

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

21-744

STATISTICAL REVIEW(S)



U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Pharmacoeconomics and Statistical Science
Office of Biostatistics

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

NDA/Serial Number: 21-744

Drug Name: Proquin 500 MG (Ciprofloxacin HCl gastric retentive tablets)

Indication(s): Uncomplicated Urinary Tract Infection

Applicant: Depomed, Inc.

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1. EXECUTIVE SUMMARY

1.1 Conclusions and Recommendations

From a statistical perspective, the results of this study indicate that Proquin™ is non-inferior to Cipro® in terms of the following endpoints.

- Microbiological Eradication at the TOC Visit (primary efficacy endpoint)
- Clinical Outcome at the TOC Visit
- Microbiological Eradication at the Follow-Up Visit
- Clinical Outcome at the Follow-Up Visit

These results remain consistent across both the PP and mITT analysis groups. In addition, the conclusions for the primary endpoint results are not dependent on the use of the amended TOC window rather than the window defined in the original protocol or the requirement that baseline pathogens be susceptible to the study drugs. Although the non-inferiority criterion is satisfied when considering Microbiological Eradication **without new infection**, the success rates for both treatment groups using this endpoint are substantially lower than the success rates utilizing the sponsor's original definition of Microbiological Eradication.

Examination of the primary efficacy endpoint by age, race, and baseline pathogen did not reveal any problematic subgroup differences.

It is the opinion of this reviewer that Proquin™ 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. However, careful consideration should be given to the clinical importance of the method for classifying subjects with New Infections for the analysis of the Microbiological Eradication endpoint since the within treatment group success rates are substantially different depending on how subjects with New Infections are classified.

1.2 Brief Overview of Clinical Studies

The sponsor has submitted the results of one phase 3 study to support the use of Proquin™ for uncomplicated urinary tract infection (uUTI). The study is titled, "Randomized, Double-Blind, Parallel Group Study to Compare the Safety and Efficacy of Ciprofloxacin Gastric Retentive (GR) QD and Ciprofloxacin Immediate Release (IR) BID in the Treatment of Uncomplicated Female Urinary Tract Infections". The primary objective of the study was to compare the efficacy of Proquin™ with CIPRO® at equal total daily doses (500 mg) in achieving microbiological eradication of pathogens associated with uUTIs at 7 (± 2) days after the completion of treatment.

1.3 Statistical Issues and Findings

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

- A sensitivity analysis is presented utilizing the original protocol-defined **TOC window of 5 to 9 days post-treatment** and confirms that the non-inferiority of the primary endpoint is not sensitive to the change in the TOC window. (Refer to *Section 3.1, Table 3*)
- A sensitivity analysis is presented utilizing a definition for Microbiological Eradication that requires subjects to be free of new infection(s) to be considered successes and confirms that the non-inferiority in terms of the **primary endpoint without new infection** is still achieved. The success rates for both treatment groups using this endpoint are substantially lower than the success rates utilizing the sponsor's original definition of Microbiological Eradication. (Refer to *Section 3.1, Table 3*)
- A sensitivity analysis is presented including the patients with a **uropathogen that was not susceptible to the study drugs** who had previously been excluded and confirms that the non-inferiority in the primary endpoint is not sensitive to the inclusion/exclusion of subjects whose baseline pathogen was not susceptible to the study drugs. (Refer to *Section 3.1, Table 3*)
- Although the sponsor defines an intent-to-treat group and efficacy population which are very similar to the reviewer's MITT and PP groups, for a given analysis of a particular endpoint at a particular time point the sponsor excluded subjects for whom that particular endpoint at that particular time point was missing. Reviews of similar products within the Division in the recent past have utilized consistent analysis groups for all endpoints and time points. In the opinion of this reviewer, this approach would likely provide a more appropriate quantification of the data. This review includes development of the analysis groups based on the evaluable nature of the primary efficacy endpoint and for analyses of the secondary efficacy endpoints, the same patient groups are utilized by imputing the missing secondary endpoints as failures. One qualitative by-treatment group conclusion was changed from the sponsor's analyses as a result of utilizing **consistent analysis groups**. (Refer to *Section 3, Figure 1 and Table 2*)
- The reasons for a subject having missing microbiological data at TOC and thus being excluded from the PP group were not clearly summarized by the sponsor in the study report. Attempts to identify the **reason for a subject not having evaluable microbiological data at TOC** were made by this reviewer. (Refer to *Section 3, Figure 1*)

2. INTRODUCTION

2.1 Overview

The sponsor has submitted the results of one phase 3 study to support the use of Proquin™ for uncomplicated urinary tract infection (uUTI). This study will be summarized and critiqued within this document.

