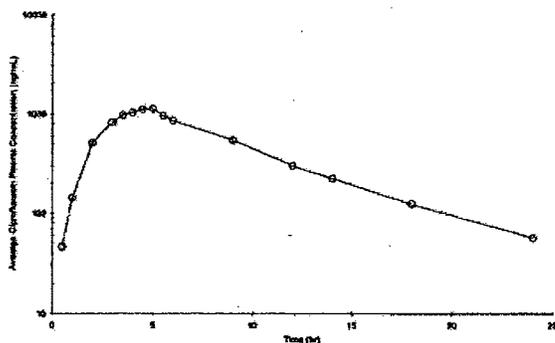


TABLE 77
PHARMACOKINETIC PARAMETERS FOR CIPROFLOXACIN IN PLASMA

PHARMACOKINETIC PARAMETER	PROQUIN™ 500 MG TABLETS (N=16) GEOMETRIC MEAN (% CV)
AUC _{0-t} (ng.h/mL)	8853.2 (32.2)
AUC _{0-∞} (ng.h/mL)	9256.0 (31.7)
C _{max} (ng/mL)	1285.5 (26.8)
T _{max} (hr) mean/SD median	4.19 ± 0.81 4.50
t _{1/2} (hr)	4.89 ± 0.80

Mean and individual ciprofloxacin cumulative urinary excretion profiles following ingestion of Proquin™ 500 mg tablets with a moderate fat content meal are presented in Figure 33. The pharmacokinetic parameters for ciprofloxacin in urine are summarized in the Table 78. Approximately 30% of the orally administered dose was recovered unchanged in the urine during the 36 hours post-dosing.

Figure 33
Mean urinary ciprofloxacin cumulative amount excreted in urine obtained in healthy elderly subjects following a single dose of Proquin™ 500 mg tablets under fed conditions

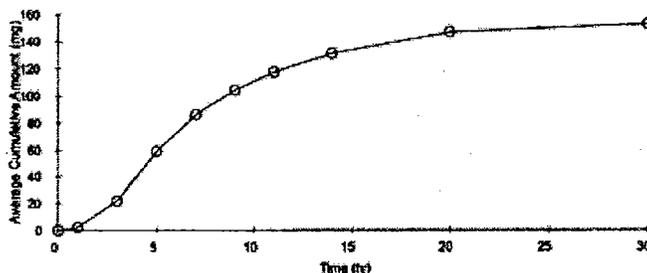


TABLE 78
PHARMACOKINETIC PARAMETERS FOR CIPROFLOXACIN IN URINE

PHARMACOKINETIC PARAMETER	PROQUIN™ 500 MG TABLETS (N=16) Mean ± SD
T _{max} Rate (hr)	5.25 ± 1.44
Max Rate (mg/hr)	24.16 ± 6.80
A _e (mg)	149.9 ^a ± 17.7
CL _r (L/hr)	17.54 ± 4.88
% Dose	30.41 ± 5.39

^a Geometric mean

Safety

There were 11 AEs reported by nine subjects during the course of the study, all of which were considered mild in severity (Table 79). The specific adverse events experienced by patients in this study (based on MedDRA preferred terminology) are listed in Table 79A. All AEs (except one episode of lightheadedness) were considered unrelated to the study drug.

Table 79
Summary of Adverse Events

	Treatment	
	A n (%)	Raw-Dose n (%)
No. of Subjects who received study treatment	18	0
Subjects Withdraw or discontinued due to AEs	0	0
Subjects with AEs	9 (50.00%)	1
Subjects with Serious AEs	0	0
Total number of AEs	11	1
Total number of Serious AEs	0	0

Table 79A
Summary of Adverse Events using preferred MedDRA terminology
As percentage of total number of subjects with AEs

Preferred Term*	Treatment A	
	n (%)	total
Total No. of AEs	11	11
Blood sodium increased	2 (18.18%)	2
Blood calcium decreased	1 (9.09%)	1
Blood chloride increased	1 (9.09%)	1
Dizziness	1 (9.09%)	1
Headache	1 (9.09%)	1
Myalgia	1 (9.09%)	1
Platelet count decreased	1 (9.09%)	1
Temipuncture site bruise	1 (9.09%)	1
white blood cells urine	1 (9.09%)	1
white blood cells urine positive	1 (9.09%)	1

*Preferred Term coded with MedDRA Version 5.1

TREATMENT A: CIPROFLOXACIN OR[®] TABLET, 1 x 500 mg, LOT # HT3692, RD

Number of Incidences per Preferred Term per Treatment

* n (percentage) x 100 = total number of incidences per treatment

Reviewer's comments:

- The sponsor compared the PK parameters in elderly patients of this study to historical younger (≤ 65 years) subject controls from Studies 81-0024, 81-0025, 81-0029, and 81-0032. The sponsor's findings (as given in Table 80 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.

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Table 80
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 ^a
		Ciprofloxacin GR 500 mg < 65 Years	Ciprofloxacin GR 500 mg ≥ 65 Years	
AUC ₀₋₄ (ng·hr/mL)	n Geometric Mean (%CV)	68 6886.7 (28.8)	18 9028.6 (30.5)	0.001
AUC _{0-∞} (ng·hr/mL)	n Geometric Mean (%CV)	66 7213.7 (28.6)	18 9429.5 (29.9)	0.001
C _{max} (ng/mL)	n Geometric Mean (%CV)	68 917.5 (42.8)	18 1273.7 (26.5)	<0.001
T _{max} (hr)	n Median Mean ± SD	68 4.50 5.52 ± 3.07	18 4.50 4.20 ± 0.81	0.002
T _{1/2} (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 ^b 23.47 23.01 ± 5.79	17 ^b 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

2. Table 81 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 selected single-dose PK studies. Note that the validity of using these historical PK data available on younger subjects is limited by study protocol differences, as noted below.

TABLE 81

PHARMACOKINETIC PARAMETER (UNIT)	ELDERLY (>65 YEARS) (STUDY 81-0032)	HEALTHY VOLUNTEERS (<65 YEARS OLD) (STUDY 81-0025) ^b	HEALTHY VOLUNTEERS (<65 YEARS OLD) (STUDY 81-0028) ^b
Proquin™ Dose (mg)	500 (single-dose)	500 (single-dose)	1000 (without antacids; single-dose)
Fat-content of meal	moderate	high	moderate
Fluid control measure	Yes	Yes	Yes
AUC ₀₋₄ (ng·h/mL)	8853.2 (32.2)	6236.7 (29.1)	7405 ^a
AUC _{0-∞} (ng·h/mL)	9256.0 (31.7)	6535.5 (28.5)	7598 ^a
C _{max} (ng/mL)	1285.5 (26.8)	691.6 (31.0)	1041 ^a
T _{max} (hr)	4.19 ± 0.81 4.50	7.04 ± 3.31 9.00	4.45 ± 1.69 4.50
t _{1/2} (hr)	4.89 ± 0.80	4.49 ± 0.83	5.11 ± 0.99
T _{max} Rate (hr)	5.25 ± 1.44	7.82 ± 3.97	5.78 ± 2.36
Max Rate (mg/hr)	24.16 ± 6.80	17.82 ± 4.76	48.24 ± 18.33
Ae (mg)	149.9 ± 17.7	131.8 (21.2)	162.4 ^a
% Dose	30	27	33.4

^a normalized to 500mg

^b values in parentheses (% CV); values after ± (SD)

The mean elderly AUC and the mean elderly Cmax were about 42% higher and about 86% higher, respectively compared to those in the healthy volunteers in Study 81-0025. The relatively greater difference in Cmax (than AUC) between the two age groups can be explained by the substantial difference in mean and median Tmax. It is evident from the data in the table above that the fat-content of the meal has an effect on the Tmax, and consequently the Cmax of ciprofloxacin. The significant difference in the rate of ciprofloxacin absorption between elderly subjects and younger subjects (Study 81-0025) is relevant because it is even expected that elderly patients will have a longer-than-normal Tmax as a result of longer gastric emptying times. Thus, as a consequence of study design differences, it was not logical to compare the Cmax (as well as other PK parameters) of the elderly subjects to healthy volunteers in Study 81-0025.

The PK of elderly subjects were compared to that of healthy younger subjects enrolled in the Antacid Drug Interaction Study 1 (81-0028) control group, as an alternative to the PK data obtained in the healthy volunteers of Study 81-0025. Healthy subjects in the control group of the Antacid Study 1 received Proquin™ alone with a moderate-fat content meal but at a dose of 1000mg; it is assumed here that the PK of Proquin™ in healthy volunteers is linear at a dose range of 500-1000mg. Considering the PK exposure values after normalization to 500mg, it appears that the ciprofloxacin AUC₀₋₄ and Cmax values in elderly subjects were slightly higher (by 20 and 24%, respectively) compared to those in younger subjects. Both the mean/median Tmax 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.

- At the time of screening, the subjects enrolled in this study had normal serum creatinine values allowing the sponsor/investigator to conclude that these subjects had normal renal function. However, when the Cockcroft-Gault equation was used to calculate creatinine clearances from the reported serum creatinine values at screening, it was revealed that 75% (12 of the 16) elderly subjects enrolled in this study had mild renal impairment (CLCr = 51-80 mL/min). The PK parameter values for ciprofloxacin based on this re-analysis are shown in the Table 82.

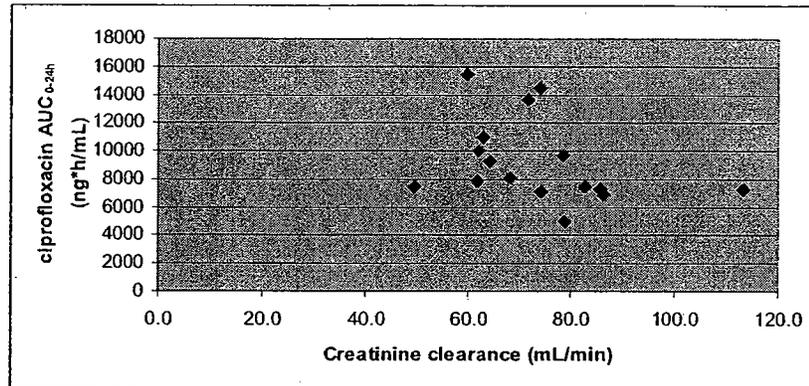
TABLE 82

Pharmacokinetic Parameter Mean ± SD (unit)	Elderly subjects with normal renal function (CLCr ≥ 80 mL/min) N=4	Elderly subjects with mild renal impairment (CLCr = 51-80 mL/min) N=12
Creatinine Clearance (mL/min)	92.05 ± 14.28	67.24 ± 8.66
Ciprofloxacin AUC _{0-24h} (ng*h/mL)	7257 ± 251	9928 ± 3203
Ciprofloxacin Cmax (ng/mL)	1074 ± 69	1407 ± 375
Ciprofloxacin Tmax (h)	4.5 ± 1.0	4.1 ± 0.8
Ciprofloxacin t _{1/2} (h)	4.8 ± 1.1	4.9 ± 0.7

It appears from Table 82 above that in elderly patients with mild renal impairment, the ciprofloxacin AUC_{0-24h} and Cmax from a single dose of Proquin™ 500mg were about 37% higher and 31% higher, respectively compared to their elderly counterparts with normal renal function (>80 mL/min). The difference in AUC_{0-24h} between the two renal groups of (mild renal impairment and normal renal function) elderly subjects in this study is similar to the exposure (AUC) difference between the same renal groups (41%) seen in Study 81-0036, a study dedicated to evaluate the effect of renal function on the PK of ciprofloxacin from a single dose of Proquin™ 500mg.

