8) Bio-Equivalence Studies (BE):

Bioequivalence study was performed between Ciproxin 750 mg (Reference Formulation) of Bayer Health Care AG, Leverkusen, Germany and Ciprofloxacin Tablets BP 750 mg (Test Formulation) of Aurobindo Pharma Limited, India.

The details of the batches used in this study are as follows:

Test (T) : Ciprofloxacin Tablets BP 500 mg

Mfg. By : Aurobindo Pharma Limited, India.

Batch No. : CC7505001 **Batch size** : 166,666 Tablets

Mfg. Date : 08/2005 **Expiry date** : 07/2007

Reference(R) : Ciproxin 750 mg Tablets

Mfg. By : Bayer Health Care AG, Leverkusen, Germany

Batch No. : BXBPCPI

Expiry Date : 02/2009

The Bio-equivalence study are enclosed overleaf.

Summary of
Bio-equivalence Report

APL RESEARCH CENTRE
(A Division of Aurobindo Pharma Ltd.)

QUALITY ASSURANCE DEPARTMENT
APL RESEARCH CENTRE
313, BACHUPALLY, QUTHUBULLAPUR MANDAL, HYDERABAD, 500 072
INDIA.

SOP NO. APL-QAD-004-01
FORM No. 01

QUALITY ASSURANCE AUTHENTICATION

Study No.: Cpf-03/05

Project Title: An open label, randomized, two treatment, two sequence, two period, cross over, single dose, comparative oral bioavailability study of Ciprofloxacin tablets BP 750 mg (Test) of Aurobindo Pharma Ltd., India and Ciproxin tablets (Reference) of Bayer Health Care AG, Leverkusen, Germany, in 24 healthy, adult, male, human subjects under fasting conditions.

The conduct of this study has been subjected to periodic inspections as mentioned below and the Quality Assurance Unit has audited this report.

Date of QA Inspection/Audit	Activity Inspected / Audited
21th February 2006	Bio statistical Report
25th February 2006	Summary Report

This report accurately describes that the methods and procedures used in the study and the reported results accurately reflect the raw data of the study.

Approved by:

Mr. S. Ravinder. M.Sc., PGDCAQM.
Scientist – Quality Assurance Department

25/02/06.
Signature & Date

APL RESEARCH CENTRE
CLINICAL PHARMACOLOGY DEPARTMENT

Study No: Cpf-03/05

An Open Label, Randomized, Two-Treatment, Two-Sequence, Two-Period, Cross-Over, Single-Dose Comparative Oral Bioavailability Study Of Ciprofloxacin Tablets BP 750 mg (Test) Of Aurobindo Pharma Ltd., India and Ciproxin tablets (Reference) Of Bayer Health Care AG, leverkusen, Germany in 24 Healthy, Adult, Male, Human Subjects Under Fasting Conditions.

SUMMARY REPORT

[Volume 1]

Date: 23rd February 2006

APL RESEARCH CENTRE
Survey No. 313, Bachupally Village, Quthubullapur Mandal,
HYDERABAD, 500072
INDIA
PHONE No.: 040-23040261/263

COMPLIANCE STATEMENT:

We attest to the fact that the data presented here is accurate and reflects the raw data. The study has been conducted as per the Protocol and SOPs of CPD, APL Research Centre and we accept the responsibility for scientific correctness of the project and the validity of the data produced in this report.

Investigator- Pharmacokinetics:

Mr. N.Nagaraj Kumar, M. Pharm
CPD, PK & BS Unit,
APL Research Centre,
313, Bachupally, Quthubullapur Mandal,
Hyderabad-500 072
India.

23/02/06
Signature

Investigator-Biostatistics:

Mr. P. Pramod Kumar Reddy, M. Sc
CPD, PK & BS Unit,
APL Research Centre,
313, Bachupally, Quthubullapur Mandal,
Hyderabad-500 072
India.

for P. Balaji 23/02/06.
Signature

Principal Investigator:

A. T. Bapuji, Ph.D
CPD,
APL Research Centre,
313, Bachupally, Quthubullapur Mandal,
Hyderabad-500 072
India.

23/02/06
Signature

TABLE OF CONTENTS

1.0 LITERATURE SURVEY

- Medical Economic Company Inc, Physician's Desk Reference, 57th Edition, 2003, P.875-881.
- Churchill Livingstone, Colin Dollery, Therapeutic Drugs, IInd edition, Volume I, 1999, P: C230-C234.
- Pharmaceutical Press, Martindale-the complete drug reference, 33rd edition, P: 182-186.
- http://www.medsafe.govt.nz/Profs/Datasheet/c/Ciprofloxacintab.htm
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1.1 CLINICAL PHARMACOLOGY

PHARMACODYNAMICS

Ciprofloxacin is a synthetic broad-spectrum fluoroquinolone antibacterial agent. It is used to treat or prevent infections that are proven or strongly suspected to be caused by bacteria. Ciprofloxacin is effective *in vitro* against virtually all gram-negative pathogens, including *Pseudomonas aeruginosa*. It is also effective against gram-positive pathogen such as *staphylococci* and *streptococci*. Anaerobes are generally less susceptible.

Mechanism of Action

During the proliferation phase of a bacterium a segmental twisting and untwisting of the chromosomes take place. An enzyme called DNA gyrase plays a decisive part in this process. Ciprofloxacin inhibits this DNA gyrase in a way that arrests the bacterial metabolism, since vital information can no longer be read from the bacterial chromosome.

PHARMACOKINETICS

Ciprofloxacin is given as an oral tablet, is rapidly and well absorbed from the gastrointestinal tract after oral administration. The absolute bioavailability is approximately 70%. Maximum serum concentrations are attained 1 to 2 hours after oral dosing. The maximum serum concentration (C_{max}) obtained, after

administration of 750 mg tablet is 4.3 μg/mL and area under the curve is 20.2 μg*hr/mL. Mean concentration 12 hours after dosing with 750 mg is 0.4 μg/mL. The serum elimination half-life in subjects with normal renal function is approximately 4 hours. Serum concentrations increase proportionately with doses up to 1000 mg. The binding of ciprofloxacin to serum proteins is 20 to 40%. After oral administration, ciprofloxacin is widely distributed throughout the body.

Time (h)	Mean Ciprofloxacin Serum Concentrations (mg/L) after Oral Administration of 750 mg
0.5	2.9
1.0	3.5
2.0	2.9
4.0	1.7
8.0	0.8
12.0	0.5

Four metabolites have been identified in human urine which together account for approximately 15% of an oral dose. They were identified as desethyleneciprofloxacin (M 1), sulphociprofloxacin (M 2), oxociprofloxacin (M 3) and formylciprofloxacin (M 4). M 1 to M 3 display antibacterial activity comparable to or inferior to that of nalidixic acid. M 4. The metabolites have antimicrobial activity, but are less active than unchanged ciprofloxacin. The serum elimination half-life in subjects with normal renal function is approximately 4 hours. Approximately 40 to 50% of an orally administered dose is excreted in the urine as unchanged drug. Thus, active tubular secretion would seem to play a significant role in its elimination. An additional 1 to 2% of the dose is recovered from the bile in the form of metabolites. Approximately 20 to 35% of an oral dose is recovered from the feces within 5 days after dosing.

INTERACTIONS

Food Interactions

Food delays the absorption of the Ciprofloxacin, resulting in peak concentrations that occur closer to 2 hours after dosing rather than 1 hour. The overall absorption of Ciprofloxacin however, is not substantially affected.

Drug / Drug Interactions

Concurrent administration of Ciprofloxacin with iron, sucralfate, highly buffered drugs (e.g. antiretrovirals) and antacids containing magnesium hydroxide or aluminum hydroxide and dairy products or mineral fortified drinks alone (eg. Milk, yoghurt, calcium fortified orange juice) may reduce the bioavailability of ciprofloxacin by as much as 90%. Concomitant administration of ciprofloxacin with theophylline decreases the clearance of theophylline can cause an undesirable increase in the serum theophylline concentration resulting in serious and fatal reactions. Ciprofloxacin also decreases caffeine clearance and inhibits the formation of Paraxanthine after caffeine administration. Combination of very high doses of quinolones (gyrase inhibitors) and certain non-steroidal anti-inflammatory agents (but not acetylsalicylic acid) can provoke convulsions. A transient rise in the concentration of serum creatinine was observed when Ciprofloxacin and Cyclosporin were administered simultaneously. The simultaneous administration of Ciprofloxacin and Warfarin may intensify the action of Warfarin. In particular cases, concurrent administration of ciprofloxacin and Glibenclamide can intensify the action of Glibenclamide (hypoglycaemia). Co-administration of Probenecid and Ciprofloxacin increases the Ciprofloxacin serum concentrations. Renal tubular transport of Methotrexate may be inhibited by concomitant administration of Ciprofloxacin potentially leading to increased plasma levels of Methotrexate. Metoclopramide accelerates the absorption of ciprofloxacin (oral) resulting in a shorter time to reach maximum plasma concentrations. Ciprofloxacin may affect the speed of reaction to such an extent that the ability to drive or to operate machinery is impaired. This applies particularly in combination with alcohol. Drugs that inhibit peristalsis are contra indicated. Ciprofloxacin should be used

with caution in patients with known or suspected CNS disorders that may predispose to seizures or lower the seizure threshold (e.g. severe cerebral arteriosclerosis, epilepsy).

ADVERSE REACTIONS

Most of the adverse events reported were described as only mild or moderate in severity, abated soon after the drug was discontinued, and required no treatment.

The *most frequently reported* drug related events, from clinical trials of all formulations, all dosages, all drug-therapy durations, and for all indications of ciprofloxacin therapy were nausea (2.5%), diarrhea (1.6%), liver function tests abnormal (1.3%), vomiting (1.0%), and rash (1.0%).

Additional medically important events that occurred in *less than 1%* of ciprofloxacin patients are listed below.

BODY AS A WHOLE: headache, abdominal pain/discomfort, foot pain, pain, pain in extremities, injection site reaction (ciprofloxacin intravenous)

CARDIOVASCULAR: palpitation, atrial flutter, ventricular ectopy, syncope, hypertension, angina pectoris, myocardial infarction, cardiopulmonary arrest, cerebral thrombosis, phlebitis, tachycardia, migraine, hypotension

CENTRAL NERVOUS SYSTEM: restlessness, dizziness, lightheadedness, insomnia, nightmares, hallucinations, manic reaction, irritability, tremor, ataxia, convulsive seizures, lethargy, drowsiness, weakness, malaise, anorexia, phobia, depersonalization, depression, paresthesia, abnormal gait, grand mal convulsion

GASTROINTESTINAL: painful oral mucosa, oral candidiasis, dysphagia, intestinal perforation, gastrointestinal bleeding, cholestatic jaundice, and hepatitis.

HEMIC/LYMPHATIC: lymphadenopathy and petechia

METABOLIC/NUTRITIONAL: amylase increase, lipase increase

MUSCULOSKELETAL: arthralgia or back pain, joint stiffness, achiness, neck or chest pain, and flare up of gout

RENAL/UROGENITAL: interstitial nephritis, nephritis, renal failure, polyuria, urinary retention, urethral bleeding, vaginitis, acidosis, breast pain.

RESPIRATORY: dyspnea, epistaxis, laryngeal or pulmonary edema, hiccough, hemoptysis, bronchospasm, pulmonary embolism.

SKIN/HYPERSENSITIVITY: allergic reaction, pruritus, urticaria, photosensitivity, flushing, fever, chills, angioedema, edema of the face, neck, lips, conjunctivae or hands, cutaneous candidiasis, hyperpigmentation, erythema nodosum, sweating.

SPECIAL SENSES: blurred vision, disturbed vision (change in color perception, over brightness of lights), decreased visual acuity, diplopia, eye pain, tinnitus, hearing loss, bad taste, chromatopsia In several instances nausea, vomiting, tremor, irritability, or palpitation were judged by investigators to be related to elevated serum levels of theophylline possibly as a result of drug interaction with Ciprofloxacin.

Post marketing Adverse events:

Agitation, agranulocytosis, albuminuria, anaphylactic reactions, anosmia, candiduria, cholesterol elevation (serum), confusion, constipation, delirium, dyspepsia, dysphagia, erythema multiforme, exfoliative dermatitis, fixed eruption, flatulence, glucose elevation (blood), hemolytic anemia, hepatic failure, hepatic necrosis, hyperesthesia, hypertonia, hypesthesia, hypotension (postural), jaundice, marrow depression (life threatening), methemoglobinemia, monoliasis (oral, gastrointestinal, vaginal) myalgia, myasthenia, myasthenia gravis (possible exacerbation), myoclonus, nystagmus, pancreatitis, pancytopenia (life threatening or fatal outcome), phenytoin alteration (serum), potassium elevation (serum), prothrombin time prolongation or decrease, pseudomembranous colitis (The onset of pseudomembranous colitis symptoms may occur during or after antimicrobial treatment.), psychosis (toxic), renal calculi, serum sickness like reaction, Stevens-Johnson syndrome, taste loss, tendinitis, tendon rupture, toxic epidermal necrolysis, triglyceride elevation (serum), twitching and vasculitis.

Changes in laboratory parameters listed as adverse events without regard to drug relationship are listed below:

Hepatic – Elevations of ALT (SGPT) (1.9%), AST (SGOT) (1.7%), alkaline phosphatase (0.8%), LDH (0.4%) and serum bilirubin (0.3%).

Hematologic – Eosinophilia (0.6%), leukopenia (0.4%), decreased blood platelets (0.1%), elevated blood platelets (0.1%), pancytopenia (0.1%).

Renal – Elevations of serum creatinine (1.1%), BUN (0.9%), crystalluria, cylindruria, and hematuria have been reported.