The study is titled, "Randomized, Double-Blind, Parallel Group Study to Compare the Safety and Efficacy of Ciprofloxacin Gastric Retentive (GR) QD and Ciprofloxacin Immediate Release (IR) BID in the Treatment of Uncomplicated Female Urinary Tract Infections". The primary objective of the study was to compare the efficacy of Proquin™ with CIPRO® at equal total

daily doses (500 mg) in achieving microbiological eradication of pathogens associated with uUTIs at 7 (± 2) days after the completion of treatment. The primary efficacy analysis was designed to demonstrate noninferiority of Proquin™ relative to CIPRO® in terms of this endpoint. Secondary efficacy objectives included (1.) to compare the efficacy of Proquin™ with CIPRO® at equal total daily doses (500 mg) in achieving clinical cure at 7 (± 2) days after the completion of treatment and (2.) to compare the efficacy of Proquin™ with CIPRO® at equal total daily doses (500 mg) in achieving clinical cure and microbiological eradication of pathogens associated with uUTIs at 5 weeks (± 7 days) after the completion of treatment.

2.2 Data Sources

The sponsor has submitted the results of one controlled phase III clinical trial in support of the efficacy of Proquin™ for the treatment of uUTI. The following data sets were submitted electronically and utilized in the review of this study.

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\\CDSESUB1\N21744\N_000\2004-07-18\CRT\DATASETS\81-0015\ANALYSISDATA\MICFILE.XPT

All submitted data sets were found to be adequately documented and organized.

3. STATISTICAL EVALUATION

Study Design

The sponsor has submitted the results of one phase III study to support the use of Proquin for uncomplicated urinary tract infection (uUTI). This study will be summarized and critiqued within this document. The study is titled, "Randomized, Double-Blind, Parallel Group Study to Compare the Safety and Efficacy of Ciprofloxacin Gastric Retentive (GR) QD and Ciprofloxacin Immediate Release (IR) BID in the Treatment of Uncomplicated Female Urinary Tract Infections". This study was an active-controlled / non-inferiority phase III clinical trial conducted at 70 centers in the United States.

The primary objective of the study was to compare the efficacy of Proquin™ with CIPRO® at equal total daily doses (500 mg) in achieving microbiological eradication of pathogens associated with uUTIs at 7 (± 2) days after the completion of treatment. The primary efficacy analysis was designed to demonstrate noninferiority of Proquin™ relative to CIPRO® in terms of this endpoint. Secondary efficacy objectives included (1.) to compare the efficacy of Proquin™ with CIPRO® at equal total daily doses (500 mg) in achieving clinical cure at 7 (± 2) days after the completion of treatment and (2.) to compare the efficacy of Proquin™ with CIPRO® at equal total daily doses (500 mg) in achieving clinical cure and microbiological eradication of pathogens associated with uUTIs at 5 weeks (± 7 days) after the completion of treatment.

The protocol specified the following criteria as being required for inclusion in the study. Note however, that criteria #4 and #5 were verified after a patient had been enrolled in the study and thus were required for inclusion in the sponsor's [modified] intent-to-treat and efficacy populations (Refer to the subsection titled, "Study Results" within this section for further discussion) but not enrollment in the study.

- (1.) Female patients at least 18 years of age.
- (2.) Patients of childbearing potential who had negative urine pregnancy test results at screening and randomization, and were to use two medically acceptable methods of birth control through Visit 2 (Test-of-Cure Visit). Abstinence was an acceptable method of birth control. For patients who were sexually active, acceptable methods of birth control included oral or transdermal contraceptives, condom, spermicidal foam, intrauterine device (IUD), progestin implant or injection, or sterilization of partner. The reason for nonchildbearing potential, such as bilateral tubal ligation, bilateral oophorectomy, hysterectomy, or a 1 year or longer postmenopausal status, was specified in the patient's case report form.
- (3.) Clinical signs and symptoms of a lower UTI (e.g., dysuria, frequency, urgency, suprapubic pain) with onset of symptoms ≤ 72 hours prior to study entry, and pyuria, which was defined as a positive urine dipstick result for leukocyte esterase.
- (4.) At least one positive, pretreatment clean catch mid-stream urine culture (defined as $\geq 10^5$ colony forming units / mL) collected on the day of enrollment in the study.
- (5.) Demonstrated susceptibility of uropathogen to both the test drug and the control drug by in vitro testing.
- (6.) Patient was willing and able to comply with the study procedures and provided written informed consent to participate in the study.

Patients meeting any of sixteen pre-specified exclusion criteria were excluded from the study. These criteria were intended to exclude those patients for whom the interpretation of their study results may have been confounded by other co-existing factors and/or those for whom the safety of that patient may have been jeopardized by enrolling in the study. For a complete listing of exclusion criteria, please see the study protocol.

After the inclusion/exclusion criteria were satisfied, patients were randomly assigned (in a 1:1 ratio) to receive one of the following treatments.

