CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 21-473

STATISTICAL REVIEW(S)

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH
OFFICE OF BIOSTATISTICS

Statistical Review and Evaluation

CLINICAL STUDIES

NDA:	21-473
Names of drug:	Cipro XR
Applicant:	Bayer
Indication:	Uncomplicated Urinary Tract Infection
Documents reviewed:	\\CDSESUB1\N21473\N_000\2002-03-04\
Project manager:	Jouhayna Saliba
	Susan Peacock
Clinical reviewer:	Regina Alivisatos, M.D.
Dates:	Received 03/04/02; user fee (10 months) 01/04/03
Statistical reviewer:	Ruthanna Davi, M.S.
Statistics team leader:	Karen Higgins, Sc.D.
Biometrics division director:	Mohammed Huque, Ph.D.

Keywords: NDA review, clinical studies, noninferiority

1 EXECUTIVE SUMMARY OF STATISTICAL FINDINGS

1.1 CONCLUSIONS AND RECOMMENDATIONS

It is the opinion of this reviewer that Cipro XR has been shown to be non-inferior to Cipro® in terms of the endpoints studied. This conclusion is robust against multiple sensitivity and subgroup analyses.

1.2 OVERVIEW OF CLINICAL PROGRAM AND STUDIES REVIEWED

The sponsor has submitted the results of one controlled clinical trial in support of the efficacy of Cipro XR in the treatment of uncomplicated urinary tract infection. The study is titled, "Prospective, Randomized, Double-Blind, Multicenter, Comparative Trial to Evaluate the Efficacy and Safety of Ciprofloxacin Once Daily Modified Release 500 mg Tablets QD for 3 Days Versus Conventional Ciprofloxacin 250 mg Tablets BID for 3 Days in the Treatment of Patients with Uncomplicated Urinary Tract Infection". This study will be thoroughly reviewed within this document.

1.3 PRINCIPAL FINDINGS

The results of the controlled clinical trial submitted in support of the efficacy of Cipro XR indicate that Cipro XR is non-inferior to Cipro® in terms of the following endpoints.

- Bacteriologic response at the test-of-cure time point
- Bacteriologic response at the follow-up visit time point
- Clinical response at the test-of-cure time point
- Clinical response at the follow-up visit time point

These results remain consistent across both the per-protocol (PP) and modified intent-to-treat (mITT) analysis groups. In addition, these results are not dependent on the use of the amended test-of-cure (TOC) and follow-up time windows rather than those defined in the original protocol. Examination of the primary efficacy endpoint by age and race did not reveal any problematic subgroup differences. Also the tabulations of the bacteriologic success at the TOC visit were fairly numerically consistent across treatment groups for each of the organisms studied.

2 STATISTICAL REVIEW AND EVALUATION OF EVIDENCE

2.1 INTRODUCTION AND BACKGROUND

The sponsor has submitted the results of one controlled clinical trial in support of the efficacy of Cipro XR in the treatment of uncomplicated urinary tract infection. The study is titled, "Prospective, Randomized, Double-Blind, Multicenter, Comparative Trial to Evaluate the Efficacy and Safety of Ciprofloxacin Once Daily Modified Release 500 mg Tablets QD for 3 Days Versus Conventional Ciprofloxacin 250 mg Tablets BID for 3 Days in the Treatment of Patients with Uncomplicated Urinary Tract Infection". The primary objective of the study was to prove that the bacteriological eradication rate using Cipro XR is not

inferior to that of conventional Ciprofloxacin at the test of cure visit in women with confirmed uncomplicated urinary tract infections.

2.2 DATA ANALYZED AND SOURCES

The sponsor has submitted the results of one controlled clinical trial in support of the efficacy of Cipro XR in the treatment of uncomplicated urinary tract infection. The following data sets were submitted electronically and were utilized in the review of this study. The reviewer found all data sets to be clearly documented and well organized.