- That renal elimination is not the sole means of ciprofloxacin elimination from the body is suggested from the observation that the AUC of ciprofloxacin in these elderly subjects was not related to creatinine clearance (Figure 34).

FIGURE 34
Relationship between creatinine clearance and ciprofloxacin AUC_{0-24h} of elderly patients



Reviewer's Labeling Recommendation:

The average ciprofloxacin plasma C_{max} and AUC in elderly patients in this study were not significantly different from those observed in younger subjects from previous studies. Because no significant safety issues were associated with these slight increases in plasma ciprofloxacin exposure, dosage adjustments are not recommended in elderly patients (>65 years old) with normal renal function to mild renal impairment.

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Study 81-0036**A Study Comparing Single Dose Pharmacokinetics of Proquin™ 500 mg Tablets in Subjects with Normal Renal Function and in Subjects with Mild and Moderate Renal Impairment****Objective:**

To compare the pharmacokinetic profile of ciprofloxacin from Proquin™ 500 mg Tablets in subjects with mild and moderate renal impairment and subjects with normal renal function

Study Design: A three-group, single-dose, multi-center, fed design

Subjects:

- Thirty non-smoking subjects (11 females/19 males; at least 21 years old) were grouped into three depending on renal function.
- The creatinine clearance for each subject was calculated based on the Cockcroft-Gault formula for determining creatinine clearance. The subjects will be classified based on their creatinine clearance values.

TABLE 83

CLASSIFICATION (BASED ON RENAL FUNCTION)	CREATININE CLEARANCE (mL/min)
Normal renal function	>80 mL/min
Mild renal impairment	51-80 mL/min
Moderate renal impairment	30-50 mL/min

- Only patients with adequate liver function [as indicated by total bilirubin, SGOT (AST), and SGPT (ALT) ≤ 2 x institution ULN] will be enrolled.
- Patients with clinically significant history or current active gastrointestinal dysfunction will be excluded.

Drug Administration: Following an overnight fast of at least 8 hours, each subject received at 0.0 hour on Day 1, one Proquin™ 500 mg Tablet with 240 mL of ambient temperature water, 30 minutes after the start of a standardized (approximately 500-600 calorie, moderate-fat content) meal.

The moderate-fat content meal consisted of the following: one egg, one slice of bacon, 9 g of butter, one English muffin, hash browns (2 oz) and 250 mL orange juice.

Fluid control: Water was provided *ad libitum* until 1.0 hour pre-dose. After drug administration water was permitted *ad libitum*. The subjects in this study were not required to receive 100 mL of water every hour or 2 hours after Proquin™.

Length of Study: The study will consist of one 4-day study period.

Blood Sample Collection: Blood samples were drawn for the determination of plasma ciprofloxacin concentration at the following time points: 0.0 (pre-dose), 0.5, 1.0, 2.0, 3.0, 3.5, 4.0, 4.5, 5.0, 5.5, 6.0, 9.0, 12.0, 14.0, 18.0, 24.0, 36.0, and 48.0 hours post-drug administration.

Analytical Method:

Analysis of ciprofloxacin was conducted using a validated HPLC assay method. The lower limit of quantitation (LLOQ) for ciprofloxacin was 24.99 ng/mL.

Pharmacokinetics:

Plasma pharmacokinetic analysis was conducted using a non-compartmental analysis. Parameters AUC_{0-t} , AUC_{0-inf} , C_{max} , T_{max} , $t_{1/2}$ and CL/F were calculated for ciprofloxacin.

Statistical analyses:

ANOVA was performed on log-transformed AUC , C_{max} and CL/F , and on untransformed T_{max} and $t_{1/2}$ at $\alpha = 0.05$. The normal renal function group was used as the "control" group.

Safety:

The incidences of all adverse events (AEs) were tabulated by treatment group and subject number.

Results and Discussion:

Subject demographics and baseline characteristics (summarized in Table 84) were similar for all three renal function groups, except for creatinine clearances.

TABLE 84

	Group 1 (Mild Renal Impairment)	Group 2 (Moderate Renal Impairment)	Group 3 (Normal Renal Function)
Number	10	10	10
Gender	7 males, 3 females	6 males, 4 females	6 males, 4 females
Race	4 Caucasian/4 Black/ 1 Asian/1 Hispanic	5 Caucasian/ 4 Black/1 Asian	10 Caucasian
Age (years) Mean \pm SD	64.2 \pm 11.6	65.9 \pm 9.9	63.5 \pm 3.6
Weight (kg) Mean \pm SD	80.1 \pm 12.6	82.8 \pm 14.6	80.1 \pm 4.0
Height (cm) Mean \pm SD	166.9 \pm 10.8	169.0 \pm 13.1	170.6 \pm 8.2
BMI (kg/m ²) Mean (range)	28.6 (24.2-35.3)	29.2 (18.7-40.2)	27.7 (24.5-36.3)
Creatinine Clearance (mL/min) Mean (range)	64.8 (53.1-78.6)	42.6 (34.5-48.5)	100.3 (88.3-109.4)

Source: Appendix 2.2.

Creatinine clearance was calculated as follows: Males: $(140 - \text{Age}) * \text{Weight} * 0.81 * (\text{Serum Creatinine})$

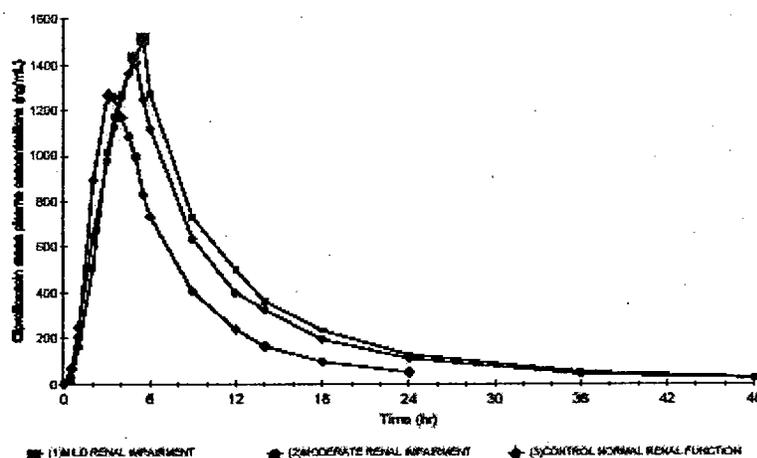
Females: $((140 - \text{Age}) * \text{Weight} * 0.81 * (\text{Serum Creatinine})) * 0.85$

Mean ciprofloxacin plasma concentration-time profiles are presented in Figure 35.

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FIGURE 35
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 85 below.

TABLE 85

Pharmacokinetic Parameter	Group 1 (Mild Renal Impairment) n = 10 Mean ± SD	p-Values [†]	Group 2 (Moderate Renal Impairment) n = 10 Mean ± SD	p-Values [†]	Group 3 (Normal Renal Function) n = 10 Mean ± SD
AUC ₀₋₄ (ng·hr/mL)*	12314.9 (29.4)	0.0453	13403.5 (37.7)	0.0119	8722.4 (22.0)
AUC ₀₋₂₄ (ng·hr/mL)*	12778.8 (28.1)	0.0397	13854.2 (37.0)	0.0105	9059.6 (21.6)
C _{max} (ng/mL)*	1545.5 (28.6)	0.6204	1752.4 (38.9)	0.1859	1363.0 (23.7)
T _{max} (hr) [‡]	4.25 (2.00 - 5.50)	0.1557	4.50 (3.00 - 6.00)	0.0348	3.25 (2.00 - 5.00)
t _{1/2} (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)

‡ Median (Min - Max)

† p-values relative to Group 3 (subjects with normal renal function)

Plasma exposures (AUC values) of ciprofloxacin were significantly increased in subjects with mild and moderate renal impairment as compared to subjects with normal renal function. Although there was a trend toward increasing C_{max} values with decreasing renal function, C_{max} values of ciprofloxacin were not statistically greater in subjects with mild and moderate renal impairment.

Ciprofloxacin clearance was significantly decreased in patients with mild and moderate renal impairment; ciprofloxacin half-lives were longer in these patients.

Safety:

- The reported adverse events are summarized in Table 86 below. None of these AEs were judged to be severe nor related to study drug.

TABLE 86

Subject No.	Group	Event (preferred term)	Relationship	Intensity	Outcome
01-103	1	Catheter site edema	Not related	Mild	Resolved
		Catheter site pain	Not related	Mild	Resolved
01-203	2	Headache	Not related	Mild	Resolved
01-301	3	Lactate dehydrogenase increased	Not related	Mild	Resolved
02-104	1	Flatulence	Not related	Mild	Resolved
02-201	2	Infusion site inflammation	Not related	Mild	Resolved

Source: Appendix 2.5.8.3.

- There were no clinically significant changes from screening to final evaluation for any laboratory parameters for any subject.
- There were no clinically significant changes from screening to final evaluation in laboratory parameters, vital signs, or physical findings for any subject.

REVIEWER'S COMMENTS:

1. Caucasians comprised 40%, 50%, and 100% of the subjects in the mild-, moderate- renally impaired, and normal renal function groups, respectively. However, there is no literature evidence that suggest that ciprofloxacin pharmacokinetic parameters are significantly affected by race.
2. The systemic exposures (as AUC_{0-1}) of ciprofloxacin in subjects with mild and moderate renal impairment were 42% and 54% higher, respectively, compared to subjects with normal renal function. The mean ages (64 to 66 years old) of the three renal function groups in this study suggest that majority of the subjects were at or approaching old age. Indeed, the difference between the mildly renally impaired patients and those with normal renal function in this study (42%) was similar to that seen in the same groups of subjects enrolled in Study 81-0032 (37%), a study that investigated the PK of Proquin™ in elderly subjects.
3. Since none of the subjects enrolled had concurrent hepatic impairment, it is likely that hepatic elimination of ciprofloxacin compensated for the mild to moderate renal dysfunction in these subjects. In addition, 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.
4. The FDA Guidance on Pharmacokinetics in Renal Function recommends either a full study design (consisting of 5 renal function groups: normal renal function, mild-, moderate-, severe-, renal impairment, and end-stage renal disease), or a reduced study design (which starts with 2 extreme groups: normal renal function versus severely renally impaired). Because the PK in renal impairment study conducted for Proquin™ excluded patients with severe renal impairment and those with end-stage renal disease (ESRD), under ordinary circumstances, the use of Proquin™ in these particular groups should be contraindicated.
5. However, the sponsor argues that no dosage reductions for Proquin™ 500 mg are needed for patients with severe renal impairment and those undergoing dialysis because the labels for Cipro® and Cipro XR® recommend ciprofloxacin dosages of up to 500 mg q18h in severely renally impaired patients and 500mg q24h in dialysis patients. The reviewer finds this proposal acceptable for the following reasons:

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- As shown by the findings of the Mass Balance Study, the elimination of ciprofloxacin and active metabolites from Proquin™ is not only via renal excretion. About an equal percentage of the dose is excreted by non-renal means.
- As shown by the findings of this PK in Renal Impairment Study, the total clearance of ciprofloxacin was 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 (CLcr < 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).
- 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.
- Based on the combined findings of the single-dose and steady state PK studies, the AUC₀₋₂₄ accumulation ratio on Day 3 of treatment is minimal (R ≅ 1.07 to 1.22) 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.