- (1.) 500 mg of ciprofloxacin GR once daily for three days by oral administration (referred to throughout this review as Proquin™)
- (2.) 250 mg of ciprofloxacin IR twice daily for three days by oral administration (referred to throughout this review as CIPRO®)

Despite the differing dosing regimen (once daily versus twice daily), a double-dummy design was employed to allow patient blinding.

The primary efficacy variable was defined in the protocol to be the Microbiological Eradication rate at the test-of-cure visit (i.e., at 7 (± 2) days after the completion of treatment). A patient was to be considered to have a successful Microbiological Eradication when her urine culture at the test-of-cure visit showed that all uropathogens $\geq 10^5$ CFU/mL present at baseline have been reduced to $< 10^4$ CFU/mL. The following definitions recommended to be used for classification of the microbiological outcome are taken from the 1998 draft FDA guidance, "Uncomplicated Urinary Tract Infection – Developing Antimicrobial Drugs for Treatment".

Eradication: A urine culture, taken within the 5- to 9-day post-therapy window, shows that all uropathogens found at entry at $\geq 10^5$ CFU/mL are reduced to $< 10^4$ CFU/mL.

Persistence: A urine culture, taken any time after completion of therapy, grows $\geq 10^4$ CFU/mL of the original uropathogen.

Superinfection: A urine culture grew $\geq 10^5$ CFU/ml of an uropathogen other than the baseline pathogen during the course of active therapy.

New Infection: A pathogen, other than the original microorganism found at baseline at a level $\geq 10^5$ CFU/mL, is present at a level $\geq 10^5$ CFU/mL anytime after treatment is finished.

Note that while the sponsor's definition of Microbiological Eradication is consistent with the guidance, designation of patients with Superinfection and/or New Infection is not. Patients who would have been classified as experiencing Superinfection or New Infection according to the guidance could have also been classified as Microbiologically Eradicated by the definition used in the protocol. Forty two and 32 subjects in the Proquin™ and CIPRO® groups, respectively, were classified as Microbiologically Eradicated (according to the protocol definition) and yet experienced a New Infection (as defined by the guidance). No cases of Superinfection were readily discernable using the electronic data provided by the sponsor since the routine time for assessment was at 7 (± 2) days after the completion of treatment. That is since subjects were not routinely measured during treatment; an infection may have been present during that time period but would not have been detected until after treatment ended and therefore would have been recorded as a New Infection. A sensitivity analysis is presented later in this section utilizing a definition for Microbiological Eradication that requires subjects to be free of new infection(s) to be considered successes and confirms that the non-inferiority in terms of the primary endpoint without new infection is still achieved. (Refer to *Section 3.1, Table 3*) However, the success rates for both treatment groups using this endpoint are substantially lower than the success rates utilizing the sponsor's original definition of Microbiological Eradication.

Secondary efficacy endpoints include (but are not limited to) the following.

- (1.) Clinical outcome at the test-of-cure visit
- (2.) Microbiological and Clinical outcomes at the follow-up visit (defined as 5 weeks ± 7 days following treatment)
- (3.) The investigator's response to the following question at the test-of-cure visit, "Do you feel that the patient's UTI has satisfactorily resolved?"
- (4.) The patient's response to the following question at the test-of-cure visit, "Do you feel that your UTI has been successfully treated?"

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 7 (± 2) days after the completion of treatment and the timing of the follow-up visit to be 5 weeks (± 7 days) after the completion of treatment. However, without an amendment to the protocol, the study report indicates that to "include more data into efficacy data analysis, the visit window for the test-of-cure visit was expanded to 4 to 11 days after the completion of study treatment". Under the newly amended time frame, 29 Proquin™ and 21 Cipro® subjects who previously were ineligible for the efficacy analysis at the test-of-cure visit are now considered eligible for analysis. The study report does not indicate that this change in the definition of the test-of-cure window was made prior to treatment unblinding and/or data analysis and in fact

seems to suggest that this modification was made with the knowledge that at least some of the test-of-cure visits had occurred outside the protocol-defined window, possibly indicating that examination of the efficacy data had begun. A sensitivity analysis is presented later in this section utilizing the original protocol-defined TOC window of 5 to 9 days post-treatment and confirms that the non-inferiority of the primary endpoint is not sensitive to the change in the TOC window. (Refer to *Section 3.1, Table 3*)

The primary efficacy objective of the study was to demonstrate non-inferiority of Proquin™ with CIPRO® in terms of microbiological eradication rates at the test-of-cure visit in women with uncomplicated UTI. The primary efficacy analysis was to be a two-sided 95% confidence interval for the difference between treatment groups. The difference was to be calculated as the proportion of subjects in the Proquin™ group with microbiological 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%.

The protocol specified that analyses of the primary efficacy parameter would be conducted using two analysis populations, the efficacy population and the intent-to-treat population. The intent-to-treat group was to include all randomized patients who met the following criteria (i.e., inclusion criteria 4 and 5).