[redacted]

[redacted]

2.3 STATISTICAL EVALUATION OF EVIDENCE ON EFFICACY / SAFETY

2.3.1 REVIEW OF STUDY NUMBER BAY-Q3939-100346

2.3.1.1 Study Design, Protocol, and Protocol Amendments

This was a multicenter, prospective, randomized, double-blind, parallel group, 3-day phase III clinical trial conducted at 58 centers in the United States. The primary objective of this study was to determine if Cipro XR 500 mg PO QD for three days was non-inferior to conventional ciprofloxacin (Cipro®) 250 mg PO BID for three days in the treatment of women with uncomplicated urinary tract infection (UTI).

Patients who fulfilled the following protocol-specified criteria were eligible for inclusion in the study.

- Non-pregnant women, 18 to 65 years of age;
- At least two of the following clinical signs and symptoms of an uncomplicated UTI: dysuria, frequency, urgency, and suprapubic pain
- Onset of symptoms ≤72 hours prior to study entry;
- One positive pretreatment clean-catch midstream urine culture at enrollment in the study, defined as $\geq 10^5$ CFU/mL (study treatment was permitted prior to the availability of urine culture results);
- Pyuria (defined as ≥10 leukocytes/mm^3 in unspun urine examined in a counting chamber) prior to study entry;
- Older women of childbearing potential, including women less than 1 year postmenopausal and/or not surgically sterilized, were required to use two reliable methods of contraception during exposure to study drug; and

- Culture and in vitro susceptibility testing was required on pretreatment clean-catch midstream urine specimens.

Patients who were male, were pregnant, nursing or not using medically accepted effective methods of birth control, or had a complicated UTI were excluded from the study. The exclusion criteria were not limited to these three items. (For complete listing of exclusion criteria, please see study protocol.)

After the inclusion/exclusion criteria were satisfied and written informed consent was obtained, patients were randomly assigned (in a 1:1 ratio without blocks) to receive one of the following two treatments.

Cipro XR 500 mg PO QD for three days or
Cipro® 250 mg PO BID for three days

The primary efficacy variable was defined to be the bacteriological response at the test-of-cure visit. Bacteriological response at the TOC visit was graded as eradication, persistence, superinfection, new infection, or indeterminate. The following definitions are from the sponsor's study report. All categories except eradication were considered failures in the analysis.

Eradication: A urine culture taken within the posttherapy window of Days +4 to +11 showed that all uropathogens isolated at study entry in a quantity >=10 5 CFU/mL were reduced to <10 4 CFU/mL.
Persistence: A urine culture taken any time after the completion of therapy grew >=10 4 CFU/mL of the original uropathogen.
Superinfection: a urine culture grew > =10 5 CFU/ml of a uropathogen other than the baseline pathogen at any time during the course of active therapy.
New Infection: a pathogen, other than the original microorganism isolated at baseline at a level >=10 5 CFU/mL, was present at a level >=10 5 CFU/mL anytime after treatment was completed.
Indeterminate: Patients in whom a bacteriological assessment was not possible to determine. Reasons for indeterminate evaluation must have been documented.

Bacteriological response at the follow-up visit and clinical responses at the test-of-cure and follow-up visits were considered secondary variables. Bacteriological response at the follow-up visit was graded as continued eradication, persistence, superinfection, recurrence, new infection, or indeterminante. The following definitions are from the spnsor's study report. All categories except continued eradication were considered failures in the analysis.

Continued Eradication: Causative organism(s) in quantities <10 4 CFU/mL at the test-of-cure and at late follow-up visits.
Persistence: Patients with a causative organism =10 4 CFU/mL noted at the test-of-cure visit (+4 to +11 days post-treatment) regardless of the results of the culture at the follow-up visit were to be carried forward.
Superinfection: A urine culture grew =10 5 CFU/mL of a uropathogen other than the baseline pathogen at any time during the course of active therapy, with symptoms of infection as previously stated.
Recurrence: Causative organism(s) in numbers <10 4 CFU/mL at the test-of-cure visit, but reappearance of the same organism(s) =10 4 CFU/mL before or at the late follow-up visit.
New Infection: A pathogen =10 5 CFU/mL other than the original microorganism found at baseline was present at a level =10 5 CFU/mL anytime after treatment was finished.
Indeterminate: Bacteriological outcome to study drug could not be evaluated for any reason (eg, post-treatment culture not obtainable). The reason must have been recorded in the CRF.