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Study 81-0028**A Three-Way Crossover, Open-Label, Single-Dose, Fed, Pharmacokinetic Interaction Study of Proquin™ 1000 mg (2 x 500 mg Tablets) With or Without Antacid in Healthy Non-Smoking Male and Female Subjects (Antacid Drug Interaction Study 1)****Objective:**

To investigate the effects of antacids (administered 2 hours before or 6 hours after Proquin™) on the pharmacokinetics of ciprofloxacin from a test formulation of Proquin™ 500 mg Tablets under fed conditions

Study Population:

Of the 28 healthy, non-smoking subjects (15 males, 13 females) enlisted into the study, 27 completed the study. One (1) of these patients who completed the study did not have reportable plasma concentration values. The mean age of the enrollees was 34 years (range = 21 to 68 years). The mean weight was 72 kg (range = 51 to 92 kg). The mean height was 1.70 m (range = 1.52 to 1.82 m). There were 22 Caucasians, three Asians, and three Blacks.

Dosing and Administration:

Each treatment with Proquin™ in this study was preceded by a standardized, approximately 500-600 calorie, moderate-fat content meal consumed within 20 minutes. The wash-out period between treatments was about 7 days.

Treatment A (Proquin™ alone):

At 0 hours, two Proquin™ 500 mg Tablets (Lot # HT3602; potency value = — , of label claim), administered at 0.0 hours with 240 mL of ambient temperature water 20 minutes after the start of the meal.

Treatment B (Antacids 2 hours before Proquin™):

At 0 hours, two Proquin™ 500 mg Tablets (Lot # HT3602; potency value = — , of label claim), administered at 0.0 hours with 240 mL of ambient temperature water 20 minutes after the start of the meal.

Two hours prior to Proquin™ dosing, subjects received 2.5 mL Concentrated Milk of Magnesia (600 mg magnesium hydroxide), followed by 7.5 mL AlternaGEL® (900 mg aluminum hydroxide) one minute later. Subjects received 100 mL of ambient temperature water after the administration of the antacids.

Treatment C (Antacids 4 hours after Proquin™):

At 0 hours, two Proquin™ 500 mg Tablets (Lot # HT3602; potency value = — , of label claim), administered at 0.0 hours with 240 mL of ambient temperature water 20 minutes after the start of the meal.

Six hours after ciprofloxacin dosing (= 5 minutes before the 6.0th hour blood draw), subjects received 2.5 mL Concentrated Milk of Magnesia (600 mg magnesium hydroxide), followed by 7.5 mL AlternaGEL® (900 mg aluminum hydroxide) one minute later. Subjects received 100 mL of ambient temperature water after the administration of the antacids.

Fluid Control Measure:

The subjects were provided with servings of water (100 mL) every one to two hours according to scheduled time periods as specified in the protocol.

Pharmacokinetic Sampling:

Blood samples will be collected according to the following schedule:

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, 10.0, 12.0, 14.0, 18.0, 24.0, and 36.0 hours post-drug administration.

Urine samples will be collected at the following time intervals:

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, 12.0-16.0, 16.0-24.0 and 24.0-36.0 hours post 0.0 hours dose (test drug dosing). The volume (at least 20 mL) collected for each interval will be recorded.

Analytical Method:

A validated HPLC method was used for the analysis of ciprofloxacin in plasma and urine samples. The lower limit of quantitation (LLOQ) was 24.986 ng/mL and 1.5 mcg/ml, for plasma and urine samples respectively.

Criteria for Evaluation:

Pharmacokinetics

The C_{max} and T_{max} were determined by visual inspection of the plasma concentration-time profiles. Using non-compartmental modeling, the following pharmacokinetic parameters were determined from the plasma profiles: Areas under the concentration-time curve from time zero to time of last measurable concentration, [AUC(0-t)], AUC(0-∞), and t_{1/2}; from urine profiles: the amount excreted in urine (A_e), renal clearance (CL_r), maximum observed excretion rate (Max Rate), midpoint of collection interval associated with the maximum observed excretion rate (T_{max} Rate), and the percent of dose excreted in urine (% Dose).

Safety

The incidence of adverse events was tabulated. Absolute values for vital signs, ECGs, laboratory parameters and physical examination were also documented and values outside the normal range were flagged. Abnormal shifts from baseline were tabulated.

Statistical Methods:

Analysis of variance (ANOVA) was performed on ln-transformed AUC_{0-t}, AUC_{0-∞} and C_{max} and on untransformed T_{max} and t_{1/2} at the significance level 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 ln-transformed AUC_{0-t}, AUC_{0-∞} and C_{max} between the test and reference formulations.

ANOVA was also performed on A_e, CL_r, %Dose, Max Rate and T_{max} Rate at $\alpha = 0.05$.

Results and Discussion:

The mean plasma concentration-time profiles of ciprofloxacin, with or without antacids (2 hours before or 6 hours after the ciprofloxacin dose) are presented in Figure 36. The summary of plasma pharmacokinetic parameters and the findings of the statistical analyses are presented in Tables 87 and 88. The systemic and urinary exposure were slightly lower with antacids but were not statistically significantly different when compared to Proquin™ alone.

FIGURE 36
Mean Plasma Ciprofloxacin concentrations
with or without antacids 2 hours before or 6 hours after ciprofloxacin

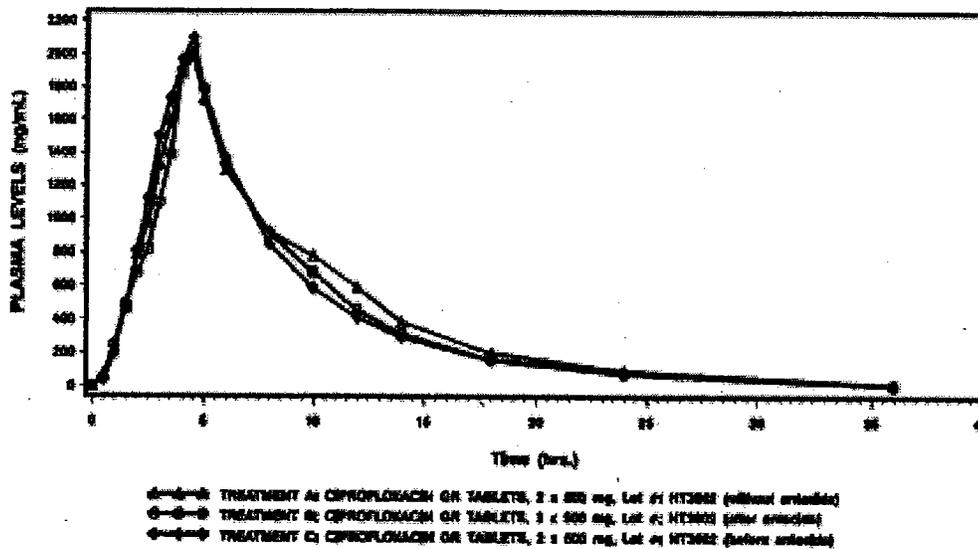


TABLE 87
Pharmacokinetic parameters for Ciprofloxacin
(without and with antacids 2 hours before or 6 hours after ciprofloxacin)
SUMMARY OF PHARMACOKINETIC RESULTS FOR CIPROFLOXACIN IN PLASMA:

Pharmacokinetic Parameters	Ciprofloxacin GR™ 2 x 500 mg Tablets (A) (Without Antacids) n = 26 Geometric Mean (%CV)	Ciprofloxacin GR™ 2 x 500 mg Tablets (B) (Ciprofloxacin administered two hours after antacids) n = 26 Geometric Mean (%CV)	Ciprofloxacin GR™ 2 x 500 mg Tablets (C) (Ciprofloxacin administered six hours before antacids) n = 26 Geometric Mean (%CV)	p-value
AUC _{0-∞} (ng·h/mL) †	14809.1 (30.3)	13345.0 (31.9)	13362.4 (35.7)	0.007‡
AUC ₀₋₂₄ (ng·h/mL) †	15194.7 (29.6)	13746.0 (31.1)	13825.9 (34.6)	0.009‡
C _{max} (ng/mL) †	2081.8 (40.1)	2129.0 (33.3)	2259.7 (35.0)	0.210‡
T _{max} (hr) †	4.45 ± 1.69† 4.50*	4.27 ± 0.59† 4.50*	3.97 ± 0.63† 4.01*	0.135
t _{1/2} (hr) †	5.11 ± 0.99†	4.89 ± 0.82†	5.32 ± 1.78†	0.338

* median value

† Arithmetic mean ± SD

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

§ Manually rounded from values obtained in Appendix 3

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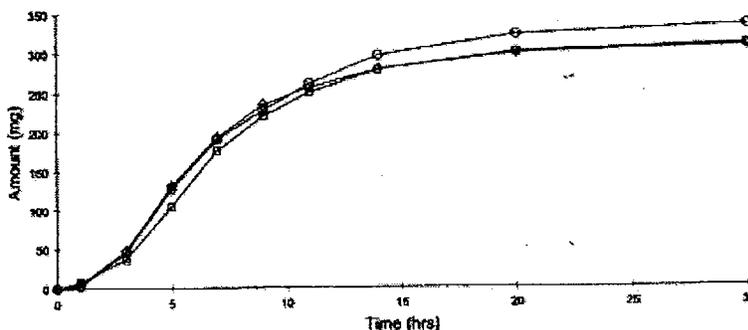
TABLE 88
 Bioequivalence assessments for Ciprofloxacin
 (with and without antacids 2 hours before or 6 hours after ciprofloxacin)

	Ciprofloxacin GR™ 2 x 500 mg Tablets (B) (Ciprofloxacin administered two hours after antacids) vs. Ciprofloxacin GR™ 2 x 500 mg Tablets (Without Antacids)(A)		
	90% C.I.	Ratio of Means (B:A)	Intra-Subject CV
AUC _{0-4h}	84.76% - 95.81%	90.11%	13.18%
AUC _{0-8h}	85.30% - 95.95%	90.46%	12.65%
C _{max}	95.02% - 110.06%	102.26%	15.79%

	Ciprofloxacin GR™ 2 x 500 mg Tablets (C) (Ciprofloxacin administered six hours before antacids) vs. Ciprofloxacin GR™ 2 x 500 mg Tablets (Without Antacids)(A)		
	90% C.I.	Ratio of Means (C:A)	Intra-Subject CV
AUC _{0-4h}	84.68% - 95.75%	90.05%	13.18%
AUC _{0-8h}	85.63% - 96.34%	90.83%	12.65%
C _{max}	100.31% - 116.22%	107.97%	15.79%

The mean ciprofloxacin amounts excreted in the urine are presented in Figure 37. The summary of urinary pharmacokinetic parameters and the findings of the statistical analysis are presented in Table 89 below.