- At least one positive, pretreatment clean catch mid-stream urine culture (defined as $\geq 10^5$ colony forming units / mL) collected on the day of enrollment in the study.
- Demonstrated susceptibility of uropathogen to both the test drug and the control drug by in vitro testing.

The efficacy population was to include all patients in the intent-to-treat population who had microbiological data available at the test-of-cure visit. While the efficacy population results were designated by the protocol as the primary interest, it is division policy to consider the results of the intent-to-treat population of at least as much importance as that of the efficacy population. Therefore this review will include discussion of the results from both analysis groups. (Refer to the subsection titled, "Study Results" within this section for further discussion regarding analysis groups.)

The protocol originally specified that 720 patients would be enrolled into the study, which was expected to provide 504 patients for the efficacy population. This sample size was calculated based on the previously described primary analysis methods using 80% power and the following assumptions.

- The microbiological eradication rate for each treatment group is 80%,
- The smallest clinically meaningful difference between treatments (delta) is 10%, and
- The subject validity rate for the efficacy population is 70%.

In the study report, the sponsor states that during the study, it became clear that the validity rate would be lower than 70%. And therefore, the protocol was amended on October 14, 2003 (i.e., Protocol Amendment 2) to address this. This amendment occurred approximately five months after initiation of the study. The sample size was revised using an assumed validity rate of 60% which resulted in the need for 960 patients to be enrolled in order to obtain 576 patients valid for the efficacy population. In addition to the change in the validity rate, the power was increased to 85%. This modification in the sample size was made prior to the study being

unblinded and before any efficacy analyses were completed. Therefore it is the opinion of this reviewer that this sample size revision in no way compromised the integrity of this study and no adjustment in the significance level (α) is warranted.

Study Results

The study enrolled 1037 patients at 70 centers in the United States. Five hundred twenty four patients were randomly assigned to treatment with Proquin™ and 513 were randomly assigned to receive CIPRO®.

Patient inclusion in or exclusion from the reviewer defined intent-to-treat (ITT), modified intent-to-treat (MITT), and per-protocol (PP) analysis groups are described in Figure 1. The reviewer defined MITT group is the same as the sponsor's intent-to-treat population and the reviewer defined PP group is the same as the sponsor's efficacy population. The specific patient numbers of subjects who are excluded from each analysis group is provided in Table 1.

Note that although the sponsor defines an intent-to-treat group and efficacy population which are the same as the reviewer's MITT and PP groups, for a given analysis of a particular endpoint at a particular time point the sponsor excluded subjects for whom that particular endpoint at that particular time point was missing. For example, a patient with missing TOC microbiological data and known clinical outcome at TOC and follow-up was excluded from analysis of the microbiological TOC endpoint but included for the clinical outcome analyses. In essence, this meant that varying patient groups were utilized for the analysis of each endpoint at each time point. While, the study protocol is somewhat unclear regarding how this issue was specified to be handled a priori, reviews of similar products within the Division in the recent past have utilized consistent analysis groups for all endpoints and time points. In the opinion of this reviewer, this approach would likely provide a more appropriate and clear quantification of the data. Therefore, development of the analysis groups below is based on the evaluable nature of the primary efficacy endpoint. For analyses of the secondary efficacy endpoints, the same patient groups are utilized by imputing the missing secondary endpoints as failures. For this reason, the efficacy analyses presented in this review will differ from those in the sponsor's submission.

However, only one qualitative by-treatment group conclusion was changed from the sponsor's analyses as a result of this approach. The lower limit of the 95% confidence interval for the difference in proportions for a secondary endpoint that had been reported as "marginally non-inferior" by the sponsor satisfies the protocol specified noninferiority margin of 10% using this approach for the analysis groups. (Refer to *Section 3.1, Table 2*)

The definitions used for the ITT and MITT groups in this review are fairly consistent with definitions used in the review of similar products for uUTI in the recent past. The ITT group includes all subjects who were randomized and received study treatment. The MITT includes all ITT subjects who had a susceptible baseline pathogen at a level $\geq 10^5$ CFU/mL. The requirement that the pathogen be susceptible was established in the sponsor's protocol. While this has not been typical practice within the Division in the review of similar products, the rates of exclusions from the MITT for this reason are fairly balanced across treatment groups and relatively infrequent. A sensitivity analysis is presented later in this section including the patients

without susceptible uropathogen who had previously been excluded and confirms that the non-inferiority in the primary endpoint is not sensitive to the inclusion/exclusion of subjects whose baseline pathogen was not susceptible to the study drugs. (Refer to *Section 3.1, Table 3*)

Creation of the PP group is in accordance with the study protocol (i.e., including all MITT patients who have microbiological data available at TOC). The reasons for a subject having missing microbiological data at TOC and thus being excluded from the PP group were not clearly summarized by the sponsor in the study report. Attempts to identify the reason for a subject not having evaluable microbiological data at TOC were made by this reviewer and are indicated in Figure 1 as that subject's reason for exclusion from the PP group. These assessments were made through use of the electronic data and the patient listings provided in study report appendices 16.2.4 and 16.2.5. While it is suspected that the events indicated in Figure 1 were the basis for the indicated subject's missing TOC microbiological data, this assessment could be flawed in that multiple factors may exist that contributed to these subjects unevaluable or missing TOC microbiological data.