Clinical outcome at the TOC visit was graded as clinical cure, clinical failure, or indeterminate. The following definitions are from the sponsor's study report. All categories of the clinical outcome at the TOC visit were considered failures except clinical cure.

Clinical Cure: Disappearance or improvement of acute signs and symptoms of infection such that alternative antimicrobial therapy was not required or administered.
Clinical Failure: No apparent response to therapy, persistence of signs and symptoms of infection, or reappearance of signs and symptoms at or before the test-of-cure visit, or use of additional antimicrobial therapy for the current infection.
Indeterminate: Patients in whom clinical assessment was not possible to determine. The reason for the indeterminate evaluation must have been documented. Patients graded as indeterminate at this visit were invalid for efficacy evaluation.

Clinical outcome at the follow-up visit was graded as continued clinical cure, failure, relapse, indeterminate. As with the other efficacy endpoints, all categories of the clinical outcome at the follow-up time point were considered failures except continued clinical cure.

Continued Clinical Cure: Continued disappearance of acute signs and symptoms of infection or continued improvement such that alternative antimicrobial therapy was not required or administered.
Failure: Patients carried forward from the test-of-cure visit.
Relapse: Reappearance of signs and symptoms of an uncomplicated UTI considered to be related to an infectious (bacterial) process such that institution of alternative antimicrobial therapy was required.
Indeterminate: Patients in whom clinical assessment was not possible to determine. The reason for indeterminate evaluation must have been documented.

As per the 1998 draft FDA guidance, "Uncomplicated Urinary Tract Infection – Developing Antimicrobial Drugs for Treatment", the original protocol defined the timing of the test-of-cure visit to be within 5 and 9 days post-treatment and the timing of the follow-up visit to be within 28 and 42 days post-treatment. However, on December 20, 2001 (approximately 1 month after the final patient visit for this study) without explanation, the protocol was amended to expand the test-of-cure visit window to 4 to 11 days post-treatment and the follow-up visit window to 25 to 50 days post-treatment. Under the newly amended time frames, 26 subjects who previously were ineligible for the efficacy analysis at the test-of-cure visit were now considered eligible for analysis. In addition, there were 30 subjects with follow-up visits that fell outside the protocol-specified time frame but within the amended window. The study report does not indicate that this protocol amendment was made prior to data analysis and in fact states that the amendment was made because a large number of patients had test-of-cure evaluations performed outside the protocol-specified window, possibly indicating that examination of the efficacy data had begun. Further exploration of this issue is given in section *2.3.1.2*.

The primary efficacy objective of the study was to demonstrate non-inferiority of Cipro XR to Cipro® in terms of the bacteriological eradication rates at the test-of-cure visit in women with uncomplicated UTI. A two-sided 95% confidence interval for the weighted difference between treatment groups was to be constructed, using Mantel-Haenszel weights (weighting by center). The difference was to be calculated as the proportion of subjects in the Cipro XR treatment group with eradication at the test-of-cure visit minus the same such proportion in the Cipro® group. Non-inferiority was defined as the lower limit of the two-sided 95% confidence interval for the difference between treatment groups being greater than –10%. Analysis of center by treatment interaction for the primary efficacy variable was planned using either the Breslow-Day test or Zelen's test.

The protocol-specified group that was to be used in the primary efficacy analysis was the per-protocol population defined as subjects meeting all of the following criteria.

- All inclusion/exclusion criteria were met;

- Study drug was given for a minimum of two days (four doses) if the clinical outcome at the test-of-cure visit was failure, or a minimum of three days (at least five doses or eight tablets) if the clinical outcome at the test-of-cure visit was Cure;
- All bacteriological outcomes were determined at the test-of-cure visit unless the patient was an early treatment failure (patients with a response of Indeterminate at the test-of-cure visit were invalid for the efficacy evaluation);
- No other systemic antibacterial agent was administered with the study drug during the study period up through the test-of-cure visit unless the patient was a treatment failure;
- No protocol violation occurred during the course of therapy influencing treatment efficacy; and
- Study blind was not broken.