2.0 OBJECTIVE, DESIGN, & OVERVIEW OF THE BIO-EQUIVALENCE STUDY

The objective of the study was to compare the rate and extent of absorption of Ciprofloxacin tablets BP 750 mg (Test) of Aurobindo Pharma Ltd., India, with that of Ciproxin tablets (Reference) of Bayer Health Care AG, leverkusen, Germany, when given in equal doses of single oral dose containing 750 mg of Ciprofloxacin in 24 healthy, adult, male, human subjects under fasting conditions.

The study design used was an open label, randomized, two-treatment, two-sequence, two-period, crossover, single-dose, comparative oral bioavailability study in 24 healthy, adult, male, human subjects under fasting conditions.

The study was conducted according to the study protocol attached as annexure-i. The volunteers in the age group of 19 to 35 years with body mass index of 19.00 to 25.86 were screened according to the inclusion and exclusion criteria. After an overnight fast (at least 10 hours) before dosing and minimum 4 hours thereafter, a single oral dose of 750 mg tablet of reference (R) or test (T) product was administered as per the randomisation schedule attached as annexure-iii. The blood samples were collected in a pre-labelled vacutainer tubes containing K_3 EDTA during each period. The washout period between the treatment schedules was 6 days.Ciprofloxacin was estimated in plasma using a validated HPLC-FLD method. The pharmacokinetic parameters were studied by using WinNonlin version 3.3,

90% confidence interval, Ratio Analysis and the intra subject variability was calculated using SAS 9.1.3 version.

3.0 DETAILS OF BIO-EQUIVALENCE STUDY

3.1 Products Evaluated

Reference (R)	:	Ciproxin tablets, each tablet contains Ciprofloxacin Hydrochloride equivalent to 750 mg of Ciprofloxacin.			
Mfg. By	:	Bayer Health Care AG, leverkusen, Germany.			
Batch No	:	BXBPCP1	Exp. Date	:	02/2009
Test (T)	:	Ciprofloxacin tablets BP 750 mg, each film coated tablet contains Ciprofloxacin Hydrochloride Ph.Eur. equivalent to 750 mg of Ciprofloxacin.			
Mfg. By	:	Aurobindo Pharma Ltd., India..			
Batch No	:	CC7505001			
Mfg. Date	:	08/2005	Exp. Date	:	07/2007

3.2 Location of the study

3.2.1 Clinical & Clinical Laboratory Facilities

Clinical Unit, Clinical Pharmacology Department,
APL Research Centre, Plot No. 33-35,
2nd and 3rd floor, Mirra Multi-speciality Hospital,
Alluri Sitaramaraju Nagar,
Opp J. P. N. Nagar, , Miyapur
Hyderabad-500 050, India.

3.2.2 Bio-analytical Unit

Clinical Pharmacology Department
APL Research Centre

Survey No. 313, Bachupally Village
Quthubullapur Mandal
Hyderabad – 500 072, India

3.2.3 Pharmacokinetic and Statistical analysis

Clinical Pharmacology Department
APL Research Centre
Survey No. 313, Bachupally Village
Quthubullapur Mandal
Hyderabad – 500 072, India

3.3 Name of the Principal investigator

Dr. A. T. Bapuji

3.4 Study protocol approval

Name of review committee: Savior-INSTITUTIONAL REVIEW BOARD
Date of approval of protocol: 10th August 2005.

3.5 Start and stop dates for each phase of the clinical study

Clinical Phase : 08th September 2005 to 16th September 2005
Check-in Period I : 08th September 2005
Check-in period II : 14th September 2005

3.6 Inclusion Criteria

- Healthy males within the age range of 18 to 50 years.
- A body mass index within 19-26.
- Given written informed consent to participate in the study.
- Absence of disease markers of HIV 1 & 2, hepatitis B & C virus and RPR.

- Absence of significant disease or clinically significant abnormal laboratory values on laboratory evaluation, medical history and physical examination during the screening.
- A normal 12-lead ECG.
- A normal chest X-ray (PA view).
- Comprehension of the nature and purpose of the study and compliance with the requirement of the entire protocol.
- No history or no evidence of hypersensitivity to Ciprofloxacin or any member of the quinolone class of antibiotics or any other ingredients of the formulation
- No history of significant systemic diseases.
- No history of psychiatric disorders.
- No donation of blood (one unit or 350 mL) within 56 days prior to receiving the first dose of study medication.
- No history of addiction to any recreational drug or drug dependence.
- No participation in any clinical study within the past 56 days.
- No receipt of any prescription drugs (e.g.: Chewable or buffered tablets (didanosine), theophyllin, caffeine, phenytoin, glyburide, cyclosporine, warfarin, probenecid, methotrexate, metoclopramide and NSAIDs.) or over-the-counter drugs (e.g.: Cold preparations, dairy products or mineral fortified drinks, fortified orange juice, antacid preparations, vitamins and natural products used for therapeutic benefits), within two weeks prior to receiving the first dose of study medication.
- No history of dehydration from diarrhea, vomiting or any other reason within a period of 24 hours prior to the study.
- No family history of neurological disorders.

- Not consumed alcohol and xanthine containing food and beverages, (chocolates, tea, coffee or cola drinks) cigarettes and tobacco products, for atleast 48 hours, prior to check-in.
- Negative results for drugs of abuse (barbiturates, benzodiazepines, opioids, amphetamines and cannabinoids) in urine during the day of check in for period I and period II.

3.7 Exclusion Criteria

- Subjects having a history of seizure.
- Subjects who have a history of alcohol consumption for more than two units/day (1 unit = 30 ml of spirit/or 1 pint of beer), or having consumed alcohol within 48 hours prior to dosing.
- Subjects who have a habit of high caffeine (more than 5 cups of coffee or tea/day) or tobacco (more than 9 cigarettes/beedies/cigars per day) consumption.
- Subjects who have a history of difficulty with donating blood or difficulty in accessibility of veins in left or right arm.
- Subjects who have taken any prescription drugs (e.g.: Chewable or buffered tablets (didanosine), theophyllin, caffeine, phenytoin, glyburide, cyclosporine, warfarin, probenecid, methotrexate, metoclopramide and NSAIDs.) or over-the-counter drugs (e.g.: Cold preparations, dairy products or mineral fortified drinks, fortified orange juice, antacid preparations, vitamins and natural products used for therapeutic benefits), within two weeks prior to receiving the first dose of study medication.
- Subjects with an unusual or abnormal diet, for whatever reason e.g. because of fasting due to religious reasons.
- Subjects having a history of Myasthenia gravis.

4.0 CLINICAL PHASE

4.1 Number of subjects enrolled in the study

24 + 2 (Standby). The planned sample size was 24 + 2 (Standby), study started with 26 subjects and 24 subjects completed the study.

4.2 Range and mean age (± SD) of subjects

Range : 19-35 Years

Mean : 25.69

SD : 4.74

4.3 Range and mean height and weight (± SD) of subjects

Height (cms)		Weight (kgs)	
Range	159-175	Range	52-75
Mean	167.12	Mean	61.81
SD	4.49	SD	6.72

4.4 Diagnostic Tests performed on the Subjects

Test	Criteria
Hemoglobin	13.0 – 18.0 gm%
RBC	4.5 – 5.9 mill/cumm
Total WBC count	4000 – 11000 /cumm
Differential Count	
a. Neutrophils	40 – 75%
b. Lymphocytes	20 – 45%
c. Eosinophils	1 – 6%
d. Monocytes	2 – 10%
e. Basophils	0- 1%
Platelet count	1.5 – 4.4 lakhs / cumm
Serum Total Bilirubin	0.0-1.0 mg/dL
SGPT	30-65 U/L
SGOT	15-37 U/L
Gamma-GT	15 – 85 U/L
Alkaline Phosphatase	50-136 U/L
Total protein	6.4-8.2 g/dL
Albumin	3.4 – 5.0 g/dL
Glucose Fasting	70 – 110 mg/dL
Total Cholesterol	< 200 mg/dL
Serum Urea	15-39 mg/dL

Test	Criteria
Serum Creatinine	0.8 – 1.3 mg/dL
Serum Uric acid	3.5 - 7.2 mg/dL
Serum Calcium	8.5-10.1 mg/dL
Serum phosphorous	2.5-4.9 mg/dL
Serum Sodium	136 – 145 mmol/L
Serum Potassium	3.5 – 5.1 mmol/L
Serum Chloride	98 – 107 mmol/L
Bleeding Time	1-5 minutes
Complete Urine Examination	
a) Specific Gravity	1.001- 1.035
b) pH	4.6 – 8.0
c) Pus Cells	0 – 5 / hpf
d) Epithelial Cells	0 – 5 / hpf

4.5 Volume and type of fluid consumed with dose

240 mL of water was consumed with each dose.

4.6 Interval between doses

A washout period of 6 days was observed between two periods.

4.7 Protocol for the administration of food and fluid

Subjects were provided standard meal (dinner) consisting of approx. 1000 K.cal during the day of check-in.

Subjects were required to fast overnight (at least 10 hours) before dosing and minimum of four hours thereafter. Post dose standardised meal on Day-1 (dosing day) consisting of approx. 2200 Kcal (divided into lunch- approx. 900 Kcal., snacks- approx. 400 Kcal., and dinner- approx. 900 Kcal.) was provided at 4.0 hours (lunch), 8.0 hours 15 minutes (snacks) and 13 hours (dinner) respectively.

During clinical residence, the meal plans were kept identical for both the periods. Information on the standardized meal, quantity and time were recorded on the relevant raw data forms.

Drinking water was not permitted one hour before dosing and until one hour post-dose, at other times drinking water was permitted *ad libitum*.

4.8 Restrictions on posture and physical activity during the study

Subjects were dosed while in sitting posture and were instructed to remain seated or ambulatory for first 2 hours following the drug administration. However postural change of the subjects were allowed, in case of the medical emergency like adverse events and scheduled vitals. Thereafter, the subjects were allowed to engage only in normal activities while avoiding severe physical exertion.

4.9 Biological fluid(s) sampled

Blood

4.10 Number of samples collected per subject

42 (21x2) blood samples per subject.

4.11 Volume of fluid collected per sample

Volume of fluid collected per sample was 6 mL.

4.12 Study sampling times

Pre-dose (0.0) and at 0.25, 0.5, 0.75, 1.0, 1.25, 1.5, 1.75, 2.0, 2.5, 3.0, 3.5, 4.0, 4.5, 5.0, 6.0, 8.0, 10.0, 12.0, 16.0 and 24.0 hours after administration of each product.

4.13 Method of sample collection

Samples were collected through an indwelling cannula and each blood sample was collected into a pre-labelled vacutainer.

4.14 Sample handling and storage procedures

The samples collected at times specified under study design were centrifuged (at 2500 RCF and 4°C for 10 minutes) to separate plasma, immediately after receiving the blood samples from all the subjects. The separated plasma samples were then transferred to deep freezer maintained at below –20°C for temporary storage up to 4.00 hours and finally transferred to /or directly to deep freezer maintained below -70°C for storage until analysis. Separated plasma samples of the subjects were transferred from Clinical Unit to Bio analytical Unit as per the SOP No: APL-CPD-228-XX.

4.15 Adverse reactions observed

None of the subjects reported any adverse event during the entire duration of the study.

4.16 Withdrawals

Subject No.	Reason for Withdrawal	Period in the study the withdrawal occurred
S2	Absent for check-in.	Period-II
S11	Positive for Cannabinoids in urine drugs of abuse during period-II check-in	Period-II

5.0 BIO-ANALYTICAL PHASE

5.1 Analyte(s) monitored

Ciprofloxacin

5.2 Analytical technique employed

Estimation of Ciprofloxacin in human plasma using HPLC with FL detection method.

5.3 Method of Detection

HPLC –FLD

5.4 Internal standard

Gatifloxacin

5.5 Method Validation

5.5.1 Precision and Accuracy

Inter-day and Intra-day accuracy and precision during assay validation are as follows:

Intra day Precision (CV%) for Ciprofloxacin

Intra day precision for LQC, MQC and HQC was ranged from 0.63 to 5.25%.

Intra day precision for LLOQ QC was ranged from 0.00 to 2.33%.

Intra day Accuracy ((%Nominal) for Ciprofloxacin

Intra day accuracy for LQC, MQC and HQC was ranged from 85.33 to 100.08%.

Intra day accuracy for LLOQ QC was ranged from 101.00 to 105.00%.

Inter day Precision (CV%) for Ciprofloxacin

Inter day precision for LQC, MQC and HQC was ranged from 1.32 to 3.56%

Inter day precision for LLOQ QC was ranged from 2.15 %.

Inter day Accuracy (%Nominal)for Ciprofloxacin

Inter day accuracy for LQC, MQC and HQC from 88.42 to 97.57%.

Inter day accuracy for LLOQ QC was ranged from 103.50 %.

5.5.2 **Stability**

a) **Data on long-term storage stability**

Long-term stability of replicate quality control samples (High Quality Control Samples and Low Quality Control Samples) were determined on 55th day stability was assessed against the freshly prepared calibration curve standards. maintained at -20°C and –70°C. The stability at –20°C was found 100.00% for LQC, and 107.48% for HQC and the stability at –70°C was found 99.78% for LQC and 106.59% for HQC for Ciprofloxacin.

b) **Data on freeze-thaw stability**

The stability of the spiked plasma samples was determined after three freeze thaw cycles. Replicate number of quality control samples was analyzed for third freeze thaw cycle. The percentage degradation was determined against Comparison samples by using freshly prepared calibration curve standards. The comparative stability of Ciprofloxacin was 90.11% for LQC and 97.70% for HQC.

c) **Data on bench top stability**

Bench top stability of replicate quality control samples was determined for 7.0 hour. Bench top stability was assessed against the freshly prepared calibration curve standards. The Comparative stability was 96.00% for LQC and 91.55%for HQC.

d) **Data on auto sampler storage stability**

In-injector stability of replicate quality control samples was determined at 37.0 hours. The percentage of degradation calculated for Ciprofloxacin for 37.0 hours was 89.00% for LQC, 91.04% for HQC.

e) **Data from any other stability studies conducted**

Short-term stock solution stability

Short-Term stability of stock solutions of Ciprofloxacin and Internal standard were stored at room temperature (~25°C), determined for 7.0 hour. The accuracy ranged from 90.38%, 96.50% for Ciprofloxacin and Internal Standard at 7.0 hour respectively.