As indicated in Figure 1 and Table 1, five Proquin™ subjects and three CIPRO® subjects were excluded from the ITT analysis group, as they did not receive study medication. One additional CIPRO® subject was excluded because although she was randomly assigned to receive CIPRO®, she received Proquin™ in error. The reasons for further exclusions from the MITT analysis group were no baseline uropathogen(s) at a level $\geq 10^5$ CFU/mL were present and the baseline uropathogen was not susceptible to both study treatments in vitro. The rates of exclusion for these reasons were fairly balanced across treatment groups at 41% and 46% for the Proquin™ and CIPRO® groups, respectively. Patients without evaluable microbiological data at the TOC visit were excluded from the PP analysis group at rates of 11% and 9% for the Proquin™ and CIPRO® groups, respectively. The underlying suspected reasons for the missing evaluable microbiological data at TOC include other antimicrobial use, TOC visit occurred outside 7-14 day window, lost to follow-up, patient consent withdrawn, adverse event, and other. The rates of these events were fairly balanced across treatment groups.

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Figure 1: Patient Disposition and Analysis Groups

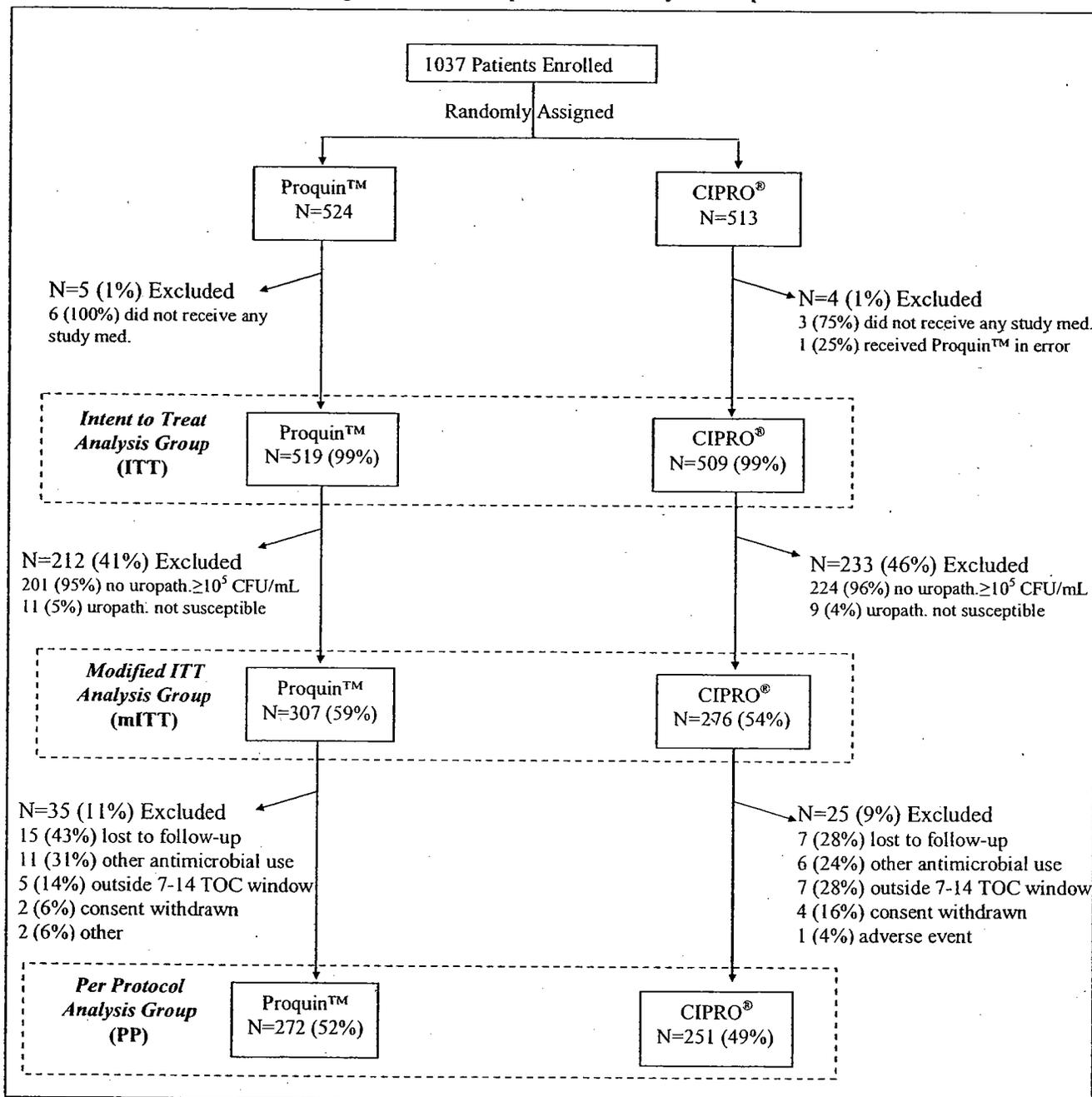


Table 1: Patient Disposition and Analysis Groups (with Explicit Patient Numbers Provided)

Description	Number of Subjects		Patient Numbers
	Proquin™	CIPRO®	
Enrolled	524	513	
Did not receive study med.	5	3	4206, 4506, 5007
Received alternate study med. in error	0	1	6011
Intent to Treat Analysis Grp	519	509	
No Uropathogen $\geq 10^5$ CFU/mL	201	224	101, 104, 203, 210, 212, 215, 216, 403, 405, 406, 410, 411, 413, 502, 604, 704, 707, 715, 719, 722, 724, 803, 814, 819, 907, 1010, 1018, 1021, 1026, 1106, 1110, 1112, 1113, 1115, 1206, 1208, 1211, 1214, 1304, 1501, 1504, 1505, 1601, 1612, 1614, 1615, 1709, 1713, 1814, 1816, 1901, 1908, 1910, 1916, 2101, 2205, 2206, 2209, 2213, 2215, 2220, 2301, 2429, 2434, 2435, 2442, 2444, 2449, 2510, 2605, 2607, 2702, 2708, 2710, 2715, 2716, 2719, 2724, 2727, 2733, 2735, 2740, 2741, 2746, 2802, 2803, 2810, 2811, 2815, 2819, 2822, 2905, 2910, 2914, 2918, 2920, 2923, 2924, 2925, 2926, 2930, 3009, 3016, 3106, 3108, 3111, 