A modified intent-to-treat (mITT) analysis was also planned including all patients who received at least one dose of study drug and had a baseline pathogen. Patients with missing or indeterminate efficacy evaluations were to be included and counted as nonsuccesses in all efficacy analyses carried out in the mITT population. While the valid-for-efficacy results were designated by the protocol as the primary interest, it is division policy to consider the results of the mITT group of at least as much importance as that of the valid-for-efficacy group. Therefore this review will include discussion of the results from both analysis groups.

The protocol originally specified that 584 patients would be enrolled into the study. This sample size was calculated using the methods of Rodary[1], based on the previously described primary analysis methods using 90% power and the following assumptions.

- The true eradication rate for each treatment group is 90%,
- The smallest clinically meaningful difference between treatments (delta) is 10%, and
- The subject validity rate is 80%.

During the study, it became clear that the validity rate would be much lower than 80% because the rate of pretreatment urine culture results with $\geq 10^5$ CFU/mL of a causative organism was lower than originally anticipated. The protocol was amended twice to address this. First, approximately five months after the finalization of the protocol the sample size was revised using an assumed validity rate of 60% which resulted in the need for 778 patients to be enrolled in order to obtain 466 valid patients. Approximately 3½ months later, the assumed validity rate was again revised, this time to 50%. In addition, an alternate method for sample size calculation was used (Farrington et. al[2]). This resulted in the need for 820 patients to be enrolled in order to obtain the now necessary 410 valid patients. All of these sample size modifications were made prior to the study being unblinded and before any efficacy analyses were completed. Therefore it is the opinion of this reviewer that these sample size revisions in no way compromised the integrity of this study and no adjustment in the significance level (α) is warranted.

[1] Rodary C, Com-Nougue C, Tournade MF. How to establish equivalence between treatments: a one-sided clinical trial in pediatric oncology. *Stat Med.* 1989;8:593-8.
[2] Farrington CP, Manning G. Test statistics and sample size formulae for comparative binomial trials with null hypothesis of non-zero risk difference or non-unity relative risk. *Stat Med.* 1990;9:1447-54.

In the course of field inspections, FDA investigators reported that ineligible subjects might be being used in the primary and secondary efficacy analyses, as records indicated that certain subjects did not meet the pretreatment urine culture requirement of having $\geq 10^5$ CFU/mL of a causative organism. Assessment of the electronic data by this reviewer did not substantiate this observation. According to the electronic data submitted with the NDA, the pretreatment urine culture requirement had been met for all subjects included in the efficacy analyses. The reader should note however, that discrepancies between the electronic data set and actual data observed could exist and would not have been identified by this analysis. Please refer to the clinical review of this application for more discussion of this item.

2.3.1.2 Results

This study enrolled 905 patients at 58 centers. Four hundred fifty two were randomly assigned to treatment with Cipro XR and 453 were randomly assigned to treatment with Cipro®. Patient inclusion in or exclusion from the *intent-to-treat* (ITT), *valid for safety*, *modified intent-to-treat* (mITT), and *per-protocol* (PP) analysis data sets are described in Figure 1.