FIGURE 37
 Mean Cumulative amount of Ciprofloxacin excreted in Urine
 (with or without antacids 2 hours before or 6 hours after ciprofloxacin)



- ◊ Treatment A: Ciprofloxacin GR tablets: 2 x 500 mg, Lot # HT3602 (without antacids)
- ◊ Treatment B: Ciprofloxacin GR tablets: 2 x 500 mg, Lot # HT3602 (administered 2 hrs post-antacids)
- ◊ Treatment C: Ciprofloxacin GR tablets: 2 x 500 mg, Lot # HT3602 (administered 6 hrs before antacids)

TABLE 89
 Pharmacokinetic parameters for Ciprofloxacin in the urine
 (without and with antacids 2 hours before or 6 hours after ciprofloxacin)

Pharmacokinetic Parameters	Ciprofloxacin™ 2 x 500 mg Tablets (A) (Without Antacids) n = 27 Mean ± SD	Ciprofloxacin™ 2 x 500 mg Tablets (B) (Ciprofloxacin administered two hours after antacids) n = 27 Mean ± SD	Ciprofloxacin™ 2 x 500 mg Tablets (C) (Ciprofloxacin administered six hours before antacids) n = 27 Mean ± SD	p-value
T _{max} Rate (hr) ‡	5.78 ± 2.36	6.33 ± 1.66	5.96 ± 1.29	0.721
Max Rate (mg/hr) ‡	48.24 ± 18.33	45.25 ± 15.22	50.70 ± 18.59	0.315
A _e (mg) ‡	324.8 (23.0)†	298.6 (25.2)†	294.8 (29.0)†	0.063
% Dose ‡	66.73 ± 15.35	61.87 ± 15.57	61.40 ± 17.79	0.063
CL _r (L/hr) ‡	23.00 ± 6.10*	23.25 ± 6.11*	23.10 ± 5.95	0.917

* n = 26
 † Geometric mean (%CV)
 ‡ Manually rounded from values obtained in Appendix 3

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Safety

- There were a total of 27 AEs (all of mild or moderate severity) reported by 7 subjects during the study. There were no serious AEs nor withdrawals due to AEs reported. None of the AEs reported were considered probably or possibly related to the study drug.
- During Treatment A (Proquin™ alone), 3 subjects experienced a total of 11 AEs.
During Treatment B (antacids 2 hours before Proquin™), 4 subjects experienced a total of 10 AEs.
During Treatment C (antacids 6 hours after Proquin™), 5 subjects experienced a total of 6 AEs.

REVIEWER'S COMMENT:

Refer to the combined reviewer's comments for Antacids Drug Interaction Study 1 and Study 2 (next individual study review).

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Study 81-0033**A Three-Way Crossover, Open-Label, Single-Dose, Fed, Pharmacokinetic Interaction Study of Proquin™ 1000 mg (2 x 500 mg Tablets) With and Without Antacids in Normal Healthy Non-Smoking Male and Female Subjects (Antacid Drug Interaction Study 2)****Objective:**

To investigate the effects of antacids (administered 2 hours after or 4 hours after Proquin™) on the pharmacokinetics of ciprofloxacin from a test formulation of Proquin™ 500 mg Tablets under fed conditions.

Study Population:

Of the 30 healthy, non-smoking subjects (18 males, 12 females) enlisted into the study, 29 completed the study. One (1) patient withdrew for personal reasons. The mean age was 41 years (2 to 62 years); mean weight was 72 kg (54 to 94 kg). The mean height was 1.69 m (1.53 to 1.94 m). There were 15 Caucasians and 15 Asians.

Dosing and Administration:

Each treatment in this study was preceded by a standardized, approximately 500-600 calorie, moderate-fat content meal consumed within 20 minutes.

Treatment A (Proquin™ alone):

At 0 hours, two Proquin™ 500 mg Tablets (Lot # HT3602; potency value = — of label claim), administered at 0.0 hours with 240 mL of ambient temperature water 20 minutes after the start of the meal.

Treatment B (Antacids 2 hours after Proquin™):

At 0 hours, two Proquin™ 500 mg Tablets (Lot # HT3602; potency value = — of label claim), administered at 0.0 hours with 240 mL of ambient temperature water 20 minutes after the start of the meal.

Five minutes before the 2nd hour ciprofloxacin post-dosing, subjects received 2.5 mL Concentrated Milk of Magnesia (600 mg magnesium hydroxide), followed by 7.5 mL AlternaGEL® (900 mg aluminum hydroxide) one minute later. Subjects received 100 mL of ambient temperature water after the administration of the antacids.

Treatment C (Antacids 4 hours after Proquin™):

At 0 hours, two Proquin™ 500 mg Tablets (Lot # HT3602; potency value = — of label claim), administered at 0.0 hours with 240 mL of ambient temperature water 20 minutes after the start of the meal.

Five minutes before the 4th hour ciprofloxacin post-dosing, subjects received 2.5 mL Concentrated Milk of Magnesia (600 mg magnesium hydroxide), followed by 7.5 mL AlternaGEL® (900 mg aluminum hydroxide) one minute later. Subjects received 100 mL of ambient temperature water after the administration of the antacids.

Fluid Control Measure: None.

Pharmacokinetic Sampling:

Blood samples will be collected at the following times:

0.0 (pre-dose), 0.5, 1.0, 2.0, 3.0, 3.5, 4.0, 4.5, 5.0, 5.5, 6.0, 9.0, 12.0, 14.0, 18.0, 24.0 and 36.0 hours post-drug administration

Analytical Method:

A validated HPLC method was used for the analysis of ciprofloxacin in plasma samples. The lower limit of quantitation (LLOQ) was 24.999 ng/mL.

Criteria for Evaluation:Pharmacokinetics

The C_{max} and T_{max} were determined by visual inspection of the plasma concentration-time profiles. Using non-compartmental modeling, the following pharmacokinetic parameters were determined from the plasma profiles: Areas under the concentration-time curve from time zero to time of last measurable concentration, [AUC(0-t)], AUC(0-∞), and t_{1/2}; from urine profiles: the amount excreted in urine (A_e), renal clearance (CL_r), maximum observed excretion rate (Max Rate), midpoint of collection interval associated with the maximum observed excretion rate (T_{max} Rate), and the percent of dose excreted in urine (% Dose).

Safety

The incidence of adverse events was tabulated. Absolute values for vital signs, ECGs, laboratory parameters and physical examination were also documented and values outside the normal range were flagged. Abnormal shifts from baseline were tabulated.

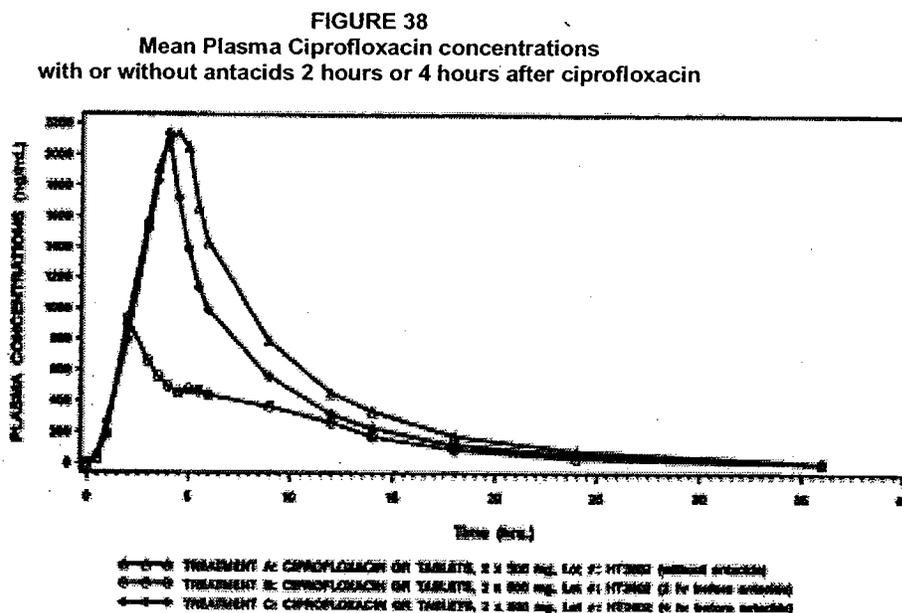
Statistical Methods:

Analysis of variance (ANOVA) was performed on ln-transformed AUC_{0-t}, AUC_{0-∞} and C_{max} and on untransformed T_{max} and t_{1/2} at the significance level 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 ln-transformed AUC_{0-t}, AUC_{0-∞} and C_{max} between the test and reference formulations.

Results and Discussion:

The mean plasma concentration-time profiles of ciprofloxacin, with or without antacids (2 hours after or 4 hours after the ciprofloxacin dose) are presented in Figure 38. The summary of pharmacokinetic parameter and the findings of the statistical analysis are presented in Tables 90 and 91.



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TABLE 90
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 _{0-4h} (ng·hr/mL)‡	14858.3 (30.3)	5572.0 (53.9) p-value < 0.001†	11558.8 (30.3) p-value = 0.0005‡
AUC _{0-8h} (ng·hr/mL)‡	15373.5 (29.4)	5825.8 (54.1) p-value < 0.001†	11954.9 (29.3) p-value = 0.0004‡
C _{max} (ng/mL)‡	2412.7 (32.9)	876.6 (72.7) p-value < 0.001†	2133.7 (34.8) p-value = 0.1735‡
T _{max} (hr)	4.10 ± 0.84† 4.00*	3.64 ± 2.78† 2.00* p-value = 0.2461‡	3.79 ± 0.54† 4.00* p-value = 0.4394‡
t _{1/2} (hr)	5.95 ± 1.06†	4.74 ± 0.82† p-value = 0.0334‡	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

TABLE 91
Bioequivalence assessments for Ciprofloxacin
(with and without antacids 2 hours or 4 hours after ciprofloxacin)

Parameters	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)		
	90% C.I.	Ratio of Means (B:A)	Intra-Subject CV
AUC _{0-4h}	33.45% - 42.13%	37.33%	26.28%
AUC _{0-8h}	34.45% - 43.01%	38.49%	25.25%
C _{max}	31.72% - 42.29%	36.63%	32.68%

Parameters	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)		
	90% C.I.	Ratio of Means (C:A)	Intra-Subject CV
AUC _{0-4h}	69.09% - 87.05%	77.55%	26.28%
AUC _{0-8h}	69.55% - 86.84%	77.71%	25.25%
C _{max}	76.93% - 102.54%	88.82%	32.68%

Safety

- There were a total of 8 AEs (all of mild severity and mostly abnormal laboratory abnormalities typical of ciprofloxacin) reported by 7 subjects during the study. There were no serious AEs nor withdrawals due to AEs reported. None of the AEs reported were considered probably or possibly related to the study drug.
- Treatment comparison:
Treatment A: 3 AEs
Treatment B: 2 AEs
Treatment C: 3 AEs

REVIEWER'S COMMENTS (for studies evaluating the effect of timing of antacid co-administration on the pharmacokinetics of ciprofloxacin):

1. Normally, antacids are to be taken after a meal and at bedtime. Since ciprofloxacin bioavailability is adversely affected by the chelating and/or pH-altering effects of antacids, the sponsor