Long-term stock solution stability

Long-term stock solutions of Ciprofloxacin and Internal standard stored below 10°C was determined for 8.0 days and 10 days against freshly prepared 1 mg/mL respective stock dilution. After 08 days the percent stabilities were 102.53% for Ciprofloxacin and after 10 days 100.45% for ISTD respectively.

5.5.3 **Selectivity**

The selectivity of the present method was established by checking the blank CPD (citrate Phosphate Dextrose) plasma (without spiking with Ciprofloxacin) obtained from different blood donors. Six different batches of plasma were screened and all the batches found to have no endogenous interference at the retention times of analyte and ISTD for Ciprofloxacin.

5.5.4 **Recovery**

Recovery of Drug

The percentage recoveries were determined by measuring the concentrations of the prepared plasma quality control samples against aqueous quality control samples respectively. Recovery for Ciprofloxacin was ranged from 56.25% to 60.76% (Mean Recovery 58.53%).

Recovery of Internal Standard

The percentage recoveries were determined by measuring the concentrations of the prepared plasma quality control samples against aqueous quality control samples respectively. Recovery for Internal Standard was 60.67%.

5.6 Analytical Results

5.6.1 Dates of subject sample analysis

Start Date: 16-11-2005

End Date: 26-11-2005

5.6.2 List number and concentration of calibration standards used for Ciprofloxacin

ID	Nominal Concentration (µg/mL)	Acceptance Levels	
		Lower	Upper
STD1	0.050	0.040	0.060
STD2	0.100	0.085	0.115
STD3	0.250	0.213	0.288
STD4	0.500	0.425	0.575
STD5	1.000	0.850	1.150
STD6	2.000	1.700	2.300
STD7	3.502	2.977	4.027
STD8	5.003	4.253	5.753
HQC	4.004	3.403	4.605
MQC	2.503	2.128	2.878
LQC	0.150	0.128	0.173

LLOQ (STD1): ± 20%
Other STDs (STD2 – STD8): ±15%
QC Samples (HQC, MQC & LQC): ±15%

5.6.3 Descriptive data including slope, intercept, correlation coefficients

CC ID	Date of Analysis	Subjects Analyzed	STD1	STD2	STD3	STD4	STD5	STD6	STD7	STD8	Slope	Intercept	r^2
			Nominal Concentration (µg/mL)										
			0.050	0.100	0.250	0.500	1.000	2.000	3.502	5.003			
CC 1	18.11.05	01 & 03	0.051	0.120*	0.265	0.490	1.006	1.922	3.460	4.893	0.8789	0.0098	0.9987
CC 2	18.11.05	04 & 05	0.049	0.113	0.261	0.485	0.994	1.895	3.401	4.792	0.7219	0.0124	0.9961
CC 3	19.11.05	06 & 07	0.050	0.139*	0.266	0.497	1.017	1.889	3.441	4.965	0.8084	0.0047	0.9991
CC 4	21.11.05	08 & 09	0.050	0.133*	0.274	0.497	1.030	1.887	3.364	4.860	1.4599	0.0117	0.9982
CC 5	21.11.05	10 & 12	0.050	0.130*	0.277	0.500	0.946	1.927	3.424	5.019	1.7083	0.0098	0.9982
CC 6	22.11.05	13 & 14	0.052	0.096	0.274	0.495	0.994	1.937	3.420	4.918	1.2564	0.0111	0.9983
CC 7	22.11.05	15 & 16	0.051	0.097	0.263	0.500	1.000	1.929	2.718*	4.953	1.5249	0.0071	0.9992
CC 8	23.11.05	17 & 18	0.050	0.102	0.275	0.495	0.997	1.904	3.387	4.904	0.7656	0.0047	0.9986
CC 9	23.11.05	19 & 20	0.051	0.101	0.270	0.501	0.991	1.923	3.395	4.881	0.6320	0.0058	0.9986
CC 10	24.11.05	21 & 22	0.051	0.100	0.270	0.497	0.986	1.927	3.409	4.910	0.7412	0.0076	0.9985
CC 11	24.11.05	23 & 24	0.051	0.100	0.275	0.498	1.000	1.903	3.370	4.870	0.6390	0.0063	0.9981
CC 12	25.11.05	25	0.051	0.100	0.272	0.498	0.997	1.915	3.402	4.883	0.2450	0.0006	0.9998
CC 13	26.11.05	Repeats	0.052	0.104	0.278	0.431	0.998	1.960	3.357	5.047	1.7346	0.0355	0.9943
		Mean	**0.051**	**0.102**	**0.271**	**0.491**	**0.997**	**1.917**	**3.402**	**4.915**			
		±SD	**0.0007**	**0.0049**	**0.0054**	**0.0185**	**0.0190**	**0.0210**	**0.0308**	**0.0678**			
		%CV	**1.46**	**4.78**	**2.01**	**3.77**	**1.91**	**1.09**	**0.91**	**1.38**			
		%Nominal	**101.31**	**101.52**	**108.30**	**98.23**	**99.65**	**95.84**	**97.15**	**98.24**			

*- Out of Acceptance limits r^2 : Regression Coefficient.

5.6.4 Limit of quantitation (LOQ)

0.050µg/mL

5.6.5 Quality Control Samples

Concentrations of the QC samples, their date of preparation and the storage conditions employed prior to their analysis.

High Quality Control – 4.004 µg/mL for Ciprofloxacin

Middle Quality Control – 2.503 µg/mL Ciprofloxacin

Lower Quality Control – 0.150 µg/mL Ciprofloxacin.

Date of Preparation: 17-11-2005

Storage condition for QC samples: Below –70°C

5.6.6 Global Precision and Accuracy

The accuracy of the concentration values for QC samples is ranged for Ciprofloxacin from. 93.15% to 103.75%. The precision for the QC concentrations is ranged 3.61% to 5.08%.

6.0 PLASMA CONCENTRATION FOR THE TEST AND REFERENCE PRODUCT

The individual and mean plasma Ciprofloxacin concentrations for Test and Reference formulations are mentioned in the Table No. 1 & 2 respectively. The linear & semi-log plots of mean plasma concentration Vs time and the semi-log plots of individual subject plasma concentration Vs time are presented as figure 1 to 25.

7.0 PHARMACOKINETIC AND STATISTICAL EVALUATION

The T_{max}, C_{max}, AUC_{0-t}, $AUC_{0-\infty}$, k_{el} and $T_{1/2}$ were determined from the plasma Ciprofloxacin data using WinNonlin version 3.3. The Comparative evaluation of Pharmacokinetic parameters of Ciprofloxacin for Test and Reference formulations are mentioned in the Table No. 3.

Summary statistics, ANOVA, 90% confidence interval, Ratio Analysis and intra subject variability were calculated using SAS 9.1.3 version. The Statistical evaluation of pharmacokinetic parameters of Ciprofloxacin is mentioned in the Table No. 4.

8.0 RESULTS AND DISCUSSIONS

The median T_{max} values for Ciprofloxacin in Ciprofloxacin tablets BP 750 mg (Test) manufactured by Aurobindo Pharma Ltd., India and Ciproxin tablets (Reference) manufactured by Bayer Health Care AG, leverkusen, Germany, were 1.75 hours for both the formulations.

. The 90% confidence intervals, for Ciprofloxacin tablets BP 750 mg (Test) manufactured by Aurobindo Pharma Ltd., India and Ciproxin tablets (Reference) manufactured by Bayer Health Care AG, leverkusen, Germany, Ln-transformed parameters for C_{max}, AUC_{0-t}, and AUC_{0-inf} were 99.53 - 111.48%, 97.43 - 109.24% and 97.66 - 108.88% respectively.

CONCLUSION

The statistical report clearly indicates that the pharmacokinetic parameters of Ciprofloxacin tablets BP 750 mg (Test) manufactured by Aurobindo Pharma Ltd., India and Ciproxin tablets (Reference) manufactured by Bayer Health Care AG, leverkusen, Germany, are within the 80-125% acceptance range.

Based on these results, the Ciprofloxacin tablets BP 750 mg (Test) manufactured by Aurobindo Pharma Ltd., India are bioequivalent to the Ciproxin tablets (Reference) manufactured by Bayer Health Care AG, leverkusen, Germany, under fasting conditions in the present study population.

10.0 LIST OF TABLES

TABLE 1

Individual and Mean Plasma Ciprofloxacin Concentration (µg/mL) for Test

Treatment	Subject	Sequence	Concentration (µg/mL) Time (hr)																							
			0.00	0.25	0.50	0.75	1.00	1.25	1.50	1.75	2.00	2.50	3.00	3.50	4.00	4.50	5.00	6.00	8.00	10.00	12.00	16.00	24.00
T	1	TR	0.000	0.057	1.160	1.751	2.078	2.235	2.506	2.384	2.070	1.600	1.509	1.371	1.034	1.136	0.921	0.835	0.584	0.430	0.353	0.144	0.000
	3	TR	0.000	0.000	0.219	0.469	0.525	0.713	1.179	1.536	1.776	2.252	2.341	1.980	1.776	1.662	1.404	1.095	0.749	0.600	0.423	0.270	0.117
	4	RT	0.000	0.249	0.934	1.212	1.638	1.836	1.823	1.670	1.507	1.211	2.352	0.896	0.716	0.624	0.569	0.489	0.391	0.224	0.156	0.071	0.000
	5	TR	0.000	0.745	1.679	3.323	2.666	2.476	2.612	2.611	2.679	2.421	2.036	1.837	1.552	1.402	1.249	1.090	0.779	0.619	0.386	0.238	0.096
	6	RT	0.000	0.080	0.579	0.814	1.547	1.912	2.720	2.851	2.680	2.281	1.925	1.793	1.596	1.356	1.123	1.124	0.809	0.579	0.451	0.238	0.087
	7	RT	0.000	0.083	1.130	1.890	1.974	2.341	2.944	3.198	3.443	2.374	2.322	1.830	1.725	1.488	1.385	1.145	0.917	0.661	0.507	0.256	0.103
	8	TR	0.000	0.000	0.110	0.375	0.523	0.612	0.629	0.994	1.567	2.187	2.051	1.545	1.365	1.247	1.078	0.920	0.714	0.530	0.421	0.235	0.097
	9	RT	0.000	0.000	0.924	1.308	1.471	1.771	1.734	2.025	2.593	2.375	1.957	1.778	1.603	1.395	1.165	1.014	0.713	0.497	0.392	0.232	0.092
	10	TR	0.000	0.089	0.850	1.164	1.505	2.578	2.290	2.248	1.921	1.695	1.432	1.316	1.239	1.019	0.990	0.819	0.609	0.423	0.312	0.169	0.067
	12	TR	0.000	0.106	1.018	1.266	1.585	2.176	2.191	2.901	2.745	2.297	2.036	1.809	1.596	1.447	1.316	1.135	0.886	0.608	0.472	0.243	0.099
	13	TR	0.000	0.000	0.267	0.884	1.333	2.126	2.665	2.610	2.568	2.257	1.784	1.653	1.457	1.365	1.196	0.998	0.755	0.616	0.416	0.287	0.120
	14	RT	0.000	0.112	1.289	0.818	1.252	1.429	2.709	2.450	2.319	2.181	1.857	1.530	1.346	1.140	1.004	0.806	0.543	0.422	0.308	0.177	0.069
	15	TR	0.000	0.000	0.196	0.916	1.525	2.087	2.914	2.754	2.493	1.980	1.583	1.494	1.339	1.106	0.990	0.866	0.605	0.386	0.336	0.160	0.062
	16	RT	0.000	0.000	0.559	0.991	1.297	1.352	2.231	2.114	1.488	2.147	2.009	1.830	1.484	2.083	1.162	1.010	0.816	0.652	0.508	0.320	0.156
	17	TR	0.000	0.000	0.375	1.421	2.184	2.901	3.133	2.878	2.706	2.345	1.859	1.636	1.418	1.293	1.125	0.970	0.739	0.553	0.400	0.233	0.091
	18	RT	0.000	0.125	0.735	1.318	1.465	1.325	1.388	1.536	1.696	1.375	1.377	1.084	1.089	0.971	0.957	0.797	0.502	0.388	0.261	0.139	0.059
	19	RT	0.000	0.129	1.107	1.789	1.799	1.446	2.176	2.675	2.001	2.097	1.851	1.988	1.654	1.520	1.232	1.170	0.757	0.527	0.381	0.210	0.081
	20	TR	0.000	0.055	0.763	1.355	1.805	1.915	1.608	1.843	1.735	1.321	1.047	1.068	0.817	0.805	0.666	0.574	0.447	0.340	0.257	0.127	0.053
	21	TR	0.000	0.075	0.946	1.432	1.119	1.260	1.566	1.518	1.810	2.037	2.414	1.923	1.763	1.705	1.507	1.203	0.888	0.608	0.492	0.255	0.091
	22	RT	0.000	0.315	1.096	1.821	2.159	2.061	2.052	2.409	1.825	1.590	1.375	1.336	1.217	1.086	1.001	0.828	0.628	0.486	0.428	0.257	0.118
	23	RT	0.000	0.072	0.953	1.632	1.680	1.888	2.321	2.231	2.408	2.462	2.008	1.767	1.570	1.474	1.287	1.061	0.840	0.617	0.494	0.280	0.101
	24	TR	0.000	0.867	2.194	2.447	2.377	2.424	2.541	2.053	1.855	1.454	1.238	1.119	0.935	0.930	0.790	0.710	0.477	0.362	0.247	0.134	0.056
	25	RT	0.000	0.312	1.085	1.651	1.943	2.364	2.794	2.852	2.329	1.781	1.580	1.341	1.189	1.035	0.937	0.761	0.604	0.408	0.306	0.152	0.052
	N		23	23	23	23	23	23	23	23	23	23	23	23	23	23	23	23	23	23	23	23	23
	Mean		0.000	0.151	0.877	1.393	1.629	1.879	2.206	2.276	2.183	1.988	1.824	1.562	1.369	1.273	1.089	0.931	0.685	0.502	0.379	0.210	0.081
	SD		0.0000	0.2272	0.4863	0.6395	0.5151	0.5770	0.6303	0.5620	0.5038	0.3945	0.3755	0.3189	0.2990	0.3226	0.2301	0.1925	0.1497	0.1181	0.0940	0.0631	0.0359
	Min		0.000	0.000	0.110	0.375	0.523	0.612	0.629	0.994	1.488	1.211	1.047	0.896	0.716	0.624	0.569	0.489	0.391	0.224	0.156	0.071	0.000
	Median		0.000	0.080	0.934	1.318	1.585	1.915	2.290	2.384	2.070	2.147	1.859	1.636	1.418	1.293	1.123	0.970	0.714	0.527	0.392	0.233	0.091
	Max		0.000	0.867	2.194	3.323	2.666	2.901	3.133	3.198	3.443	2.462	2.414	1.988	1.776	2.083	1.507	1.203	0.917	0.661	0.508	0.320	0.156
	CV%		Missing	150.60	55.46	45.90	31.62	30.70	28.58	24.70	23.08	19.85	20.59	20.42	21.84	25.33	21.13	20.67	21.85	23.54	24.84	30.03	44.21