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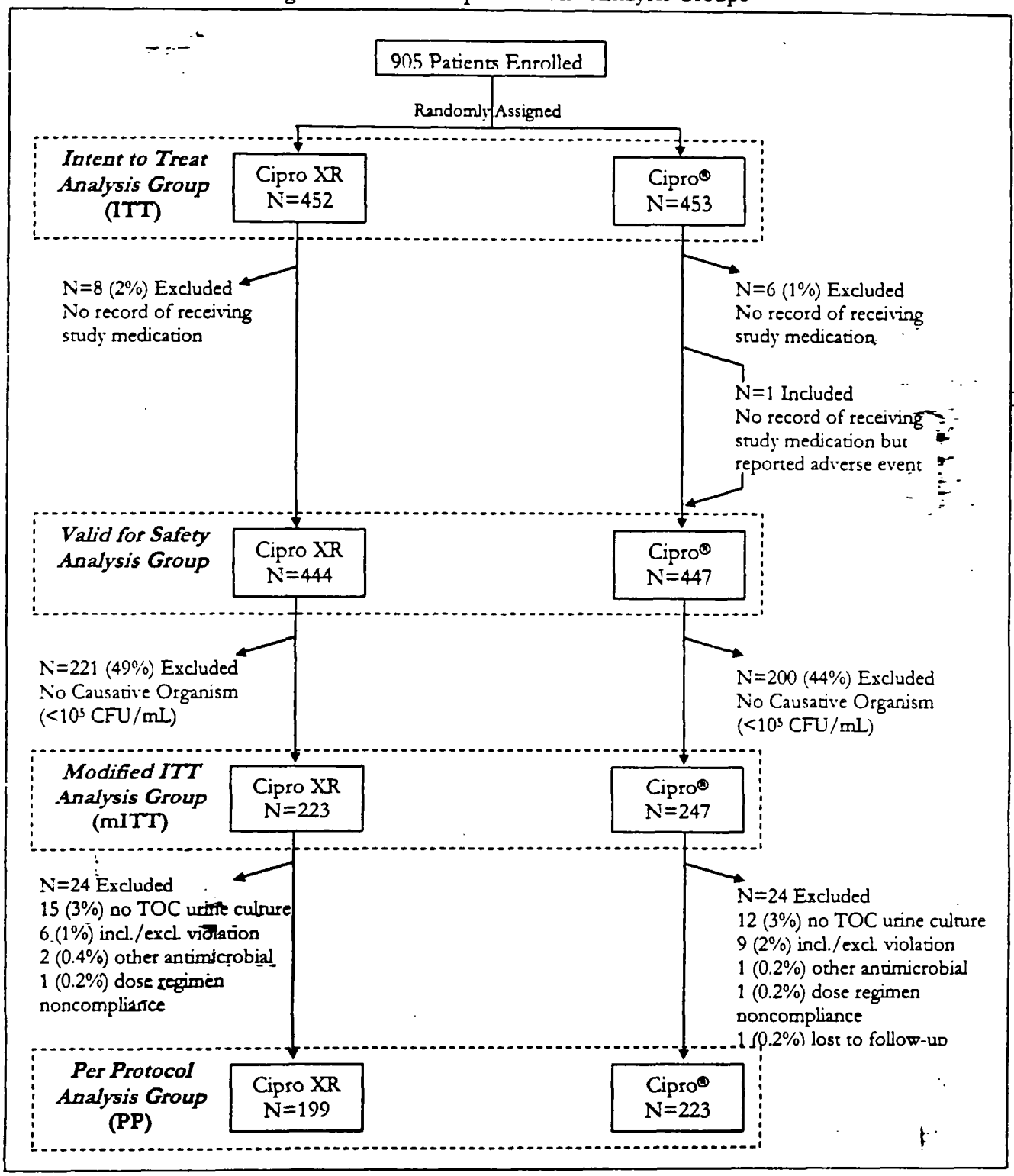
Figure 1: Patient Disposition and Analysis Groups



As indicated in Figure 1, fourteen subjects were excluded from the valid for safety analysis group, as there was no record of them receiving study medication. One additional patient, for whom records did not indicate that study medication had been received, reported an adverse event. This subject was included in the valid for safety group. The only reason for further exclusions from the mITT analysis group in both treatments groups was no causative organism reported in a quantity $\geq 10^5$. The Cipro XR group had a slightly higher rate of patients (49%) with no causative organisms at a level $\geq 10^5$ CFU/mL compared with the Cipro® group (44%). Further exclusions from the PP analysis group were made for the follow reasons; no TOC urine culture, violation of inclusion and/or exclusion criteria, use of another antimicrobial, noncompliance with the dosage regimen, and lost to follow-up. The frequencies of these exclusions were similar between the two treatment groups.

Demographic and baseline variables (including causative orgainsm) for the PP and valid for safety analysis groups are summarized in Table 1.