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- conducted two antacids drug interaction studies (81-0028 and 81-0033) to determine the appropriate timing of antacid co-administration relative to the Proquin™ dose. Since there was no difference in ciprofloxacin elimination half-life in the presence and absence of antacids, the interaction is not likely caused by altered ciprofloxacin elimination.
2. Based on the findings of Study 81-0028 (Antacids-Proquin™ Interaction Study 1), antacids co-administration at 2 hours before or 6 hours after Proquin™ tablets will not influence the oral bioavailability of ciprofloxacin. This means that Proquin™ may be administered 2 hours after antacids or 6 hours before antacids. This finding is quite different from the recommended timing of antacids co-administration in the Cipro® and Cipro®-XR labels, i.e., Cipro® IR or XR should be administered at least 6 hours after antacids or 2 hours before antacids. In an antacid drug interaction study conducted by the sponsor of Cipro®-XR, administration of Cipro®-XR 4h after antacids slightly reduced ciprofloxacin exposure, i.e, the AUC by 25% and the Cmax by 19%. It is speculated that this difference in the antacids-drug interaction profiles between Proquin™ and Cipro® dosage forms lies in the difference in *in vivo* release rates as evidenced by the difference in the ciprofloxacin Tmax (4.5 to 9 hours versus 2 hours, when given with a meal). At 2 hours following the antacid dose, the chelating/pH-altering effect of antacids would be greater on either the two Cipro® dosage forms because a substantial amount of the drug is released immediately and thus is readily available to interact with the residual antacids in the stomach or be prone to the residual alkalinity from the previous dose of antacids. In the case of Proquin™, at least 6 hours would have elapsed after the last dose of antacids before it would reach the peak ciprofloxacin concentrations.
 3. Based on the findings of Study 81-0033, 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. The effect of administering antacids at 2 hours after the Cipro® dose is not expected to be clinically significant because the reported Tmax of both Cipro®-IR and Cipro®-XR is 1.0 - 1.5 hours. Thus, at t = 2 hours post-Cipro® dose, much of the drug had been released from the dosage form and would have already been absorbed. On the other hand, for Proquin™ with a Tmax of at least 4.5 hours, co-administration of antacids at t=2 hours after the Proquin™ dose will likely have a significant reduction effect on ciprofloxacin absorption.
 4. The co-administration of antacids 4 hours after Proquin™ results in a final ciprofloxacin AUC₀₋₂₄ of about 70% of that Cipro® immediate release (70%=0.77 x 91% of Cipro® AUC). From a PK/PD perspective, this proposed timing of antacid co-administration with Proquin™ is acceptable; the AUC/MIC_{90 E.coli} ratio for ciprofloxacin when antacids are given 4 hours after Proquin™ 500mg will be about 128 (still above the optimal ratio of 100 for fluoroquinolones needed to ensure a positive clinical outcome), given an *E.coli* MIC₉₀ of 0.045 mcg/mL. The corresponding Cmax/MIC₉₀ when antacids are given 4 hours after the Proquin™ dose will be 24 (still above 10, the optimal cut-off ratio for fluoroquinolones in relation to selection of resistant *E.coli*).
 5. 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.

Labeling recommendation (for Drug interaction – effect of antacids on ciprofloxacin pharmacokinetics):

The co-administration of antacids 2 hours before and 6 hours after ciprofloxacin dosing did not statistically significantly alter the oral bioavailability of Proquin™. On the other hand, antacid co-administration 2 hours after or 4 hours after ciprofloxacin dosing significantly reduced the AUC and Cmax of ciprofloxacin, albeit to a much lesser extent at 4 hours than after 2 hours post-ciprofloxacin dose. Because the calculated AUC/MIC and the Cmax/MIC of ciprofloxacin (given 4 hours before antacids) did not decrease beyond the

optimal PK/PD parameter values needed to ensure a positive clinical outcome, the co-administration of antacids at 4 hours following the ciprofloxacin dose is considered acceptable. Thus, antacids may be given 2 hours before or at least 4 hours after Proquin™ dosing.

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Study 81-0027**A Two-Way Crossover, Open-Label, Single-Dose, Fed, Bioavailability Study of the Effect of Omeprazole 40 mg on the Pharmacokinetics of Proquin™ 2 x 500 mg Tablets in Healthy Non-Smoking Male and Female Subjects****Objective:**

To compare the peak and systemic absorption of ciprofloxacin from a test formulation of Proquin™ 500mg Tablets given with or without omeprazole (Prilosec®) 40mg Delayed-Release Capsules QD under fed conditions.

Study Population:

Twenty-eight healthy, non-smoking male and female subjects entered the study. All 27 subjects who completed the study were valid for pharmacokinetic and statistical evaluations.

Dosing and Administration:

Each treatment of Proquin™ in this study was preceded by a standardized, approximately 500-600 calorie, moderate-fat content meal consumed within 20 minutes. There was a 7-day wash out period between treatment periods.

Treatment A (Proquin™ alone):

At 0 hours, two Proquin™ 500 mg Tablets (Lot # HT3602; potency value = — of label claim), administered at 0.0 hours with 240 mL of ambient temperature water.

Treatment B (Omeprazole 2 hours before Proquin™):

On Day -2, Day -1, and Day 1: Two hours prior to the moderate-fat breakfast, one omeprazole 40mg capsule (Prilosec® 40mg Delayed-Release Capsule), administered orally with 100 mL of ambient temperature water.

At 0 hours, two Proquin™ 500 mg Tablets (Lot # HT3602; potency value = — of label claim), administered at 0.0 hours with 240 mL of ambient temperature water 20 minutes after the start of the meal.

Fluid Control:

On Day 1: For both treatments, 100 mL of ambient temperature water was administered on an almost hourly basis after 2 hours post-dose until 24 hours after the Proquin™ dose.

Pharmacokinetic Sampling:

Blood samples were collected at 0, 0.5, 1.0, 1.5, 2.0, 2.5, 3.0, 3.5, 4.0, 4.5, 5.0, 6.0, 8.0, 10.0, 12.0, 14.0, 18.0, 24.0, and 36 hours post-drug Proquin™ administration.

Urine (at least 20 mL) was collected during the following time intervals: prior to dosing, 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, 24.0-36.0 hours post Proquin™ dose. For each time interval, the pH and volume of the pooled urine were measured.

Analytical Method:

A validated HPLC method was used for the analysis of ciprofloxacin in plasma samples. The lower limit of quantitation (LLOQ) was 24.999 ng/mL.

Criteria for Evaluation:**Pharmacokinetics**

The C_{max} and T_{max} were determined by visual inspection of the plasma concentration-time profiles. Using non-compartmental modeling, the following pharmacokinetic parameters were determined from the plasma profiles: Areas under the concentration-time curve from time zero to time of last measurable

concentration, $AUC(0-t)$, $AUC(0-\infty)$, and $t_{1/2}$; from urine profiles: the amount excreted in urine (A_e), renal clearance (CL_r), maximum observed excretion rate (Max Rate), midpoint of collection interval associated with the maximum observed excretion rate (T_{max} Rate), and the percent of dose excreted in urine (% Dose).

Safety

The incidences of all adverse events were tabulated. Absolute values for vital signs, ECGs, laboratory parameters and physical examination were also documented and values outside the normal range were flagged. Abnormal shifts from baseline were tabulated.

Statistical Methods:

Analysis of variance (ANOVA) was performed on In-transformed AUC_{0-t} , $AUC_{0-\infty}$ and C_{max} and on untransformed T_{max} and $t_{1/2}$ at the significance level 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 In-transformed AUC_{0-t} , $AUC_{0-\infty}$ and C_{max} between the test and reference formulations.

Results and Discussion:

Pharmacokinetics

The mean plasma concentration-time profiles of ciprofloxacin, with or without omeprazole are presented in Figure 39. The summary of plasma pharmacokinetic parameters and the findings of the statistical analyses are presented in Tables 92 and 93. 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.

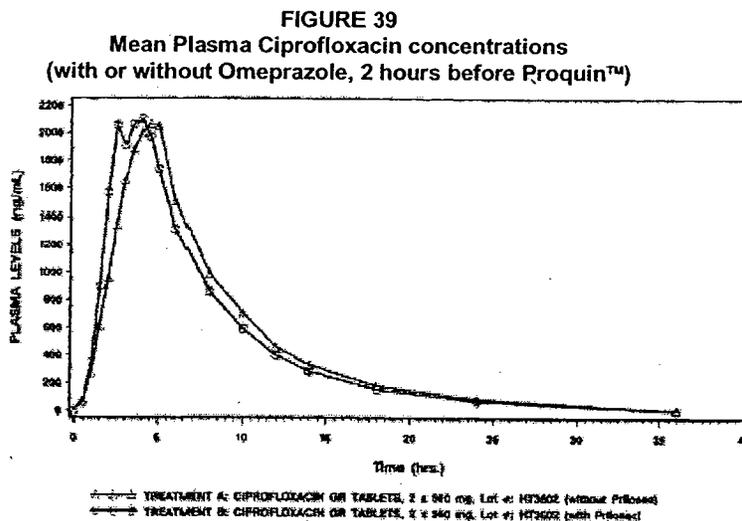


TABLE 92
Pharmacokinetic parameters for Ciprofloxacin
(without and with Omeprazole 2 hours before ciprofloxacin)

Pharmacokinetic Parameters	2 x Ciprofloxacin GR TM 500 mg Tablets without Omeprazole (A) (n = 27) Geometric Mean (%CV)	2 x Ciprofloxacin GR TM 500 mg Tablets with Omeprazole (B) (n = 27) Geometric Mean (%CV)	p-value
AUC ₀₋₂₄ (ng·hr/mL) †	15445.9 (24.9)	14938.5 (25.5)	0.421 [‡]
AUC _{0-inf} (ng·hr/mL) ‡	15964.1 (23.9)	15388.9 (24.8)	0.370 [‡]
C _{max} (ng/mL) ‡	2544.5 (25.6)	2612.6 (28.7)	0.626 [‡]
T _{max} (hr) ‡	3.95 ± 0.94 [†] 4.00 [‡]	3.47 ± 1.09 [†] 3.50 [‡]	0.083
t _{1/2} (hr) ‡	5.05 ± 0.92 [†]	4.85 ± 0.80 [†]	0.096

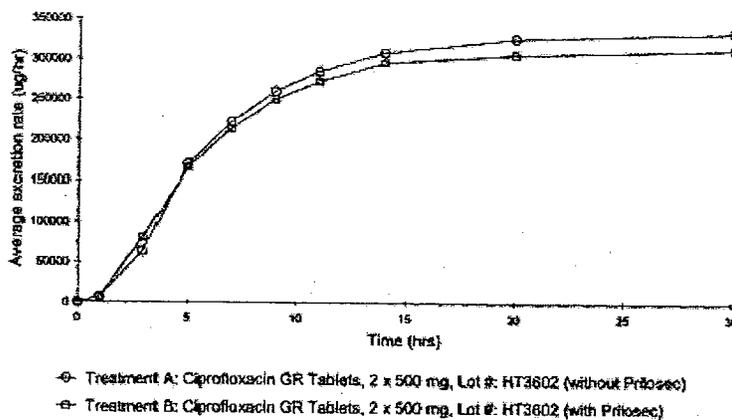
† Median values ‡ Mean ± SD † The p-value is from ANOVA on log-transformed data
‡ Manually rounded from values obtained in Appendix 3

TABLE 93
Bioequivalence assessments for Ciprofloxacin
(with and without Omeprazole 2 hours before ciprofloxacin)

Parameters	Ciprofloxacin GR TM 500 mg Tablets – with Omeprazole (B) vs. Ciprofloxacin GR TM 500 mg Tablets – without Omeprazole (A)		
	90% C.I.	Ratio of Means (B:A)	Intra-Subject CV
AUC ₀₋₂₄	90.04% - 103.76%	96.66%	15.24%
AUC _{0-inf}	89.83% - 103.30%	96.33%	15.02%
C _{max}	93.48% - 113.01%	102.78%	20.39%

The mean ciprofloxacin amounts excreted in the urine are presented in Figure 40. The summary of urinary pharmacokinetic parameters and the findings of the statistical analysis are presented in Table 94 below.