3206, 3209, 3216, 3226, 3305, 3307, 3612, 3615, 3702, 3708, 3805, 3813, 3919, 3927, 3928, 3930, 3934, 3937, 3942, 3946, 3947, 4101, 4109, 4114, 4118, 4120, 4122, 4204, 4208, 4209, 4211, 4215, 4303, 4314, 4320, 4323, 4326, 4327, 4332, 4413, 4511, 4603, 4609, 4617, 4625, 4807, 4812, 4816, 4817, 4820, 4821, 4829, 4907, 4915, 5004, 5005, 5006, 5104, 5105, 5108, 5403, 5408, 5411, 5511, 5702, 5705, 5706, 6008, 6303, 6305, 6307, 6402, 6403, 6503, 6508, 6509, 6510, 6513, 6516, 6518, 6522, 6602, 6608, 6617, 6618, 6801, 6808, 6814, 6815, 6817, 6903, 6905, 7103, 7105
Pathogen not susceptible	11	9	202, 716, 1701, 1801, 2001, 2304, 3211, 3302, 3709, 3801, 6102
Modified ITT Analysis Grp	307	276	
Other antimicrobial use*	11	6	208, 1902, 2603, 3001, 3602, 4318, 4505, 4629, 4704, 4910, 6811
Outside 7-14 d TOC window*	5	7	501, 1012, 2508, 3704, 6107
Terminated study prematurely due to			
• Lost to follow-up*	15	7	612, 1014, 2402, 2406, 2422, 2440, 2445, 2725, 3907, 4107, 4310, 4311, 4315, 4808, 6006
• Consent withdrawn*	2	4	1025, 6812
• Adverse event*	0	1	
• Other* (in study 1 day)	2	0	2315, 4504
Per-Protocol Analysis Grp	272	251	

*These subjects were identified by the sponsor as having been excluded from the efficacy population or not having evaluable TOC microbiological data. Further examination of the electronic data by this reviewer revealed the events listed above in connection with these subjects. It is suspected but not completely unmistakable that these events were the basis for the indicated subjects being excluded from the efficacy population or their TOC microbiological data being unevaluable. It is possible that other factors may also exist that contributed to these subjects being excluded from the efficacy population or their TOC microbiological data being unevaluable.

Demographic and baseline variables for all subjects enrolled in the trial and for the MITT analysis group were provided by the sponsor and are summarized in Table 2. No statistically significant by-treatment group differences in demographic or baseline characteristics were observed in either all subjects enrolled or the MITT analysis group. As would be expected since the MITT analysis group is a subset of all subjects enrolled, numerical trends in the two groups were similar.