Table 1: Demographic and Baseline Variables Summary Statistics

		PP Analysis Group		Safety Analysis Group	
		Cipro XR N=199	Cipro® N=223	Cipro XR N=444	Cipro® N=447
Age (years)	Mean (Median)	34.3 (33.0)	35.1 (34.0)	35.2 (33.0)	34.8 (33.0)
	Range	18.0 – 64.0	12.7 – 65.0	18.0 – 79.0	18.0 – 76.0
Weight (kg)	Mean (Median)	70.5 (65.9)	70.5 (67.3)	71.1 (65.9)	70.8 (67.5)
	Range	39.5 – 159.5	41.4 – 134.1	39.5 – 159.5	41.4 – 145.0
Race	Caucasian	154 (77%)	179 (80%)	350 (79%)	358 (80%)
	Black	17 (9%)	18 (8%)	43 (10%)	37 (8%)
	Asian	5 (3%)	5 (2%)	9 (2%)	12 (3%)
	American Indian	1 (<1%)	1 (<1%)	2 (<1%)	2 (<1%)
	Hispanic	21 (11%)	20 (9%)	39 (9%)	38 (9%)
	Other	1 (<1%)	0 (0%)	1 (<1%)	0 (0%)
Duration of Infection	1 day	22 (11%)	37 (17%)	66 (15%)	69 (15%)
	2 days	92 (46%)	97 (43%)	189 (43%)	190 (43%)
	3 days	76 (38%)	79 (35%)	167 (38%)	171 (38%)
	4 days	9 (5%)	10 (4%)	22 (5%)	16 (4%)
	5 days	0 (0%)	0 (0%)	0 (0%)	1 (<1%)
Number of Episodes in Last 12 mo.	None	133 (67%)	155 (70%)	280 (63%)	284 (64%)
	One	51 (26%)	51 (23%)	122 (27%)	117 (26%)
	Two	15 (8%)	17 (8%)	41 (9%)	43 (10%)
	Three	0 (0%)	0 (0%)	1 (<1%)	3 (<1%)
Pre-therapy Causative Organisms (subj. may have >1 organism)	Staphylococuss Saprophyticus	6 (3%)	7 (3%)	8 (2%)	7 (2%)
	Enterococcus Faecalis	11 (6%)	21 (9%)	11 (2%)	21 (5%)
	Escherichia Coli	160 (80%)	181 (81%)	182 (41%)	201 (45%)
	Klebsiella Pneumoniae	9 (5%)	14 (6%)	10 (2%)	14 (3%)
	Klebsiella Ornithinolytica	0 (0%)	2 (<1%)	0 (0%)	2 (<1%)
	Proteus Mirabilis	12 (6%)	7 (3%)	12 (3%)	10 (2%)
	Proteus Vulgaris	1 (<1%)	0 (0%)	1 (<1%)	0 (0%)
	Enterobacter Cloacae	2 (1%)	2 (<1%)	2 (<1%)	2 (<1%)
	Enterobacter Aerogenes	2 (1%)	3 (1%)	2 (<1%)	3 (1%)
	Citrobacter Koseri	0 (0%)	2 (<1%)	0 (0%)	2 (<1%)
	Stenotrophomonas Maltophilia	1 (<1%)	0 (0%)	1 (<1%)	0 (0%)
	No baseline pathogen	NA	NA	221 (50%)	200 (45%)

There were no statistically significant differences between treatment groups in these variables in either the PP or valid for safety analysis groups. Since the mITT group includes subjects in the PP analysis group with only an additional 24 Cipro XR and 23 Cipro® subjects, the summary statistics for demographic and baseline characteristics using the mITT analysis group are very similar to that of the PP analysis group. Therefore these results are not included in this review.

Bacteriological response at the test-of-cure visit is the primary efficacy variable. Bacteriological response at the follow-up visit and clinical responses at the test-of-cure and follow-up visits are considered secondary variables. These results are summarized in Table 2 for both the PP and mITT analysis groups.