Missing = Can not be Calculated

LOQ =0.050 µg/mL

Note: All the BLQ's were made zero

TABLE 2

Individual and Mean Plasma Ciprofloxacin Concentration (µg/mL) for Reference

Treatment	Subject	Sequence	Concentration (µg/mL) Time (hr) 0.00	0.25	0.50	0.75	1.00	1.25	1.50	1.75	2.00	2.50	3.00	3.50	4.00	4.50	5.00	6.00	8.00	10.00	12.00	16.00	24.00
R	1	TR	0.000	0.000	0.100	0.391	0.764	0.845	1.099	1.325	1.428	1.664	2.000	1.644	1.241	1.358	1.152	0.906	0.658	0.448	0.376	0.174	0.051
	3	TR	0.000	0.000	0.334	0.990	1.359	1.488	1.965	2.133	1.984	2.015	0.976	1.897	1.448	1.510	1.319	0.870	0.719	0.511	0.460	0.224	0.103
	4	RT	0.000	0.000	1.078	1.249	1.237	1.577	1.681	1.812	1.597	1.299	1.008	0.940	0.807	0.690	0.647	0.534	0.362	0.261	0.184	0.093	0.000
	5	TR	0.000	0.720	1.597	2.716	3.064	3.469	2.848	2.962	2.892	2.429	2.104	1.880	1.526	1.482	1.324	1.112	0.843	0.574	0.418	0.241	0.085
	6	RT	0.000	0.000	0.329	0.609	0.821	0.777	1.118	1.426	1.789	2.870	3.096	2.585	2.086	1.968	1.733	1.460	0.955	0.732	0.500	0.279	0.105
	7	RT	0.000	0.141	0.768	1.282	1.321	2.231	3.039	3.667	3.395	3.098	2.656	2.242	1.942	1.737	1.422	1.195	0.841	0.642	0.512	0.291	0.124
	8	TR	0.000	0.000	0.070	0.281	0.475	0.552	1.046	1.625	1.940	2.184	1.848	1.574	1.392	1.346	1.129	0.955	0.713	0.534	0.369	0.200	0.087
	9	RT	0.000	0.085	0.737	1.866	2.820	3.524	3.210	2.814	2.328	1.947	1.697	1.469	1.379	1.193	1.099	0.911	0.648	0.490	0.366	0.222	0.090
	10	TR	0.000	0.287	1.358	1.995	2.320	2.126	1.911	1.849	1.761	1.391	1.271	1.151	1.102	0.964	0.832	0.637	0.538	0.370	0.276	0.138	0.057
	12	TR	0.000	0.150	0.711	2.099	2.079	1.808	1.840	2.054	2.115	1.695	1.638	1.497	1.313	1.225	1.045	0.882	0.649	0.462	0.356	0.225	0.084
	13	TR	0.000	0.122	0.720	1.325	1.712	2.256	2.405	2.439	2.309	2.177	1.798	1.484	1.374	1.296	1.110	0.981	0.678	0.487	0.376	0.243	0.076
	14	RT	0.000	0.466	1.038	1.130	1.400	2.600	2.744	3.162	2.612	1.799	1.459	1.347	1.162	0.979	0.889	0.717	0.514	0.370	0.303	0.158	0.056
	15	TR	0.000	0.000	0.098	0.356	0.992	1.285	2.104	3.265	2.759	2.351	1.863	1.646	1.440	1.289	1.032	0.847	0.600	0.419	0.324	0.153	0.054
	16	RT	0.000	0.000	0.147	0.315	0.527	0.705	0.852	0.897	0.951	1.019	1.647	1.823	2.006	2.217	1.472	1.111	0.858	0.669	0.606	0.363	0.182
	17	TR	0.000	0.000	0.062	0.525	0.891	1.326	1.633	1.979	2.281	2.303	2.493	2.216	1.974	1.733	1.472	1.156	0.772	0.585	0.423	0.251	0.081
	18	RT	0.000	0.000	0.135	0.460	0.512	0.570	0.743	0.844	1.110	1.558	1.845	1.553	1.432	1.478	1.215	0.960	0.690	0.499	0.427	0.224	0.071
	19	RT	0.000	0.098	1.067	1.869	2.166	1.888	2.297	2.677	2.299	2.086	1.854	1.641	1.515	1.395	1.289	1.094	0.761	0.597	0.419	0.223	0.083
	20	TR	0.000	0.000	0.527	0.840	0.948	1.091	1.225	1.235	1.252	1.589	1.426	1.428	1.286	1.043	0.920	0.716	0.516	0.372	0.310	0.160	0.069
	21	TR	0.000	0.365	1.017	1.444	1.558	1.519	1.316	1.203	1.187	1.028	0.942	0.919	0.849	0.735	0.644	0.552	0.378	0.292	0.221	0.104	0.000
	22	RT	0.000	0.000	0.311	0.681	1.258	1.989	1.947	2.158	2.506	2.105	1.751	1.599	1.416	1.349	1.188	1.030	0.806	0.605	0.519	0.318	0.147
	23	RT	0.000	0.209	0.993	1.383	1.772	2.329	2.103	2.144	2.344	2.124	1.855	1.587	1.467	1.353	1.187	0.976	0.735	0.596	0.442	0.239	0.090
	24	TR	0.000	0.123	0.717	1.355	1.601	2.123	2.677	2.397	1.929	1.703	1.352	1.155	0.969	0.905	0.807	0.663	0.376	0.373	0.304	0.149	0.058
	25	RT	0.000	0.000	0.195	0.540	0.956	1.336	1.595	1.724	1.636	1.648	2.201	2.359	1.778	1.391	1.251	1.020	0.666	0.512	0.329	0.181	0.066
	N		23	23	23	23	23	23	23	23	23	23	23	23	23	23	23	23	23	23	23	23	23
	Mean		0.000	0.120	0.613	1.117	1.415	1.714	1.887	2.075	2.018	1.917	1.773	1.636	1.431	1.332	1.138	0.925	0.664	0.496	0.383	0.211	0.079
	SD		0.0000	0.1849	0.4527	0.6690	0.7071	0.8206	0.7122	0.7612	0.6139	0.5177	0.5233	0.4246	0.3475	0.3647	0.2690	0.2216	0.1595	0.1214	0.0993	0.0662	0.0397
	Min		0.000	0.000	0.062	0.281	0.475	0.552	0.743	0.844	0.951	1.019	0.942	0.919	0.807	0.690	0.644	0.534	0.362	0.261	0.184	0.093	0.000
	Median		0.000	0.000	0.711	1.130	1.321	1.577	1.911	2.054	1.984	1.947	1.798	1.587	1.416	1.349	1.152	0.955	0.678	0.499	0.376	0.223	0.081
	Max		0.000	0.720	1.597	2.716	3.064	3.524	3.210	3.667	3.395	3.098	3.096	2.585	2.086	2.217	1.733	1.460	0.955	0.732	0.606	0.363	0.182
	CV%		Missing	153.74	73.82	59.87	49.97	47.89	37.75	36.68	30.42	27.01	29.52	25.95	24.28	27.38	23.64	23.95	24.01	24.49	25.90	31.36	50.20

Missing = Can not be Calculated

LOQ =0.050 µg/mL

Note: All the BLQ's were made zero

TABLE 3

Comparative Evaluation of Pharmacokinetic Parameters of Ciprofloxacin

Subject	Sequence	Tmax (hr)		Cmax (µg/mL)		No of points for kel		AUC last (hr*µg/mL)		kel (1/hr)		kel start (hr)		kel stop (hr)		T1/2 (hr)		AUC INF (hr*µg/mL)		AUC % Extrap (%)	
		Treatment		Treatment		Treatment		Treatment		Treatment		Treatment		Treatment		Treatment		Treatment		Treatment	
		R	T	R	T	R	T	R	T	R	T	R	T	R	T	R	T	R	T	R	T
1	TR	3.00	1.50	2.000	2.506	6	11	12.432	12.462	0.16	0.17	6.00	2.50	24.00	16.00	4.32	4.06	12.748	13.302	2.48	6.32
3	TR	1.75	3.00	2.133	2.341	6	3	14.624	15.586	0.12	0.11	6.00	12.00	24.00	24.00	5.69	6.47	15.470	16.673	5.47	6.52
4	RT	1.75	3.00	1.812	2.352	3	3	8.398	8.811	0.17	0.19	10.00	10.00	16.00	16.00	4.03	3.62	8.937	9.184	6.03	4.06
5	TR	1.25	0.75	3.469	3.323	3	3	18.677	17.996	0.13	0.12	12.00	12.00	24.00	24.00	5.24	5.98	19.319	18.820	3.33	4.38
6	RT	3.00	1.75	3.096	2.851	3	5	18.699	16.542	0.13	0.14	12.00	8.00	24.00	24.00	5.36	4.99	19.508	17.171	4.14	3.66
7	RT	1.75	2.00	3.667	3.443	5	8	19.827	18.933	0.12	0.14	8.00	4.50	24.00	24.00	5.78	4.98	20.863	19.674	4.96	3.77
8	TR	2.50	2.50	2.184	2.187	7	7	13.339	13.334	0.14	0.13	5.00	5.00	24.00	24.00	5.04	5.44	13.968	14.096	4.50	5.40
9	RT	1.25	2.00	3.524	2.593	3	4	15.734	15.587	0.12	0.12	12.00	10.00	24.00	24.00	5.94	5.75	16.503	16.350	4.66	4.67
10	TR	1.00	1.25	2.320	2.578	7	8	11.837	13.004	0.14	0.14	5.00	4.50	24.00	24.00	4.88	4.82	12.238	13.467	3.28	3.44
12	TR	2.00	1.75	2.115	2.901	4	9	14.239	17.381	0.12	0.14	10.00	4.00	24.00	24.00	5.71	4.91	14.928	18.083	4.62	3.88
13	TR	1.75	1.50	2.439	2.665	5	3	15.197	16.280	0.13	0.10	8.00	12.00	24.00	24.00	5.17	6.64	15.762	17.431	3.58	6.60
14	RT	1.75	1.50	3.162	2.709	5	5	13.082	13.569	0.14	0.13	8.00	8.00	24.00	24.00	5.02	5.37	13.491	14.108	3.03	3.82
15	TR	1.75	1.50	3.205	2.914	7	8	13.521	13.522	0.16	0.15	5.00	4.50	24.00	24.00	4.43	4.62	13.864	13.933	2.47	2.95
16	RT	4.50	1.50	2.217	2.231	6	7	16.120	16.864	0.10	0.11	6.00	5.00	24.00	24.00	6.96	6.51	17.948	18.331	10.18	8.00
17	TR	3.00	1.50	2.493	3.133	5	3	16.469	16.360	0.14	0.12	8.00	12.00	24.00	24.00	4.94	5.67	17.049	17.106	3.40	4.36
18	RT	3.00	2.00	1.845	1.696	3	12	12.816	11.104	0.15	0.15	12.00	2.50	24.00	24.00	4.66	4.51	13.293	11.490	3.59	3.36
19	RT	1.75	1.75	2.677	2.675	10	4	16.375	16.060	0.15	0.13	3.50	10.00	24.00	24.00	4.67	5.23	16.935	16.672	3.31	3.67
20	TR	2.50	1.25	1.589	1.915	6	7	11.025	10.197	0.13	0.14	6.00	5.00	24.00	24.00	5.33	5.10	11.555	10.588	4.58	3.69
21	TR	1.00	3.00	1.558	2.414	13	6	8.310	16.876	0.17	0.14	1.75	6.00	16.00	24.00	4.06	4.84	8.920	17.512	6.84	3.64
22	RT	2.00	1.75	2.506	2.409	4	5	16.446	14.485	0.10	0.10	10.00	8.00	24.00	24.00	6.75	6.62	17.879	15.609	8.02	7.20
23	RT	2.00	2.50	2.344	2.462	7	6	15.945	17.280	0.14	0.13	5.00	6.00	24.00	24.00	5.13	5.28	16.614	18.052	4.03	4.27
24	TR	1.50	1.50	2.677	2.541	4	9	11.646	12.357	0.14	0.15	10.00	4.00	24.00	24.00	5.11	4.73	12.072	12.739	3.53	3.00
25	RT	3.50	1.75	2.359	2.852	3	8	14.051	13.496	0.13	0.15	12.00	4.50	24.00	24.00	5.25	4.49	14.554	13.835	3.46	2.45
N		23	23	23	23	23	23	23	23	23	23	23	23	23	23	23	23	23	23	23	23
Mean		2.14	1.85	2.495	2.595	5.43	6.26	14.296	14.699	0.14	0.14	7.88	6.96	23.30	23.30	5.19	5.24	14.975	15.401	4.50	4.48
SD		0.862	0.592	0.6073	0.4091	2.446	2.632	2.9770	2.6234	0.018	0.021	3.067	3.215	2.305	2.305	0.731	0.809	3.1518	2.7952	1.829	1.476
Min		1.00	0.75	1.558	1.696	3.00	3.00	8.310	8.811	0.10	0.10	1.75	2.50	16.00	16.00	4.03	3.62	8.920	9.184	2.47	2.45
Median		1.75	1.75	2.359	2.578	5.00	6.00	14.239	15.586	0.14	0.14	8.00	6.00	24.00	24.00	5.13	5.10	14.928	16.350	4.03	3.88
Max		4.50	3.00	3.667	3.443	13.00	12.00	19.827	18.933	0.17	0.19	12.00	12.00	24.00	24.00	6.96	6.64	20.863	19.674	10.18	8.00
CV%		40.26	32.05	24.34	15.76	45.01	42.04	20.82	17.85	13.57	15.80	38.92	46.22	9.89	9.89	14.08	15.42	21.05	18.15	40.65	32.92