		MITT Analysis Group			All Enrolled Subjects		
		Proquin™ N=307	Cipro® N=276	By-trt. p-value†	Proquin™ N=524	Cipro® N=513	By-trt. p-value†
Age (years)	<40	170 (55.4%)	137 (49.6%)	0.310	296 (56.5%)	275 (53.6%)	0.610
	40-65	120 (39.1%)	118 (42.8%)		196 (37.4%)	202 (39.4%)	
	≥65	17 (5.5%)	21 (7.6%)		32 (6.1%)	36 (7.0%)	
	Mean (SD)	39 (15.0)	40 (14.8%)	0.342	39 (15.1)	39 (14.8)	0.577
	Median	38	40		36	38	
	(Min, Max)	(18, 83)	(18, 86)		(18, 89)	(18, 86)	
Gender	Female	307 (100%)	276 (100%)	NA	524 (100%)	513 (100%)	NA
	Male	0 (0%)	0 (0.0%)		0 (0.0%)	0 (0.0%)	
Race	Caucasian	244 (79.5%)	232 (84.1%)	0.116	401 (76.5%)	415 (80.9%)	0.324
	Black	21 (6.8%)	15 (5.4%)		39 (7.4%)	30 (5.8%)	
	Asian	6 (2.0%)	2 (0.7%)		9 (1.7%)	4 (0.8%)	
	Hispanic	36 (11.7%)	23 (8.3%)		72 (13.7%)	58 (11.3%)	
	Native American	0 (0.0%)	1 (0.4%)		1 (0.2%)	2 (0.4%)	
	Other	0 (0.0%)	3 (1.1%)		2 (0.4%)	4 (0.8%)	
Height (in)*	Mean (SD)	64 (2.7)	64 (2.9)	0.702	65 (2.7)	64 (2.9)	0.269
	Median	64	65		64	64	
	(Min, Max)	(54, 74)	(50, 72)		(54, 74)	(50, 72)	
Weight (lb)*	Mean (SD)	153 (36.9)	156 (35.0)	0.347	156 (41.5)	159 (41.8)	0.222
	Median	143	149		146	149	
	(Min, Max)	(97, 350)	(97, 300)		(93, 437)	(85, 385)	

* Small amount of missing data (<1%) for these endpoints were ignored.

† The p-value for the treatment effect was based on the two-sample t-test for numeric data. Fisher's Exact test was used to assess by-treatment group differences in categorical data.

3.1 Evaluation of Efficacy

The primary efficacy variable was defined in the protocol to be the microbiological eradication rate at the TOC visit. Secondary efficacy endpoints include (but are not limited to) clinical outcome at the TOC visit and microbiological and clinical outcomes at the follow-up visit. The protocol-defined primary analysis group for this study was the PP group; however, the results for the MITT group are also presented. It is Division policy that the MITT group is of at least as much importance as the efficacy population. This is necessary to allow for an assessment of the product in an unselected/unbiased group of patients where the integrity of the random treatment assignment is as intact as possible. The comparisons of the primary and highlighted secondary efficacy endpoints in the PP and MITT groups are summarized in Table 1.

Note that the results in Table 2 differ from those of the sponsor. The sponsor excluded subjects for whom a particular endpoint at a particular time point was missing resulting in the use of varying patient groups for analysis of each endpoint at each time point. Development of the analysis groups (i.e., PP and MITT) in this review is based on the evaluable nature of the

primary efficacy endpoint. For analyses of the secondary efficacy endpoints, the same patient groups are utilized by imputing the missing secondary endpoints as failures. It is the opinion of this reviewer that this provides a more appropriate and clear quantification of the efficacy data. Although the point estimation of the rates of success for each endpoint has been altered from what was presented in the study report, only one qualitative by-treatment group conclusion was changed as a result of this approach. The sponsor had reported that the Clinical Outcome for Proquin™ relative to Cipro® at the follow-up visit in the efficacy population was “marginally non-inferior” with 196 successes in the 259 Proquin subjects and 175 successes in the 222 Cipro subjects and 95% confidence interval for the difference in proportions (-10.6%, 4.4%). The analysis presented in Table 2 for the Clinical Outcome at follow-up indicates that the difference between the two treatments is within the protocol-defined non-inferiority margin of 10%.

	PP Analysis Group*			MITT Analysis Group		
	Proquin™ N=272	Cipro® N=251	95% Confidence Interval for Difference in Proportions	Proquin™ N=307	Cipro® N=276	95% Confidence Interval for Difference in Proportions
Microbiological Eradication at the TOC Visit (primary efficacy endpoint)	254 (93.4%)	225 (89.6%)	(-1.0%, 8.5%)	254 (82.7%)	225 (81.5%)	(-5.0%, 7.4%)
Clinical Outcome at the TOC Visit (secondary efficacy endpoint)	233 (85.7%)	216 (86.1%)	(-6.4%, 5.6%)	233 (75.9%)	216 (78.3%)	(-9.2%, 4.5%)
Microbiological Eradication at the Follow-Up Visit (secondary efficacy endpoint)	182 (66.9%)	168 (66.9%)	(-8.1%, 8.1%)	182 (59.3%)	168 (60.9%)	(-9.5%, 6.4%)
Clinical Outcome at the Follow-Up Visit (secondary efficacy endpoint)	196 (72.1%)	175 (69.7%)	(-5.5%, 10.1%)	196 (63.8%)	175 (63.4%)	(-7.4%, 8.3%)

* Protocol-specified analysis group for the primary efficacy analysis was the PP analysis group.