Table 2

	PP Analysis Group		mITT Analysis Group*	
	Cipro XR N=199	Cipro® N=223	Cipro XR N=223	Cipro® N=247
Bacteriologic Success at the Test-of-Cure Time Point (Primary Efficacy Endpoint)				
Eradication	188 (94.5%)	209 (93.7%)	188 (84.3%)	209 (84.6%)
95% Confidence Interval for Difference in Proportions				
Continuity Corrected	(-3.9%, 5.6%)		(-7.6%, 6.2%)	
Uncorrected	(-3.5%, 5.1%)		(-7.1%, 5.8%)	
Bacteriologic Success at the Follow-up Time Point (Secondary Efficacy Endpoint)				
Eradication	151 (75.9%)	165 (74.0%)	151 (67.7%)	165 (66.8%)
95% Confidence Interval for Difference in Proportions				
Continuity Corrected	(-6.4%, 10.5%)		(-7.9%, 9.5%)	
Uncorrected	(-5.9%, 10.1%)		(-7.5%, 9.1%)	
Clinical Response at the Test-of-Cure Time Point (Secondary Efficacy Endpoint)				
Success	189 (95.0%)	206 (92.4%)	189 (84.8%)	206 (83.4%)
95% Confidence Interval for Difference in Proportions				
Continuity Corrected	(-2.2%, 7.9%)		(-5.8%, 8.4%)	
Uncorrected	(-1.7%, 7.5%)		(-5.4%, 7.9%)	
Clinical Response at the Follow-up Time Point (Secondary Efficacy Endpoint)				
Success	166 (83.4%)	187 (83.9%)	166 (74.4%)	187 (75.7%)
95% Confidence Interval for Difference in Proportions				
Continuity Corrected	(-6.8%, 7.5%)		(-9.2%, 7.1%)	
Uncorrected	(-6.4%, 7.0%)		(-8.8%, 6.6%)	

* Patients in the mITT analysis group with no urine culture (when applicable), violation of inclusion and/or exclusion criteria, use of another antimicrobial, noncompliance with the dosage regimen, or who were lost to follow-up were counted as nonsuccesses in this efficacy analysis.

Interpretation the results in Table 2 (utilizing a protocol-defined delta of 10%) indicate that Cipro XR is non-inferior to Cipro® in terms of all the endpoints examined, including the

TOC bacteriologic response (primary endpoint) as well as the follow-up bacteriological response and clinical responses at both visits (secondary endpoints).

The original protocol defined the timing of the test-of-cure visit to be within 5 and 9 days post-treatment and the timing of the follow-up visit to be within 28 and 42 days post-treatment. However, on December 20, 2001 (approximately 1 month after the final patient visit for this study) without explanation, the protocol was amended to expand the test-of-cure visit window to 4 to 11 days post-treatment and the follow-up visit window to 25 to 50 days post-treatment. Under the newly amended time frames, 26 subjects who previously were ineligible for the efficacy analysis at the test-of-cure visit were now considered eligible for analysis. In addition, there were 30 subjects with follow-up visits that fell outside the protocol-specified time frame but within the amended window. The study report does not indicate that this protocol amendment was made prior to data analysis and in fact states that the amendment was made because a large number of patients had test-of-cure evaluations performed outside the protocol-specified window, possibly indicating that examination of the efficacy data had begun. This reviewer conducted the analyses of the bacteriologic endpoint in adherence with the original protocol, i.e., including only the subjects with a test-of-cure visit within the protocol-defined test-of-cure window. The qualitative conclusions from this analysis are not different from those made above (see Table 2) where the amended TOC time frame is used. This provides reassurance that the results of the above analysis likely were not an artifact of the newly defined time frames. The numerical results of the original protocol-defined analysis are summarized in Table 3.

Table 3**

	PP Analysis Group		mITT Analysis Group*	
	Cipro XR N=187	Cipro® N=209	Cipro XR N=211	Cipro® N=233
Bacteriologic Success at the Test-of-Cure Time Point (Primary Efficacy Endpoint)				
Eradication	176 (94.1%)	195 (93.3%)	176 (82.9%)	195 (83.7%)
95% Confidence Interval for Difference in Proportions				
Continuity Corrected	(-5.9%, 5.0%)		(-8.6%, 5.9%)	
Uncorrected	(-5.4%, 4.5%)		(-8.1%, 5.5%)	
Bacteriologic Success at the Follow-up Time Point (Secondary Efficacy Endpoint)				
Eradication	144 (77.0%)	153 (73.2%)	144 (68.2%)	153 (65.7%)
95% Confidence Interval for Difference in Proportions				
Continuity Corrected	(-5.8%, 12.0%)		(-7.4%, 11.0%)	
Uncorrected	(-5.3%, 11.5%)		(-6.9%, 10.5%)	

* Patients in the mITT analysis group with no urine culture, violation of inclusion and/or exclusion criteria, use of another antimicrobial, noncompliance with the dosage regimen, or who were lost to follow-up were counted as nonsuccesses in this efficacy analysis.