FIGURE 40
Mean Cumulative amount of Ciprofloxacin excreted in Urine
(with or without Omeprazole 2 hours ciprofloxacin)



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TABLE 94
Pharmacokinetic parameters for Ciprofloxacin
(with or without Omeprazole 2 hours before ciprofloxacin)

Pharmacokinetic Parameters	2 x Ciprofloxacin GR TM 500 mg Tablets without Omeprazole (A) (n = 27) (Mean ± SD)	2 x Ciprofloxacin GR TM 500 mg Tablets with Omeprazole (B) (n = 27) (Mean ± SD)	p-value
T _{max,50%} (hr) ‡	5.00 ± 1.24	4.33 ± 1.36	0.075
Max Rate (mg/hr) ‡	57.51 ± 17.56	52.00 ± 18.21	0.203
Ae (mg) ‡	327.3 (20.3) [†]	301.3 (27.3) [†]	0.294
Cl _r (L/hr) ‡	21.99 ± 5.88	21.23 ± 6.15	0.425
% Dose ‡	33.38 ± 6.78	31.28 ± 8.53	0.294

[†] Geometric mean (%CV)

Safety

- During Treatment A (ProquinTM alone), 6 subjects experienced a total of 9 AEs. During Treatment B (Proquin with Omeprazole), 6 subjects experienced a total of 9 AEs.
- All reported AEs were mild and considered to be unrelated to study drug.

Reviewer's comments:

1. The label of Cipro XR[®] states: "When CIPRO XR was administered as a single 1000 mg dose concomitantly [sic] with omeprazole (40 mg once daily for three days) to 18 healthy volunteers, the mean AUC and C_{max} of ciprofloxacin were reduced by 20% and 23%, respectively." However, since the total amount of ciprofloxacin excreted in urine was not significantly different from when CIPRO[®] XR was given alone, and the urine ciprofloxacin concentrations exceed the MIC₉₀ for *E. coli* by at least 100- fold, omeprazole and CIPRO[®] XR can be co-administered without dose adjustment.
2. When ProquinTM was administered as a single 1000 mg dose with omeprazole (40 mg once daily for three days, 2 hours before ProquinTM), the mean AUC and C_{max} of ciprofloxacin were changed by -3.0% and +3.0%, respectively. Based on these findings, it can be concluded that omeprazole (when given at least 2 hours before ProquinTM) does not alter the systemic exposure of ciprofloxacin from ProquinTM.
3. The proton-pump inhibitory (PPI) activity of omeprazole and other PPIs is highest when given on an empty stomach. In consideration of this, the ProquinTM label should state that if ProquinTM and omeprazole are to be given to the same patient, omeprazole should be given ~~on an empty stomach~~ and Proquin should be given with a meal.

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Study 81-0029**A Four-Way Crossover, Open-Label, Single-Dose, Fed, Comparative Pharmacokinetic Study of Cipro® 500 mg Tablets and Three Different Formulations of Proquin™ 500 mg Tablets (Standard, Fast, and Slow Release) in Healthy Non-Smoking Male and Female Subjects for Investigation of In-Vivo/In-Vitro Correlation**

Objective: To generate pharmacokinetic data for in-vitro/in-vivo correlation of ciprofloxacin from three different formulations of Proquin™ 500 mg Tablets (Standard Release, Fast Release, and Slow Release) and Cipro® 500 mg Tablets (Immediate Release) under fed conditions

Study Design: Randomized, four-way cross-over, open-label, single-dose, fed design

Study Population: All 16 enrolled healthy, non-smoking subjects (8 males, 8 females) with a mean age of 36 years (18 to 66 years) completed the study. The mean weight was 74 kg (54 to 91 kg); the mean height was 1.70 m (1.55 to 1.81 m). There were 12 Caucasians, 2 Asians and 2 Blacks.

Dosing and Administration: Subjects received one of the following treatments at 0.0 hour on Day 1 of each study period, according to a randomization scheme. Each formulation was administered with 240 mL of ambient temperature water 30 minutes after the start of a standardized, approximately 500-600 calorie, moderate fat content meal. There was a 1-week washout period between treatments.

1. Treatment A (Fast-Release Product) – Proquin™ 500 mg Tablet, IVVC04
2. Treatment B (Standard-Release Product) – Proquin™ 500 mg Tablet
3. Treatment C (Slow-Release Product) – Proquin™ 500 mg Tablet, IVVC08
4. Treatment D (Immediate-Release Reference Product) – Cipro® 500 mg Tablet

Fluid Control Measure: None

Pharmacokinetic Sampling:

Blood samples were drawn in each treatment period according to the following schedule: 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, 10.0, 12.0, 14.0, 18.0, 24.0 hours post-drug administration

Pharmacokinetic and Statistical Analyses:

Model-independent pharmacokinetic analysis was performed based on plasma ciprofloxacin concentrations to obtain the following parameters:

AUC_{0-t} , AUC_{0-inf} , C_{max} , T_{max} , and elimination $t_{1/2}$

Statistical comparisons (as originally stated in the protocol) were not performed because bioequivalence with the reference Cipro® formulation was not intended for the various Proquin™ formulations.

Analytical Method: The plasma concentrations of ciprofloxacin were determined using a validated HPLC method. The LLOQ was 24.000 ng/mL.

Safety:

The incidences of all adverse events were tabulated. Absolute values for vital signs, ECGs, laboratory parameters and physical examination were also documented and values outside the normal range were flagged. Abnormal shifts from baseline were tabulated.

Establishment of a Level A In-Vitro-In-Vivo Correlation (IVIVC) Model:

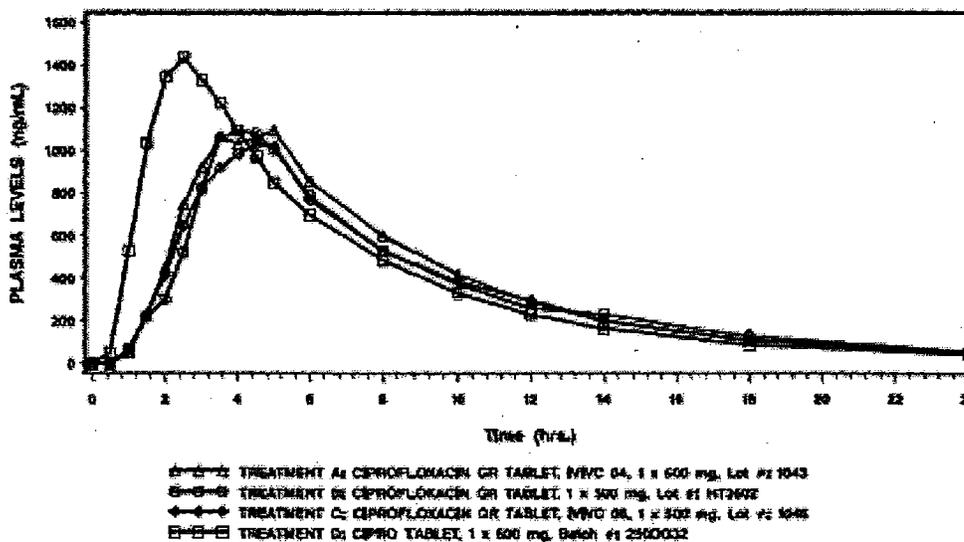
A Level A IVIVC model was constructed using a deconvolution approach that modeled mean immediate release and Proquin™ standard release plasma concentration-time profiles to reconstruct in-vivo release for various Proquin™ formulations.

A polynomial fitting function was used to obtain a correlation between in-vitro and in-vivo release of ciprofloxacin.

Results:

The mean ciprofloxacin plasma concentration-time profiles of various Proquin™ 500mg formulations and the reference Cipro® 500mg immediate-release formulation is shown in Figure 41.

FIGURE 41
Mean Plasma Ciprofloxacin Concentrations (N=16)



The pharmacokinetic parameters of ciprofloxacin obtained from various Proquin™ formulations and the reference Cipro™ immediate-release formulation is shown in Table 95.

TABLE 95

Pharmacokinetic Parameters	Ciprofloxacin GR™ 500 mg Tablets, IVVC 04 (A) n = 16 Mean ± SD	Ciprofloxacin GR™ 500 mg Tablets (B) n = 16 Mean ± SD	Ciprofloxacin GR™ 500 mg Tablets, IVVC 08 (C) n = 16 Mean ± SD	CIPRO® 500 mg Tablets (D) n = 16 Mean ± SD
AUC ₀₋₂₄ (ng.hr/ mL) §	8823.8 ± 2200.9 7859.2 to 9788.4*	8336.4 ± 2536.8 7224.6 to 9448.2*	8216.2 ± 3059.1 6875.5 to 9556.9*	9360.1 ± 2564.4 8236.2 to 10484.0*
AUC _{0-∞} (ng.hr/ mL) §	9221.9 ± 2300.4 8213.7 to 10230.1*	8742.8 ± 2713.5† 7508.8 to 9976.8*	8591.7 ± 3144.1 7213.8 to 9969.7*	9692.4 ± 2634.1 8538.0 to 10846.8*
C _{max} (ng/mL) §	1401.2 ± 415.5 1219.1 to 1583.3*	1273.6 ± 464.5 1070.1 to 1477.2*	1239.1 ± 428.1 1051.5 to 1426.8*	1703.2 ± 425.9 1516.5 to 1889.8*
T _{max} (hr)	4.03 ± 0.94 3.75*	4.56 ± 2.63 4.00*	3.94 ± 0.73 3.75*	2.22 ± 0.73 2.01*
t _{1/2} (hr)	4.93 ± 0.87	5.10 ± 0.88†	4.90 ± 0.86	4.94 ± 0.80
K _e (hr ⁻¹)	0.145 ± 0.0279	0.140 ± 0.0263†	0.146 ± 0.0272	0.144 ± 0.0261

* median value; † n = 15; ‡ 90% Confidence Interval; § Manually rounded from values obtained in Appendix 3

Safety:

Five subjects experienced a total of 10 treatment-emergent AEs during the study.

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Table 96 below summarizes these Adverse Events according to severity and Treatment.

TABLE 96
Summary of Adverse Events

TREATMENT	A Proquin™ 500mg Fast- Release (IVIVC 04 hrs)	B Proquin™ 500mg Standard- Release (=IVIVC 06 hrs)	C Proquin™ 500mg Slow-Release (IVIVC 08 hrs)	D Cipro® 500mg (Immediate- Release)
No. of Subjects who received treatment	16	16	16	16
Subjects withdrawn or dismissed due to AE	0	0	0	0
Subjects with AEs	2 (12.5%)	1 (6.25%)	1 (6.25%)	3 (18.75%)
Subjects with serious AEs	3	1	1	5
Total numbers of AEs	0	0	0	0

Reviewer's comments:

1. The various formulations of Proquin™ (slow-release, standard-release, and fast-release) exhibited varying AUC_{0-t} values that were slightly lower (by 6%, 11%, and 12%, respectively) compared to the reference immediate-release ciprofloxacin formulation. The C_{max} of the various formulations appeared to be a function of the T_{max} , i.e., the formulation with the shortest T_{max} (reference immediate-release tablet) demonstrated the highest ciprofloxacin C_{max} . The ciprofloxacin elimination half-life was not formulation-dependent.
2. It appears from the safety data summarized in Table 96 above that the incidence of AEs in this in-vivo study was somewhat related to ciprofloxacin exposure (AUC and C_{max}), i.e., higher exposure led to higher AE incidence. However, all these reported AEs were considered by the investigators as mild in severity and none of these AEs were considered to be possibly/probably/likely related to the ciprofloxacin treatment.
3. In this study, the bioequivalence of the Proquin™ Standard-Release formulation with the reference Cipro® 500mg Immediate-release formulation was not ascertained. Based on the arithmetic mean AUC_{0-t} values, Proquin™ 500mg produced a systemic ciprofloxacin exposure that was 89% of that following a dose of Cipro® 500mg immediate-release tablet. The mean and median T_{max} values of Proquin™ were shorter (by 2.34 hours and 1.98 hours, respectively) and consequently, the C_{max} produced was lower (by 25%) compared to the reference Cipro® 500mg immediate-release formulation.
4. The review of the IVIVC model appears in the next section.