TABLE 4

Summary Statistics of Pharmacokinetic Parameters of Ciprofloxacin

Statistics		C_{max} (µg/mL)	AUC_{0-t} (hr.µg/mL)	AUC_{0-inf} (hr.µg/mL)	T_{max} (hr)*
Test Formulation	N	23	23	23	23
	Mean	2.595	14.699	15.401	1.75
	S.D.	0.4089	2.6233	2.7951	0.592
	C.V. (%)	15.76	17.85	18.15	32.05
Reference Formulation	N	23	23	23	23
	Mean	2.495	14.296	14.975	1.75
	S.D.	0.6073	2.9770	3.1518	0.862
	C.V. (%)	24.34	20.82	21.05	40.26

* For T_{max} instead of mean, median has been used

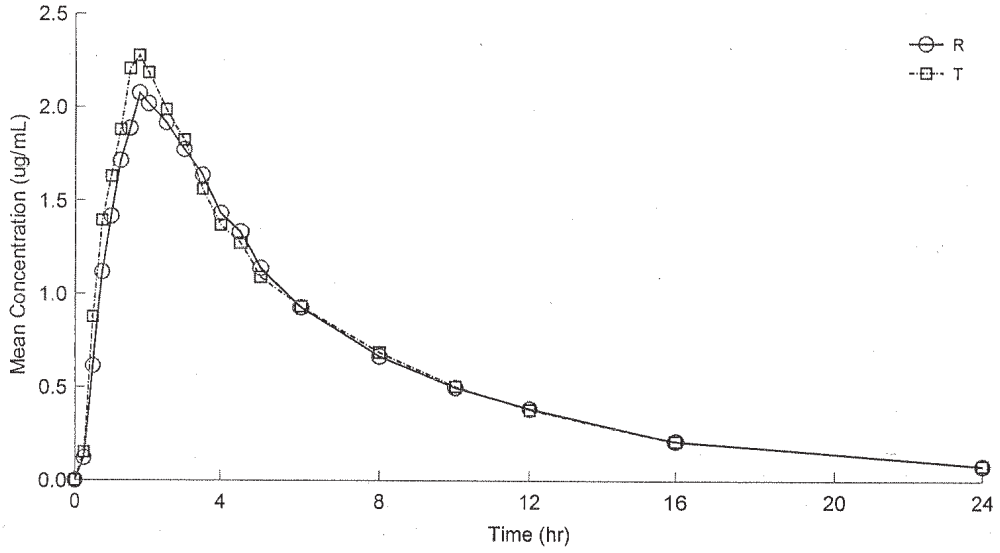
ANOVA p-value		C_{max}	AUC_{0-t}	AUC_{0-inf}
Untransformed	Sequence	0.5242	0.3768	0.3439
	Period	0.0415	0.0705	0.0377
	Treatment	0.2714	0.3909	0.3707
Lntransformed	Sequence	0.5293	0.4401	0.4104
	Period	0.0394	0.0945	0.0555
	Treatment	0.1301	0.3593	0.3426

Parameters	Lntransformed Data					
	Geometric Mean		(T/R) Ratio	90% Confidence Interval	Intra Subject CV	Power
	Test	Reference	(%)	(%)	(%)	(%)
C_{max}	2.562	2.433	105.33	99.53 - 111.48	11.21	100
AUC_{0-t}	14.456	14.012	103.17	97.43 - 109.24	11.31	100
AUC_{0-inf}	15.136	14.678	103.12	97.66 - 108.88	10.74	100

10.0 LIST OF FIGURES

FIGURE 1

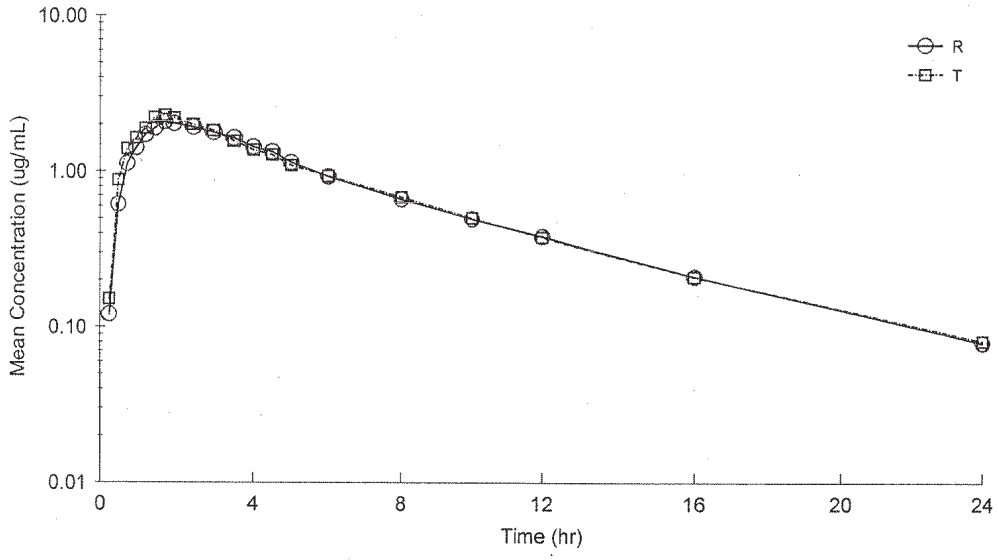
Linear Plot Of Mean Plasma Ciprofloxacin Concentrations Versus Time In Adult, Healthy, Male Human Subjects (N=23)



User Chart
C:\CPD-BE\Ciprofloxacin\Cpf 0305\Linear mean plot.pco (17-Feb-2006)

FIGURE 2

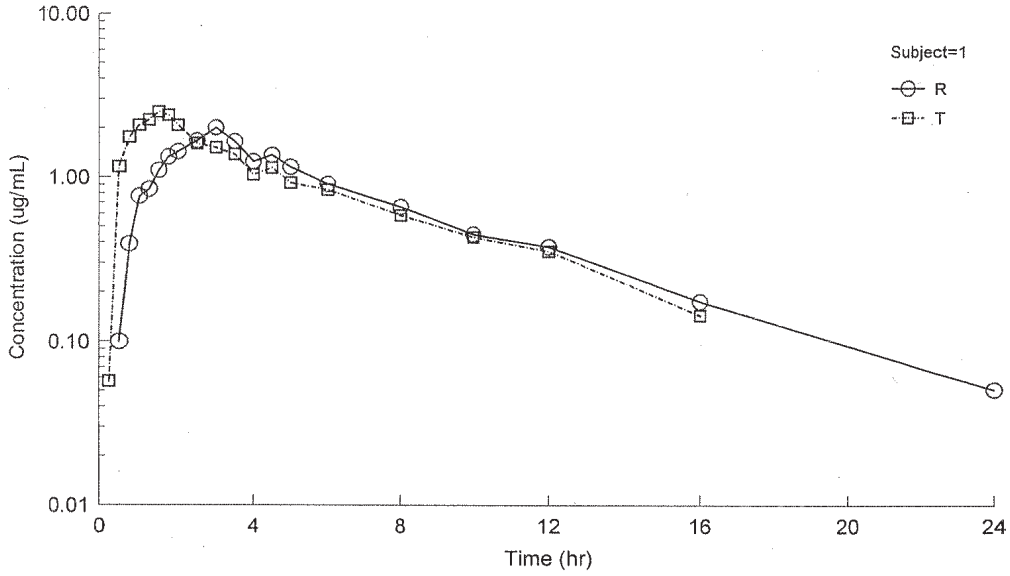
Semi – log Plot of Mean Plasma Ciprofloxacin Concentrations Versus Time in Adult, Healthy, Male, Human Subjects (N=23)



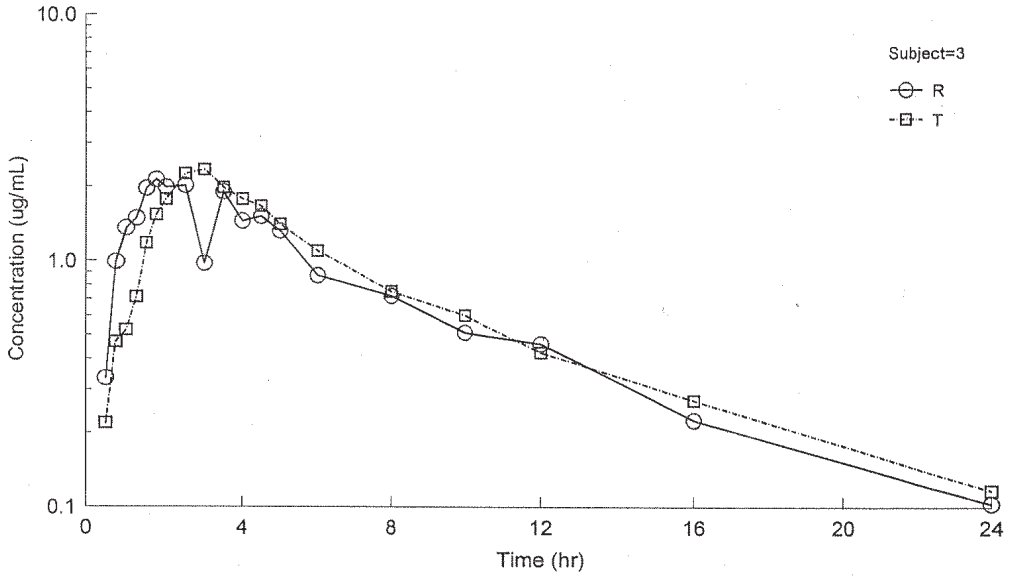
User Chart
C:\CPD-BE\Ciprofloxacin\Cpf 0305\Semilog mean plot.pco (17-Feb-2006)

FIGURE 3 and 4

Semi-log Individual Subject Plasma Ciprofloxacin Concentrations Versus Time (Subjects 1 and 3)



User Chart
C:\CPD-BE\Ciprofloxacin\Cpf 0305\Indi semilog plots.pco (17-Feb-2006)

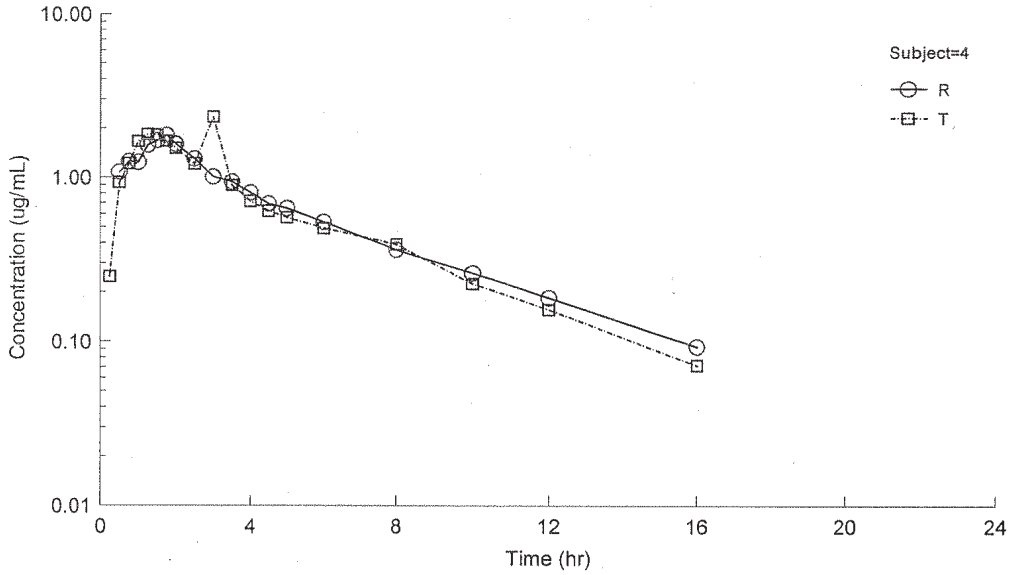


User Chart
C:\CPD-BE\Ciprofloxacin\Cpf 0305\Indi semilog plots.pco (17-Feb-2006)