** Analysis groups defined according to original-protocol-defined TOC time window of within 5 and 9 days post-treatment.

2.4 FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

Table 4 displays the bacteriological response at the TOC time point by demographic variables. With only two exceptions (Cipro XR treated subjects ages 31 to 44 and Cipro XR treated Hispanic subjects), the eradication rates for each treatment group appear to be similar within subgroups. In the two subgroups mentioned where there are relatively large numerical differences between treatment groups in eradication rates, this reviewer is in agreement with the sponsor that these results are likely due to random variation.

Table 4: Tabulations of Bacteriologic Success at the TOC Time Point (Primary Efficacy Endpoint) by Age and Race

	PP Analysis Group	
Eradication Rate	Cipro XR	Cipro®
All Patients	188/199 (94.5%)	209/223 (93.7%)
Age		
18 to 30 years	83/84 (98.8%)	92/97 (94.8%)
31 to 44 years	64/74 (86.5%)	69/71 (97.2%)
45 to 65 years	41/41 (100.0%)	48/55 (100.0%)
Race		
Caucasian	146/154 (94.8%)	166/179 (92.7%)
Black	17/17 (100.0%)	18/18 (100.0%)
Asian	5/5 (100.0%)	5/5 (100.0%)
American Indian	1/1 (100.0%)	1/1 (100.0%)
Hispanic	18/21 (85.7%)	19/20 (95.0%)
Uncodable	1/1 (100.0%)	0/0 (NA)

Table 5 displays the bacteriological response at the TOC time point by organism. The eradication rates were similar in the two treatment groups for each of the organisms.

Table 5: Tabulations of Bacteriologic Success at the TOC Time Point (Primary Efficacy Endpoint) by Organism

	PP Analysis Group	
Eradication Rate	Cipro XR	Cipro®
Staphylococcus Saprophyticus	5/6 (83.3%)	7/7 (100.0%)
Enterococcus Faecalis	10/11 (90.9%)	17/21 (81.0%)
Escherichia Coli	156/160 (97.5%)	176/181 (97.2%)
Klebsiella Pneumoniae	7/9 (77.8%)	11/14 (78.6%)
Klebsiella Ornithinolytica	0/0 (NA)	2/2 (100.0%)
Proteus Mirabilis	11/12 (91.7%)	7/7 (100.0%)
Proteus Vulgaris	1/1 (100.0%)	0/0 (NA)
Enterobacter Cloacae	2/2 (100.0%)	2/2 (100.0%)
Enterobacter Aerogenes	2/2 (100.0%)	3/3 (100.0%)
Citrobacter Koseri	0/0 (NA)	2/2 (100.0%)
Stenotrophomonas Maltophilia	1/1 (100.0%)	0/0 (NA)

2.5 STATISTICAL AND TECHNICAL ISSUES

The following statistical issues and their impact have been described in the context of the review. Please refer to the specified section for details.

- Sample size revisions as a result of overestimating the validity rate (ref: *Section 2.3.1.1*)
- Redefinition of acceptable time windows for collection of TOC and follow-up efficacy data (ref: *Sections 2.3.1.1 and 2.3.1.2*)

2.6 STATISTICAL EVALUATION OF COLLECTIVE EVIDENCE

The results of this study indicate that Cipro XR is non-inferior to Cipro® in terms of the following endpoints.

- Bacteriologic response at the test-of-cure time point
- Bacteriologic response at the follow-up visit time point
- Clinical response at the test-of-cure time point
- Clinical response at the follow-up visit time point

These results remain consistent across both the PP and mITT analysis groups. In addition, these results are not dependent on the use of the amended TOC and follow-up time windows rather than those defined in the original protocol. Examination of the primary efficacy endpoint by age and race did not reveal any problematic subgroup differences. Also the tabulations of the bacteriologic success at the TOC visit were fairly numerically consistent across treatment groups for each of the organisms studied.

2.7 CONCLUSIONS AND RECOMMENDATIONS

It is the opinion of this reviewer that Cipro XR has been shown to be non-inferior to Cipro® in terms of the endpoints studied. This conclusion is robust against multiple sensitivity and subgroup analyses.

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