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Study 85-0001

Establishment of a Level A in-vitro-in-vivo Correlation

Objective:

To calculate the *in vivo* release kinetics of three test Proquin™ formulations from their observed plasma concentration-time profiles and to correlate these *in vivo* release profiles with their *in vitro* dissolution profiles with the aim of arriving at a robust Level A IVIVC.

Methods and Software:

The model independent, numerical deconvolution and convolution technique, based on the trapezoidal formula, was applied for the calculation of the *in vivo* release kinetics and for the simulation of plasma concentration profiles.

Data Used for Calculations:

In Vitro

The *in vitro* release (dissolution rate) of ciprofloxacin from the same batches of Proquin™ test formulations used for the development of the IVIVC model were determined in 900 mL 0.1N hydrochloric acid using USP dissolution apparatus I (basket, 100 rpm, 37°C). Since the product is designed to be retained in the stomach where drug release occurs, the pH range of these media are biorelevant as it is representative of the typical pH range of gastric fluid.

In Vivo

The mean plasma concentration profiles of the three different formulations Proquin™ 500mg Tablets (Standard Release, Fast Release and Slow Release), taken from Study 81-0029, were used to assess the release kinetics of the drug in the gastrointestinal tract.

Calculation of *In Vivo* Release Profiles

The *in vivo* release kinetics of Ciprofloxacin from the tested formulations was calculated from their plasma concentration levels by the numerical deconvolution method. The average plasma concentration profile observed from the Cipro® 500mg Tablets (Immediate Release) served as this weighting function.

Development and Validation of the IVIVC

Following the standard method, the percentages released *in vivo* were plotted against percent released *in vitro* for the same time points from the three test formulations. The correlation was based on data points up to 6 h, because the *in vivo* release of all three tested formulations is completed in this time period. The resulting polynomial function describing the correlation of % released *in vitro* (X) and % released *in vivo* (Y) was determined.

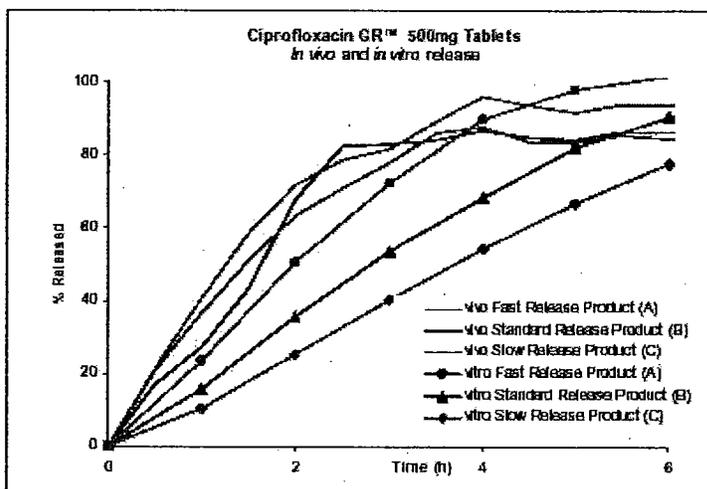
To ascertain the reliability of the developed IVIVC model, the "internal predictability" was evaluated, as described in the FDA Guidance on IVIVC. The following steps were followed:

- *In vitro* release data are converted into *in vivo* release data by using the IVIVC model.
- The *in vivo* release profiles are convoluted with the plasma profile of the immediate release tablet (unit impulse response) to calculate the corresponding plasma concentrations up to 12 h. In this case, the plasma concentrations between 12.5 and 24 h were then extrapolated using the elimination rate constant.
- The predicted plasma concentrations are compared with the observed plasma data and the percent prediction error (%PE) of the IVIVC model is calculated with regard to the bioavailability parameters C_{max} and AUC.

Results:

The comparison of the *in vitro* and *in vivo* release profiles of the test formulations, used for the development of IVVC model, is shown in Fig. 42. As can be seen from the figure, the *in vivo* dissolution is systematically faster than the release *in vitro* and the rank order among them is not as consistent as in the *in vitro* profiles.

FIGURE 42
In vitro release data compared to the *in vivo* release profiles calculated by deconvolution using the Cipro® tablet as the unit impulse response



The percentages released *in vivo* were plotted against percent released *in vitro* for the same time points from the three test formulations (Figure 43). The X and Y data plotted are shown in the following table. The resulting polynomial function describing the correlation of % released *in vitro* (X) and % released *in vivo* (Y) is as follows:

Regression equation: $Y = 0.94X + 0.06$ R² = 0.94

This equation is usable from 0.5 h onwards.

FIGURE 43
Correlation between percent released *in vivo* (Y-axis) and percent released *in vitro* (X-axis)

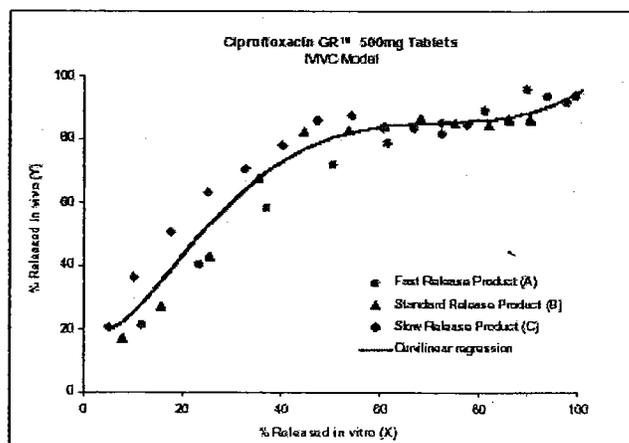
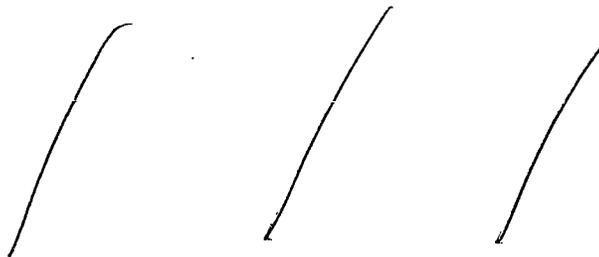


TABLE 97
In-Vitro and In-Vivo Drug Release Data used in IVVC Model



Validation:

Internal predictability is depicted graphically in Figures 44A, 44B, and 44C below. The close agreement between simulated and observed profiles demonstrates the goodness of the prediction obtained with the IVVC model for each of the three formulations.

FIGURE 44A
Mean plasma concentration profiles observed *in vivo* and predicted with the IVVC Model (Proquin™ Fast-Release)

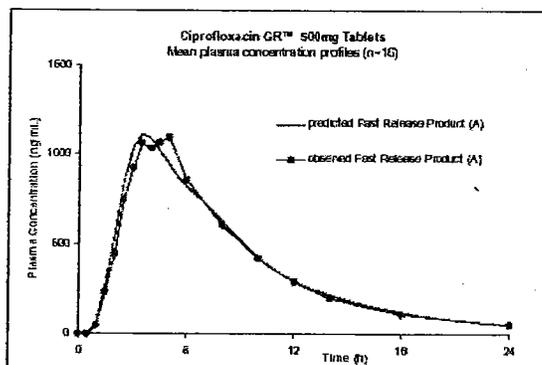


FIGURE 44B
Mean plasma concentration profiles observed *in vivo* and predicted with the IVVC Model (Proquin™ Standard-Release)

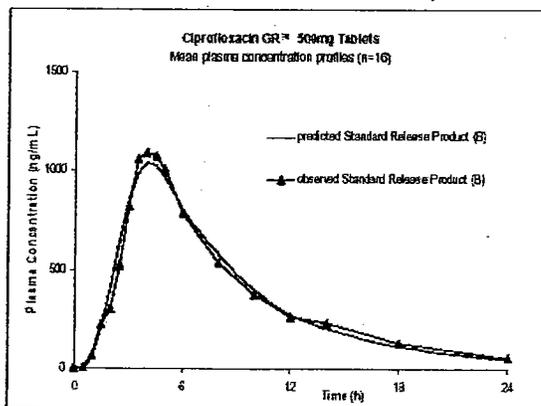
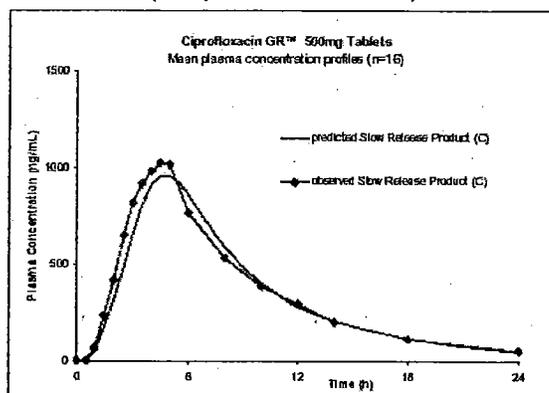


FIGURE 44C
Mean plasma concentration profiles observed *in vivo* and predicted with the IVIVC Model
(Proquin™ Slow-Release)



The ratios of predicted versus observed values for the usual bioequivalence criteria as well as the calculated % Prediction Error (PE) and mean absolute percent prediction error (MAPPE) are listed in the following table. The calculated %PE values for C_{max} and AUC are well below the maximal error ($\pm 15\%$ for each formulation and $\pm 10\%$ for MAPPE) permissible for the internal validation and is thus of acceptable quality.

TABLE 98

PK-parameters	Fast Release Product (A)			Standard Release Product (B)			Slow Release Product (C)			%MAPPE
	predicted	observed	%PE	predicted	observed	%PE	predicted	observed	%PE	
C _{max}	1112.836	1003.835	1.74	1042.411	1052.319	-4.57	982.6102	1028.824	-8.42	4.24
AUC(0-24h)	9013.01	8816.42	2.23	8290.78	8255.92	-0.77	8023.60	8221.77	-2.41	1.80

Conclusions:

- The developed IVIVC model meets the prediction criteria for the internal validation of a Level A IVIVC as set forth in regulatory guidances by a safe margin. This can be utilized in additional product development tasks like product variations during scale-up or line extensions.
- Furthermore, the correlation between the *in vitro* and *in vivo* data sets indicates that the selected *in vitro* test is biorelevant and can be used to set biorelevant *in vitro* dissolution specifications for the product.