FIGURE 5 and 6

Semi-log Individual Subject Plasma Ciprofloxacin Concentrations Versus Time

(Subjects 4 and 5)



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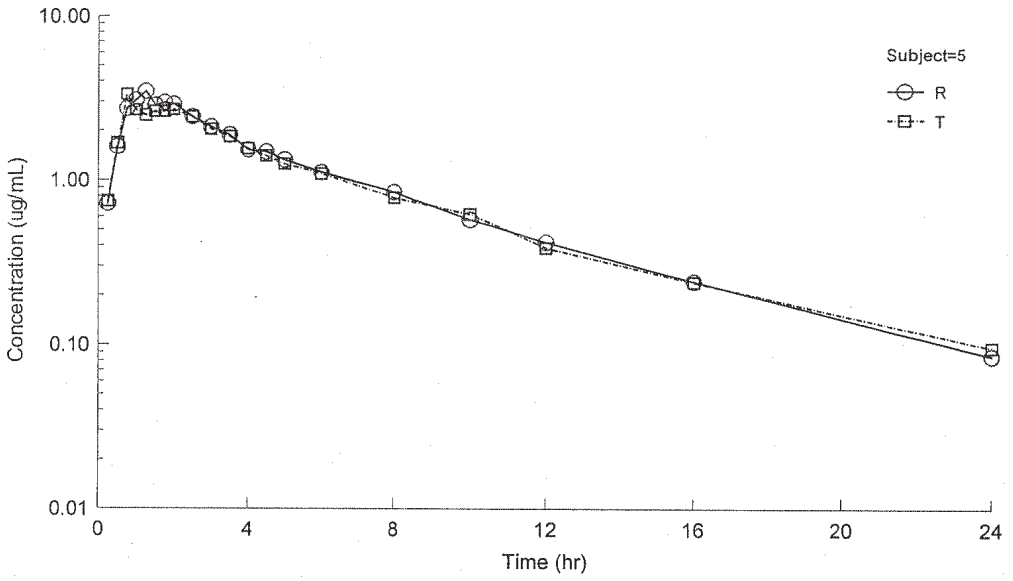
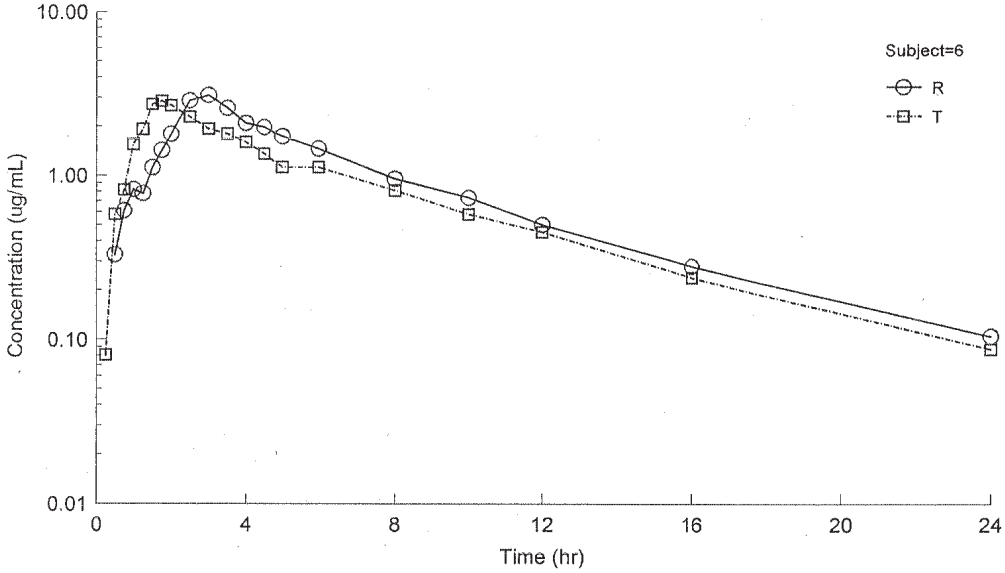
C:\CPD-BE\Ciprofloxacin\Cpf 0305\Indi semilog plots.pco (17-Feb-2006)



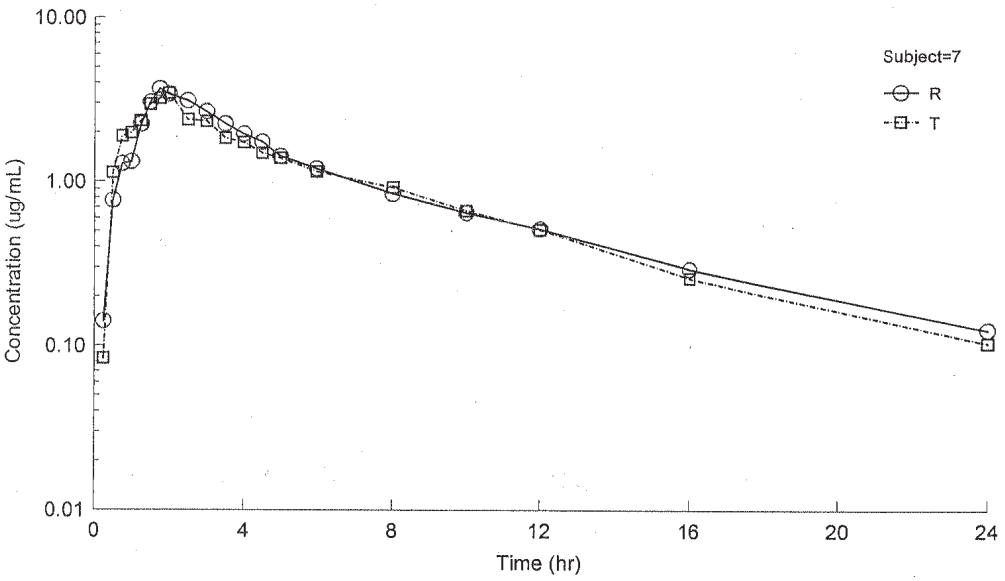
User Chart
C:\CPD-BE\Ciprofloxacin\Cpf 0305\Indi semilog plots.pco (17-Feb-2006)

FIGURE 7 and 8

Semi-log Individual Subject Plasma Ciprofloxacin Concentrations Versus Time (Subjects 6 and 7)



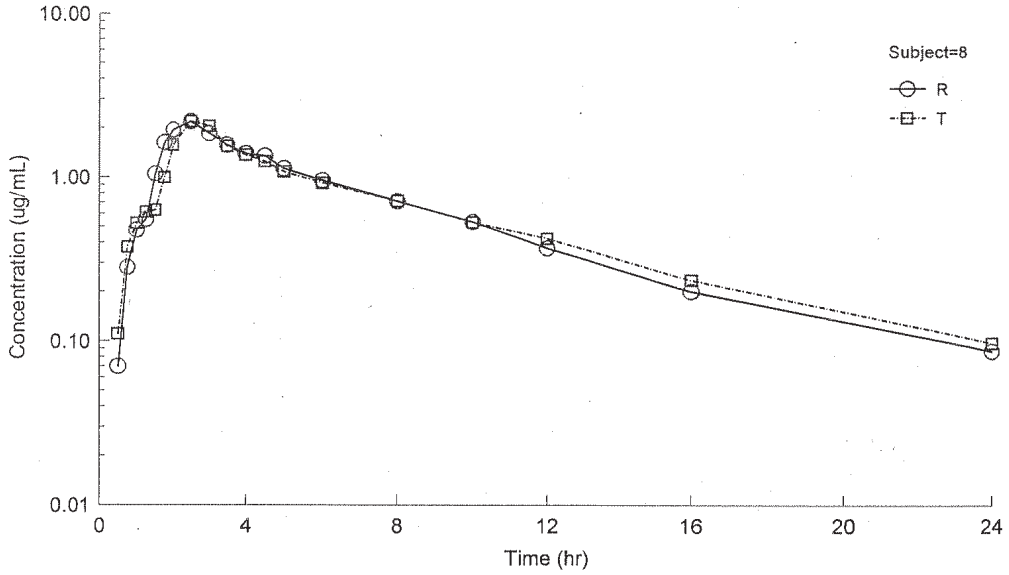
User Chart
C:\CPD-BE\Ciprofloxacin\Cpf 0305\Indi semilog plots.pco (17-Feb-2006)



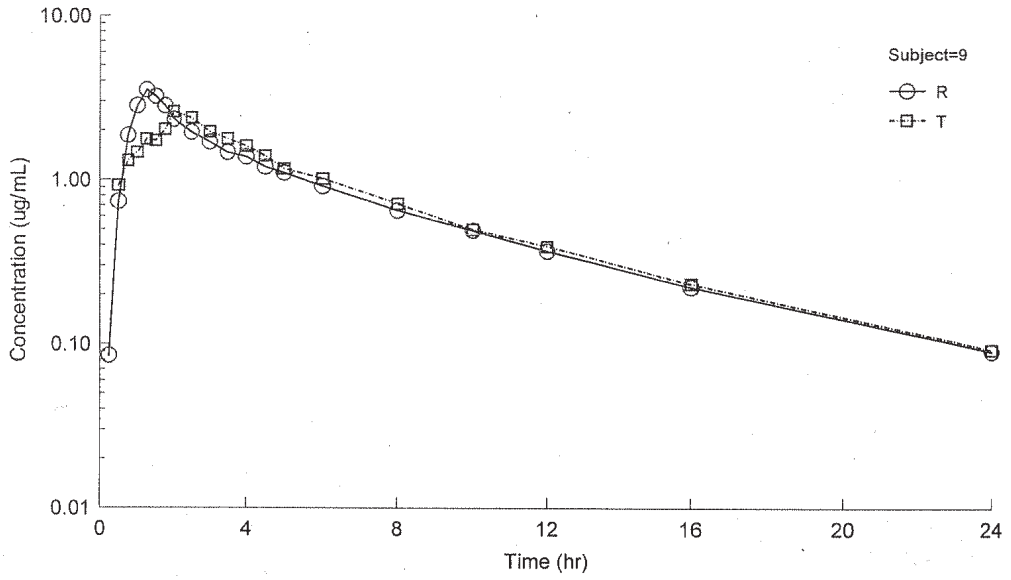
User Chart
C:\CPD-BE\Ciprofloxacin\Cpf 0305\Indi semilog plots.pco (17-Feb-2006)

FIGURE 9 and 10

Semi-log Individual Subject Plasma Ciprofloxacin Concentrations Versus Time (Subjects 8 and 9)



User Chart
C:\CPD-BE\Ciprofloxacin\Cpf 0305\Indi semilog plots.pco (17-Feb-2006)

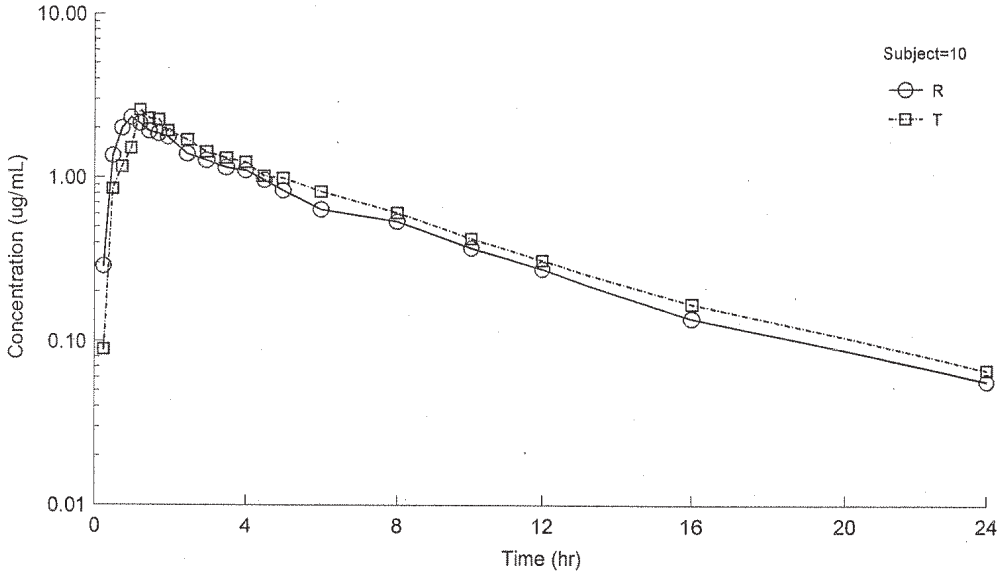


User Chart
C:\CPD-BE\Ciprofloxacin\Cpf 0305\Indi semilog plots.pco (17-Feb-2006)

FIGURE 11 and 12

Semi-log Individual Subject Plasma Ciprofloxacin Concentrations Versus Time

(Subjects 10 and 12)



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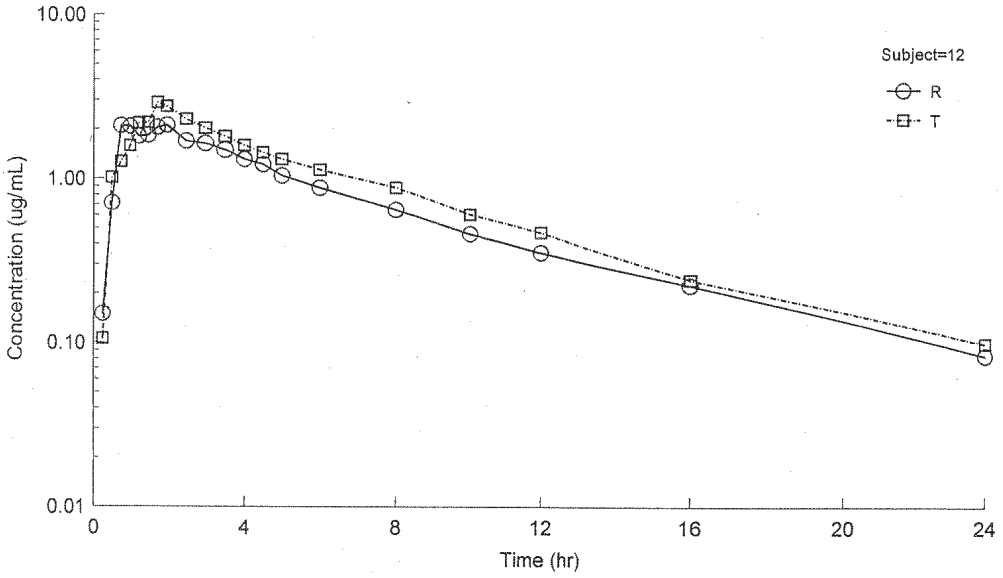