Study 85-0002**Setting biorelevant *in vitro* release specifications****Objective:**

To set biopharmaceutical *in vitro* release specifications for Proquin™ batches based on acceptable *in vivo* performance as predicted by the Level A IVIVC model generated by a convolution-deconvolution technique

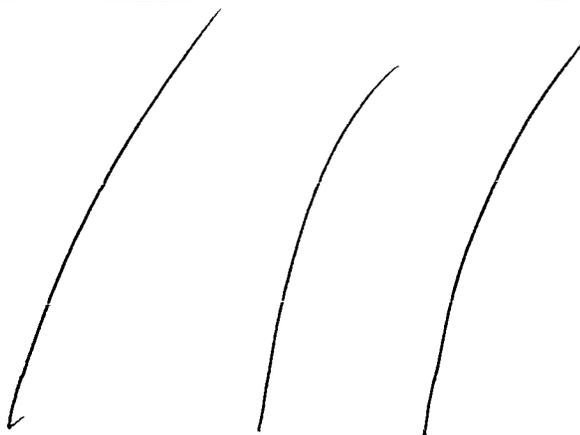
Methodology:

1. Time profiles were generated for theoretical side batches with *in vitro* release profiles that differed from the profile of the Standard Release Product by approximately $\pm 20\%$ at the sampling times previously used for measuring the dissolution rate.
2. These theoretical *in vitro* release profiles were then converted into *in vivo* release profiles with the help of the established IVIVC model
3. The Level A IVIVC model was then applied to simulate the plasma concentration-time profiles for the corresponding single dose administration from the resulting *in vivo* release profiles. The plasma profile of the immediate release tablet (Cipro® 500mg Tablets) was used as the weighting function.
4. The ratios of the predicted C_{max} and AUC values from the hypothetical side batches were compared to the observed values of the tested Standard Release Product and used as bioequivalence test criteria (acceptance range 80-125%), as outlined in the regulatory guidance.

Results:

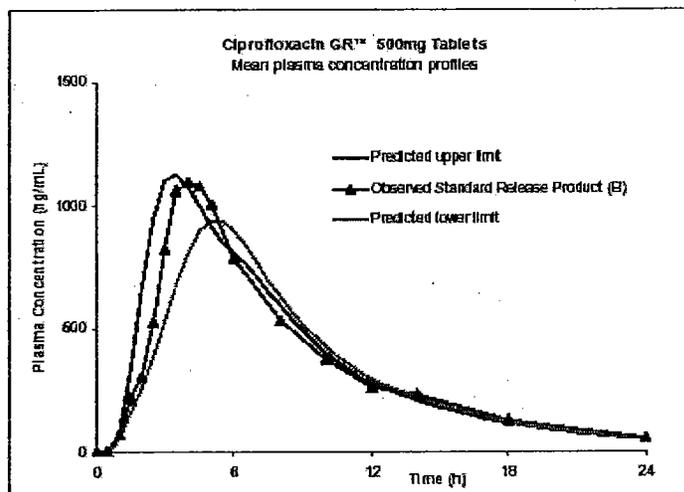
The *in vitro* release profiles of the theoretical side batches are plotted in Figure 45 together with the profile of the biobatch (Standard Release Product) tested *in vivo*.

FIGURE 45
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 46.

FIGURE 46
 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 Table 99 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 99

PK parameters	Relative bioavailability (%)				
	Predicted UL	Predicted LL	Observed Standard (B)	UL/Standard	LL/Standard
C _{max} (ng/mL)	1125.516	938.521	1032.319	103.0	85.7
AUC _(0-24h) (ng.h/mL)	8876.28	7993.95	8355.32	108.2	95.7

The following *in vitro* release specifications were proposed:

TABLE 100
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

Reviewer's comments:

1. The Proquin™ 500mg AUC_{0-24h} was 89% and the C_{max} was 75% of the reference Cipro™ 500mg used in the *in vivo* study. Table 101 below summarizes the estimated % relative bioavailability of

the theoretical side batches relative to Cipro® IR (instead of relative to the Proquin™ standard-release formulation).

TABLE 101

	ESTIMATED BIOAVAILABILITY RELATIVE TO CIPRO® 500MG IMMEDIATE-RELEASE TABLETS (%)	
	UL/Standard ^a X correction factor	LL/Standard ^a X correction factor
C _{max}	77.25	64.28
AUC(0-24h)	94.52	85.17

Correction factors: 0.75 (C_{max}); 0.89 (AUC)

Ratio is the predicted %bioavailability relative to Proquin™ standard-release tablets.

- It appears from the Table 101 above that the AUC_{0-24h} of the LL side batch will be comparable to that of the immediate-release reference formulation. From a predicted AUC_{0-24h} of 7994 ng*h/mL (Table 99), the resulting AUC/MIC is 178 (for *E.coli* with MIC₉₀ = 0.045 mcg/mL). In addition, although the C_{max} of the LL theoretical side batch appears low (64% of Cipro® 500mg), the predicted C_{max} = 936.5 ng/mL will result in a C_{max}/MIC of 21, a value that is acceptable from the standpoint of microbial resistance development.
- Based on the satisfactory PK-PD parameters of the theoretical (upper-limit and lower-limit) side-batches of Proquin™, the proposed *in vitro* release specifications for Proquin™ 500mg tablets are acceptable.

**APPEARS THIS WAY
ON ORIGINAL**

C. Consult Review (including Pharmacometric Reviews)
None.

D. Cover Sheet and OCPB Filing/Review Form

DEPOMED, INC.

Intending Pharmaceuticals

18 July 2004

Renata Albrecht, M.D.
Food and Drug Administration
Center for Drug Evaluation and Research
Electronic NDA Submissions
5901-B Amundson Road
Beltsville, MD 20750

Product Name: Proquin™ 500 mg (ciprofloxacin HCl gastric retentive tablets)
NDA No: 21-744
Re: New Drug Application

Dear Dr. Albrecht,

On behalf of Depomed, Inc., enclosed is the New Drug Application (NDA) for Proquin™ (ciprofloxacin HCl gastric retentive tablets, 500 mg), also referred to as "C-GR" tablets.¹ Proquin™ is indicated solely for the treatment of uncomplicated urinary tract infections (acute cystitis) caused by susceptible strains of the designated microorganisms listed in the proposed package insert.

This Proquin™ NDA includes full reports of investigations of the product's safety and efficacy conducted by Depomed, including clinical safety and efficacy information from Phase II and Phase III clinical trials in female patients with uncomplicated urinary tract infections (UTI). The application also provides data from non-clinical and biopharmaceutical studies, and Chemistry, Manufacturing, and Control information.

This application is submitted as a "full" or "stand alone" NDA under § 505(b)(1) of the Federal Food, Drug and Cosmetic Act (FDCA), and is designated as such in the enclosed form, FDA-356h. We enclose a position paper ("505(b)(1) Position Paper") that explains our basis for concluding that this application is a 505(b)(1) NDA. As explained in the (b)(1) Position Paper, there are four grounds upon which the Division of Special Pathogens and Immunologic Drug Products ("DSPIDP") can conclude that this application is a 505(b)(1) NDA. First, to the extent that this NDA includes information from the scientific literature, the information amounts to common or general prior scientific knowledge, and Depomed is including such information, because the NDA "is required to contain all other information

¹ As explained in this letter, Depomed proposes a new "tablet, gastric retentive" dosage form monograph for Proquin™. We are uncertain what term FDA might ultimately determine to be the new dosage form monograph for Proquin™. We are also uncertain of the standards for FDA's decision. Throughout this NDA Depomed uses different terms to refer to Proquin™, including Proquin™ XR 500 mg (Ciprofloxacin HCl extended release) Tablets. These terms are fully described in the Modules 2-5 summaries and reports. Despite the use of these terms, Depomed maintains that Proquin™ is a novel gastric retentive dosage form.

1340 O'Brien Drive
Menlo Park, CA 94025-1436
T. 650. 462-5900
F. 650. 462-9993

NDA 21-744

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www.depomedinc.com

BEST POSSIBLE COPY

OCPB Filing/Review Form

Office of Clinical Pharmacology and Biopharmaceutics
New Drug Application Filing and Review Form

General Information About the Submission

	Information		Information
NDA Number	21,744	Brand Name	Proquin™
OCPB Division (I, II, III)	DPEIII	Generic Name	Ciprofloxacin HCl
Medical Division	HFD-590 (DSPIDP)	Drug Class	Fluoroquinolone
OCPB Reviewer	Gerlie C. De Los Reyes	Indication(s)	Uncomplicated UTI
OCPB Team Leader	Philip M. Colangelo	Dosage Form	Gastric-retentive oral tablets
Date of Submission	18 July 2004	Dosing Regimen	500 mg QD
Estimated Due Date of OCPB Review		Route of Administration	oral
PDUFA Due Date	17 June 2005	Sponsor	Depomed, Inc.
Division Due Date		Priority Classification	Standard

Clin. Pharm. and Biopharm. Information

	"X" if included at filing	Number of studies submitted	Number of studies reviewed	Critical Comments If any
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data, etc.	X			
Tabular Listing of All Human Studies	X			
HPK Summary	X			
Labeling	X			
Reference Bioanalytical and Analytical Methods	X			
I. Clinical Pharmacology				
Mass balance:		1	1	
Isozyme characterization:				
Blood/plasma ratio:				
Plasma protein binding:	X	1	1	
Pharmacokinetics (e.g., Phase I) -				
Healthy Volunteers-				
single dose:	X	1	1	
multiple dose:	X	1	1	
Patients-				
single dose:				
multiple dose:				
Dose proportionality -				
fasting / non-fasting single dose:				
fasting / non-fasting multiple dose:				
Drug-drug interaction studies -				
In-vivo effects on primary drug:	X	3	3	Antacids, omeprazole, warfarin
In-vivo effects of primary drug:		1	1	warfarin
In-vitro:	X			
Subpopulation studies -				
ethnicity:				
gender:				
pediatrics:				
geriatrics:	X	1	1	
renal impairment:		1	1	Mild and moderate renal impairment
hepatic impairment:				
PD:				
Phase 2:				
Phase 3:	X			
PK/PD:				
Phase 1 and/or 2, proof of concept:	X	2	2	Single-dose and steady state

Phase 3 clinical trial:				
Population Analyses -				
Data rich:				
Data sparse:				
II. Biopharmaceutics				
Absolute bioavailability:				
Relative bioavailability -				
solution as reference:				
alternate formulation as reference:	X			
Bioequivalence studies -				
traditional design; single / multi dose:	X	2	2	Versus Cipro® 250 mg BID (Day 1 through Day 3)
replicate design; single / multi dose:				
Food-drug interaction studies:	X	1	1	
Dissolution:	X	1	1	
(IVIVC):	X	1	1	
Bio-waver request based on BCS				
BCS class				
III. Other CPB Studies				
Genotype/phenotype studies:				
Chronopharmacokinetics				
Pediatric development plan				
Literature References	X			
Total Number of Studies				
Filability and QBR comments				
	"X" if yes	Comments		
Application filable ?	X	Reasons if the application is <u>not</u> filable (or an attachment if applicable) For example, is clinical formulation the same as the to-be-marketed one?		
Comments sent to firm ?		Comments have been sent to firm (or attachment included). FDA letter date if applicable.		
QBR questions (key issues to be considered)	<ol style="list-style-type: none"> 1. Is there sufficient clinical data to serve as basis for dosage recommendations of ProquinTM gastric-retentive tablets in patients with renal and/or hepatic impairment? 2. Could ProquinTM be considered an extended-release preparation of ciprofloxacin HCl? 3. Is it acceptable to use class (fluoroquinolone) labeling for a modified release dosage form of ciprofloxacin? 4. Since the in vitro study showed slight inhibition of CYP2C9 activity at test concentrations much lower compared to in vivo C_{max}, do we require an in vivo drug interaction study with warfarin? 			
Other comments or information not included above				
Primary reviewer Signature and Date				
Secondary reviewer Signature and Date				

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

/s/

Gerlie Gieser
5/18/05 07:26:04 AM
BIOPHARMACEUTICS

Phil: You signed off on this (5/17/2005).

Phil Colangelo
5/18/05 01:27:19 PM
BIOPHARMACEUTICS