User Chart
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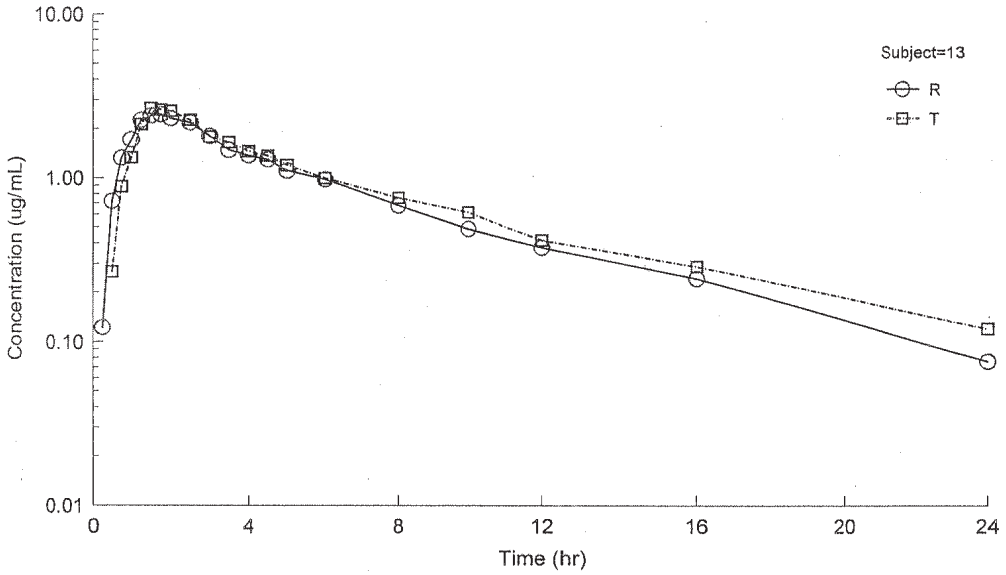
FIGURE 13 and 14

Semi-log Individual Subject Plasma Ciprofloxacin Concentrations Versus Time

(Subjects 13 and 14)



User Chart
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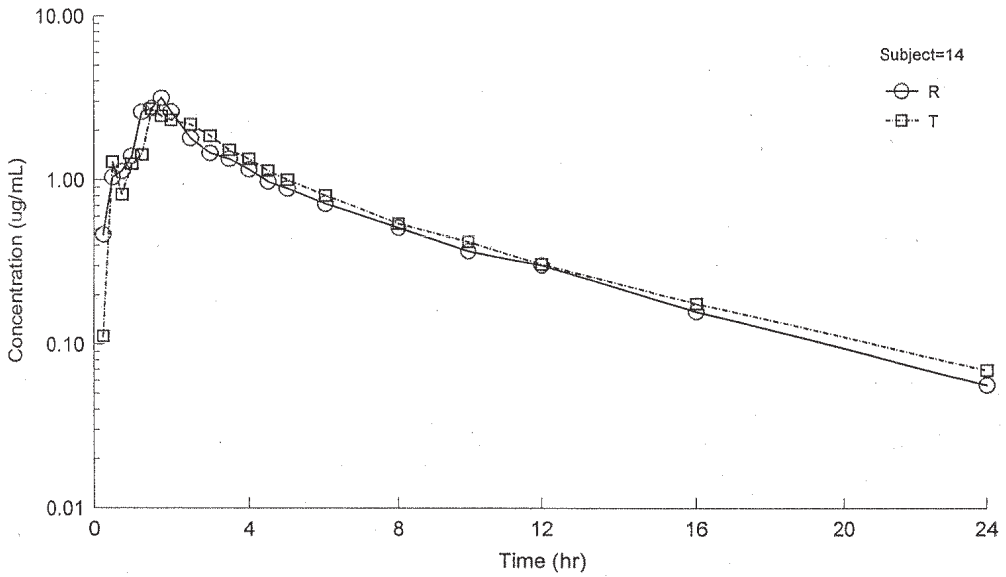
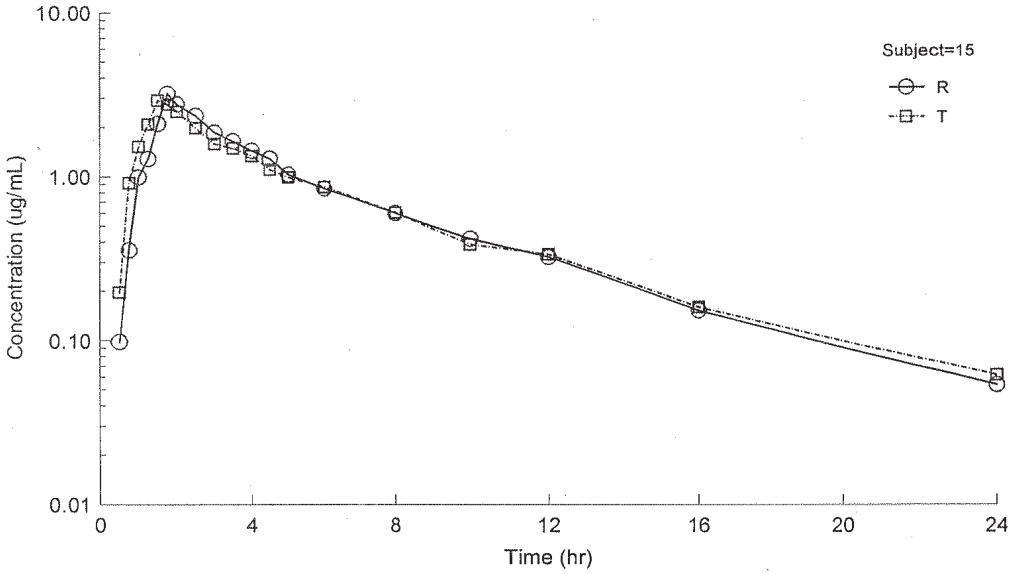


User Chart
C:\CPD-BE\Ciprofloxacin\Cpf 0305\Indi semilog plots.pco (17-Feb-2006)

FIGURE 15 and 16

Semi-log Individual Subject Plasma Ciprofloxacin Concentrations Versus Time (Subjects 15 and 16)



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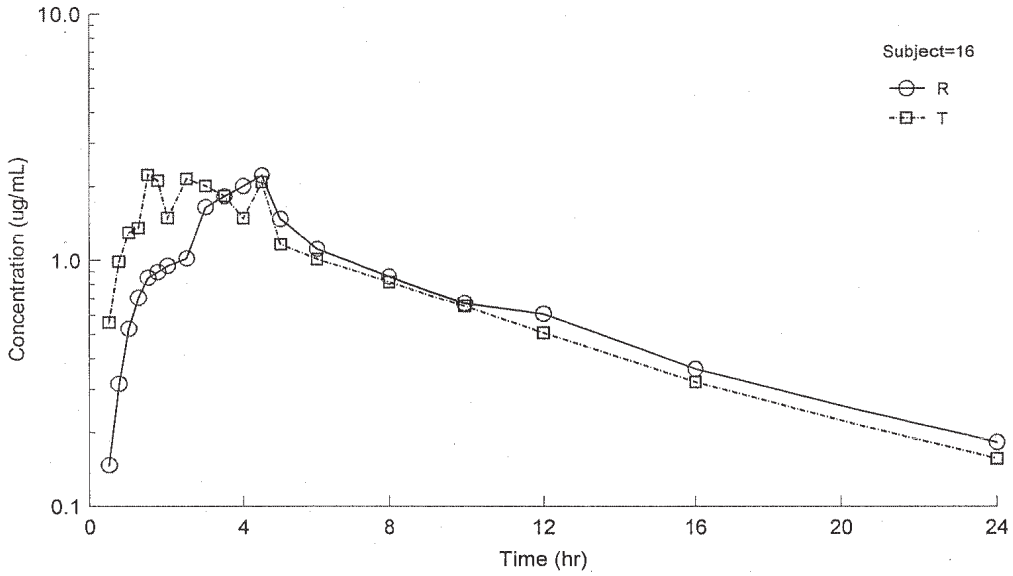
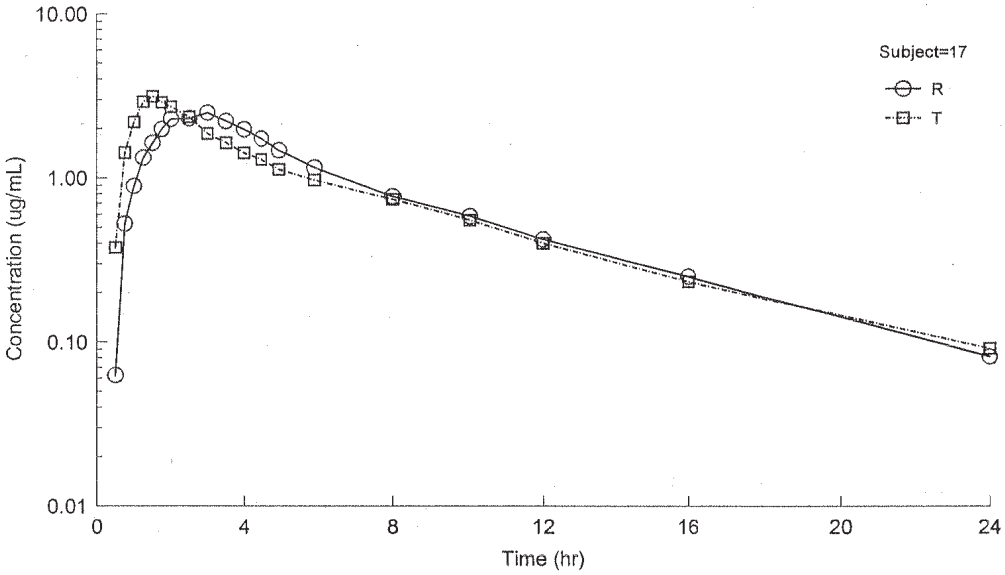


User Chart
C:\CPD-BE\Ciprofloxacin\Cpf 0305\Indi semilog plots.pco (17-Feb-2006)

FIGURE 17 and 18

Semi-log Individual Subject Plasma Ciprofloxacin Concentrations Versus Time (Subjects 17 and 18)



User Chart
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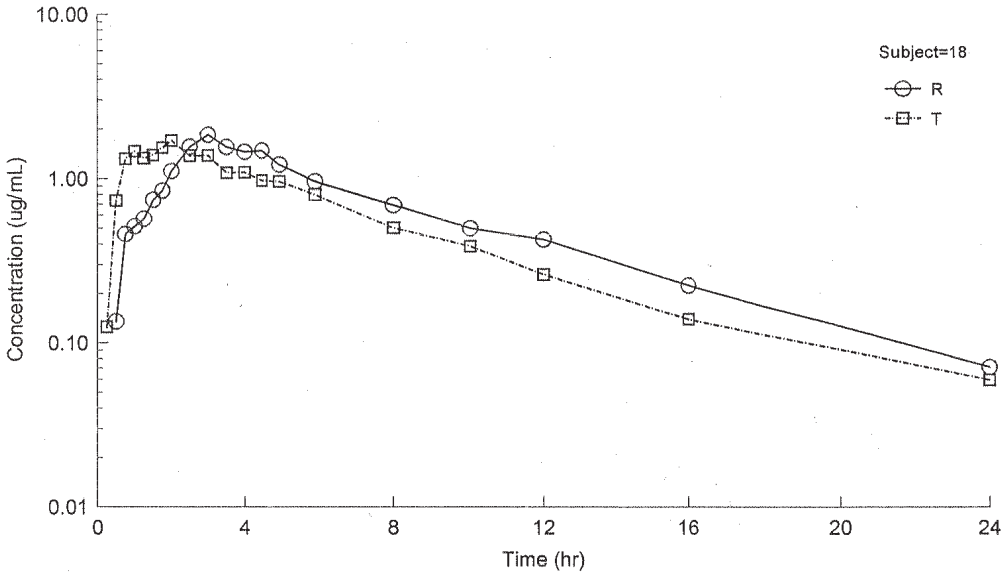
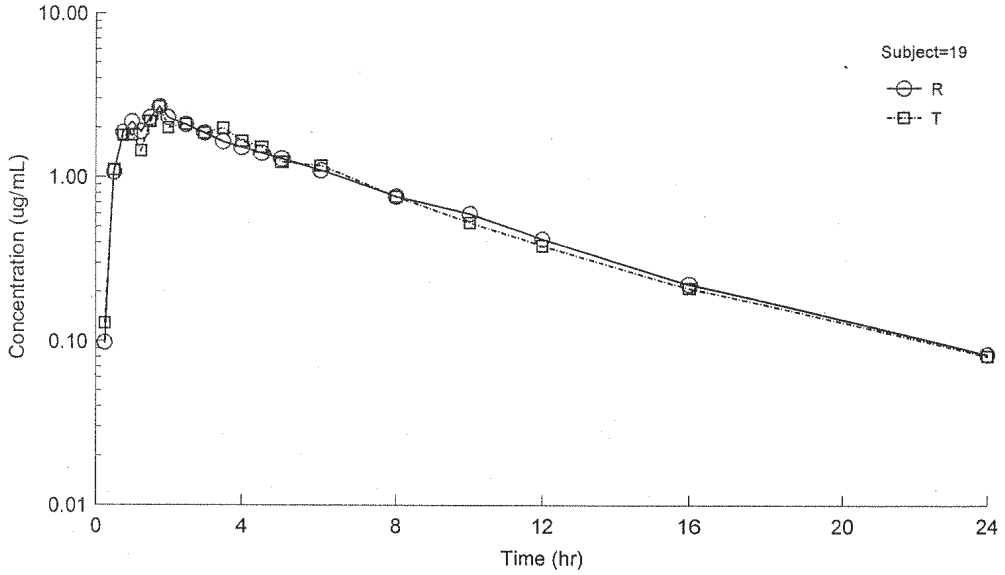


User Chart
C:\CPD-BE\Ciprofloxacin\Cpf 0305\Indi semilog plots.pco (17-Feb-2006)

FIGURE 19 and 20

Semi-log Individual Subject Plasma Ciprofloxacin Concentrations Versus Time (Subjects 19 and 20)



User Chart
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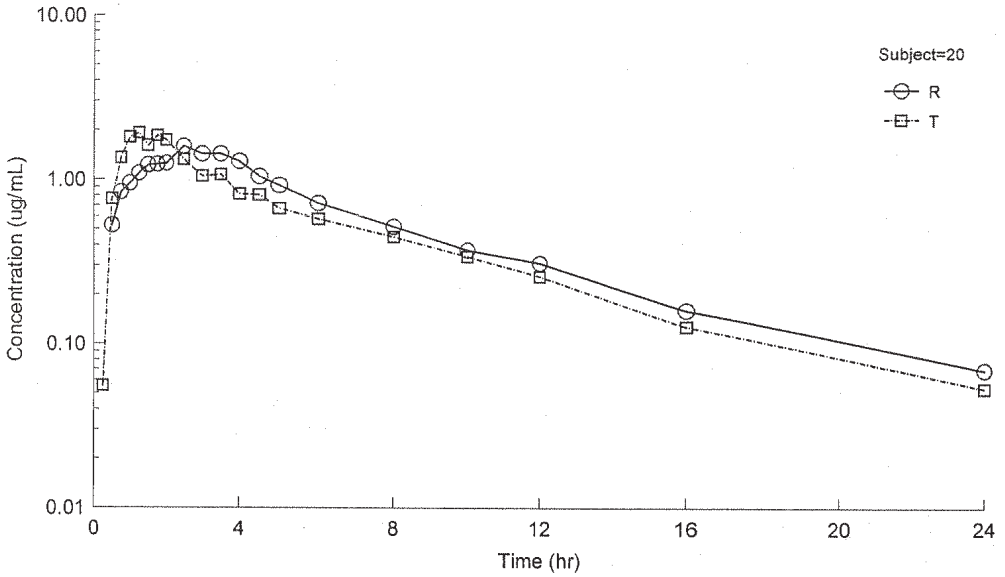
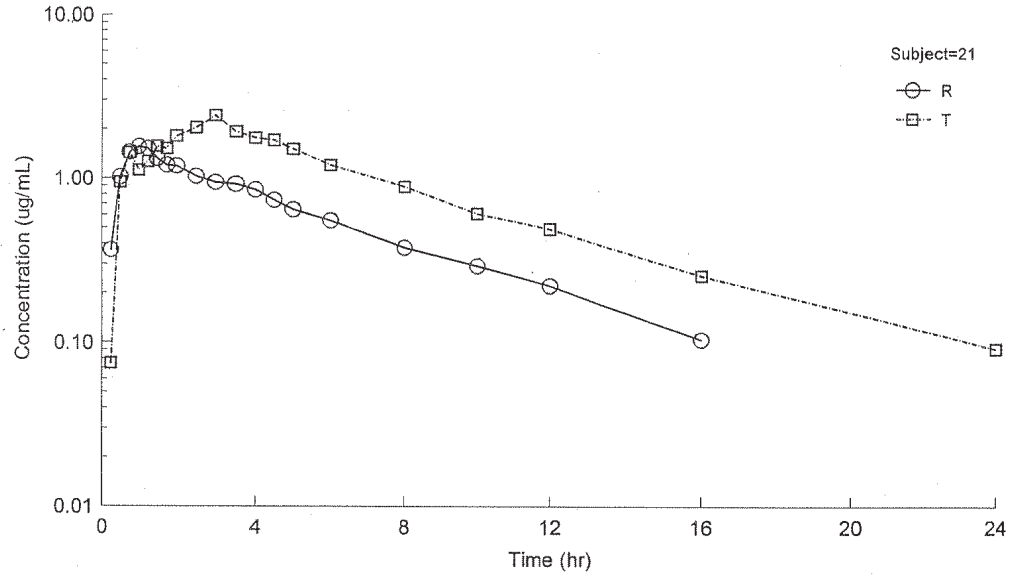


User Chart
C:\CPD-BE\Ciprofloxacin\Cpf 0305\Indi semilog plots.pco (17-Feb-2006)

FIGURE 21 and 22

Semi-log Individual Subject Plasma Ciprofloxacin Concentrations Versus Time

(Subjects 21 and 22)



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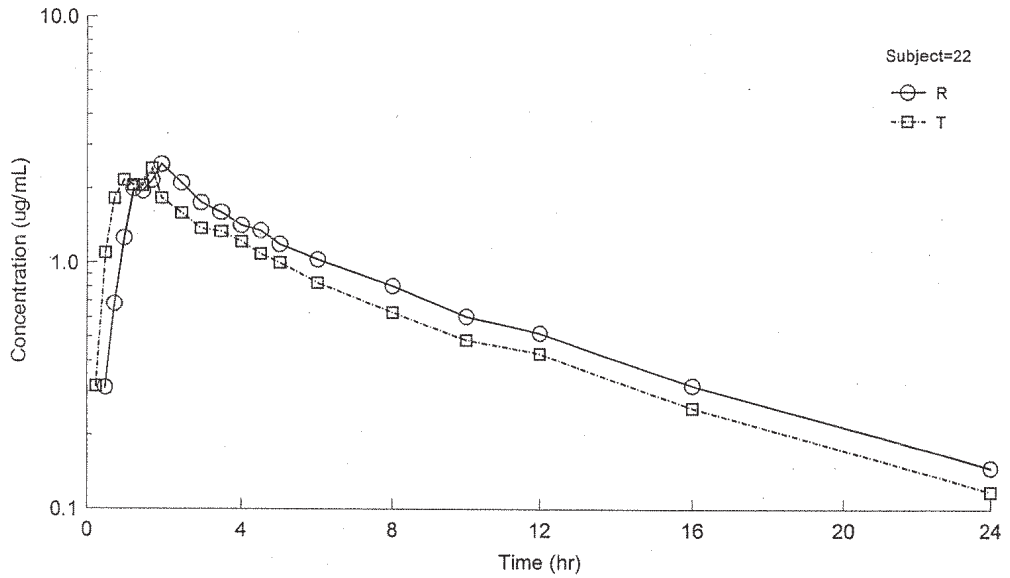
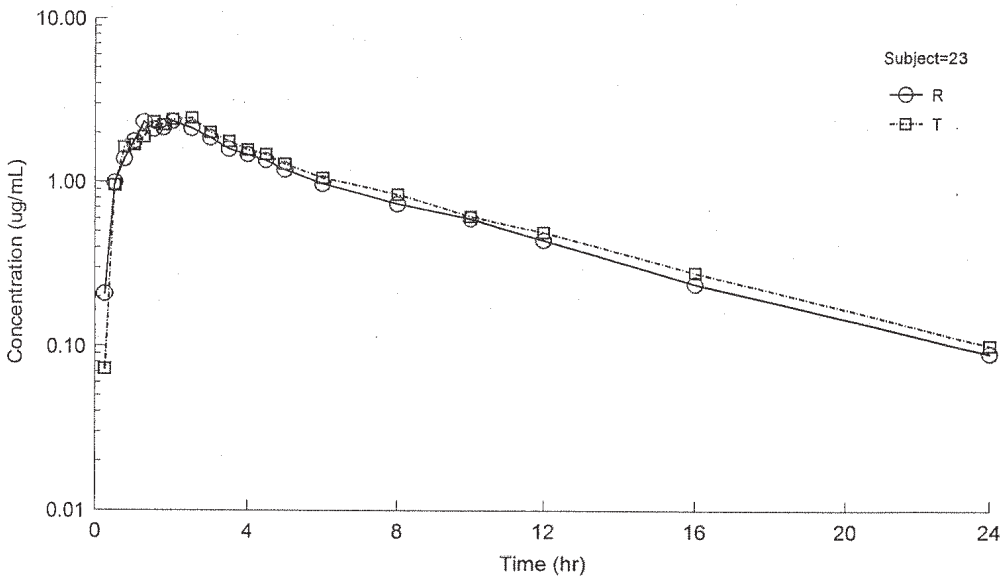


User Chart
C:\CPD-BE\Ciprofloxacin\Cpf 0305\Indi semilog plots.pco (17-Feb-2006)

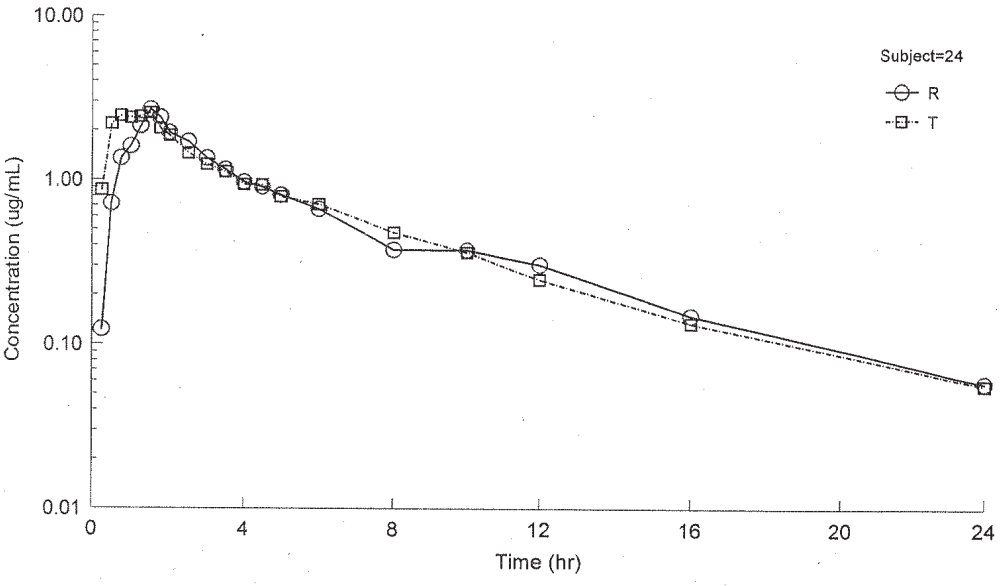
FIGURE 23 and 24

Semi-log Individual Subject Plasma Ciprofloxacin Concentrations Versus Time

(Subjects 23 and 24)



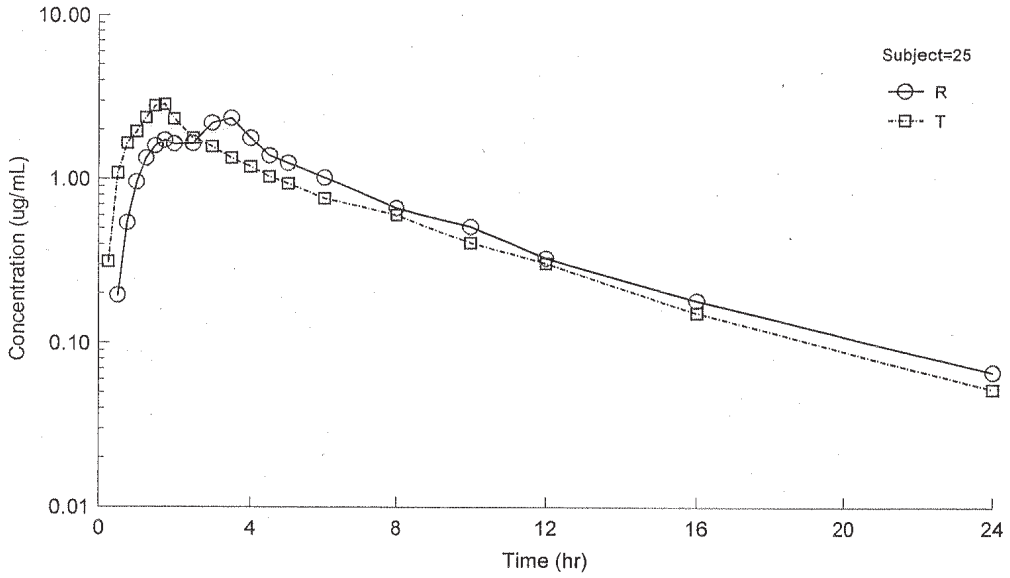
User Chart
C:\CPD-BE\Ciprofloxacin\Cpf 0305\Indi semilog plots.pco (17-Feb-2006)



User Chart
C:\CPD-BE\Ciprofloxacin\Cpf 0305\Indi semilog plots.pco (17-Feb-2006)

FIGURE 25

Semi-log Individual Subject Plasma Ciprofloxacin Concentrations Versus Time (Subjects 25)



User Chart
C:\CPD-BE\Ciprofloxacin\Cpf 0305\Indi semilog plots.pco (17-Feb-2006)

12.0 LIST OF ANNEXURES

(i) Protocol for Study No: Cpf-03/05.

(ii) Informed Consent Document For Study No: Cpf-03/05 (Both English and Telugu Version)

(iii) Randomisation Schedule