Interpretation of the results in Table 2 (utilizing a protocol-defined delta of 10%) indicate that Proquin™ is non-inferior to Cipro® in terms of the primary endpoint, TOC Microbiological Eradication. In addition, all the secondary endpoints examined, including the follow-up Microbiological Eradication and Clinical Outcome at both TOC and follow-up satisfy a noninferiority margin of -10% suggesting that Proquin™ is non-inferior to Cipro® in terms of these endpoints.

Three sensitivity analyses of TOC Microbiological Eradication are presented in Table 3. These analyses were conducted to address the following irregularities in the design of the study.

- (1.) 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 7 (± 2) days after the completion of treatment. However, without an amendment to the protocol, the study report indicates that to “include more data into efficacy data analysis, the visit window for the test-of-cure visit was expanded to 4 to 11 days after the completion of study treatment”. This sensitivity analysis is conducted utilizing the original protocol-defined **TOC window of 5 to 9 days post-treatment** and confirms that the non-inferiority of the primary endpoint is not sensitive to the change in the TOC window.

- (2.) In the primary efficacy analysis, a patient was classified as Microbiologically Eradicated when her urine culture at the test-of-cure visit showed that all uropathogens $\geq 10^5$ CFU/mL present at baseline have been reduced to $<10^4$ CFU/mL. This definition allowed patients who experienced new infection(s) to be classified as Microbiologically Eradicated. This sensitivity analysis is conducted utilizing a definition for Microbiological Eradication that requires subjects to be free of new infection(s) to be considered successes and confirms that the non-inferiority in terms of the **primary endpoint without new infection** is still achieved. Note that the success rates for both treatment groups using this endpoint are substantially lower than the success rates presented in Table 2. For a discussion of which endpoint is more appropriate and clinically relevant, please refer to the clinical review of this submission.
- (3.) The MITT utilized in Table 2 includes all ITT subjects who had a **susceptible** baseline pathogen at a level $\geq 10^5$ CFU/mL. The requirement that the pathogen be susceptible was established in the sponsor’s protocol but has not been typical practice within the Division in the review of similar products. This sensitivity analysis is conducted including the patients without susceptible uropathogen who had previously been excluded and confirms that the non-inferiority in the primary endpoint is not sensitive to the inclusion/exclusion of subjects whose baseline pathogen was not susceptible to the study drugs.

Table 3: Sensitivity Analyses of the Primary Efficacy Endpoint						
	PP Analysis Group			MITT Analysis Group		
	Proquin™ N=272	Cipro® N=251	95% CI for Diff in Proportions	Proquin™ N=307	Cipro® N=276	95% CI for Diff in Proportions
Protocol-Defined TOC Window of 5 to 9 Days Post-Treatment*						
Microbiological Eradication	N=243 226 (93.0%)	N=231 211 (91.3%)	(-3.2%, 6.5%)	N=278 226 (81.3%)	N=256 211 (82.4%)	(-7.7%, 5.4%)
Microbiological Eradication Without New Infection†						
Microbiological Eradication Without New Infection	N=272 212 (77.9%)	N=251 193 (76.9%)	(-6.1%, 8.2%)	N=307 212 (69.1%)	N=276 193 (69.9%)	(-8.4%, 6.6%)
Susceptible Organism Requirement for Inclusion in MITT Ignored‡						
Microbiological Eradication	N=283 259 (91.5%)	N=260 231 (88.8%)	(-2.3%, 7.7%)	N=318 259 (81.4%)	N=285 231 (81.1%)	(-5.8%, 6.6%)

* Analysis is conducted utilizing the original protocol-defined TOC window of 5 to 9 days post-treatment.

† Analysis is conducted utilizing a definition for Microbiological Eradication that requires subjects to be free of new infection(s) to be considered successes.

‡ Analysis is conducted including the patients without susceptible uropathogen who had previously been excluded from the MITT.

3.2 Evaluation of Safety

No safety endpoints have been identified in the review of this product as requiring formal examination through statistical hypothesis testing methods using the data from this study. Therefore, the reader is referred to the clinical review for a discussion and summary of the safety of Proquin™.

4. FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

4.1 Gender, Race and Age

Table 4 displays the Microbiologic Eradication rates at the TOC visit by race and age. Subgroup analyses by gender were not conducted as 100% of the patients enrolled in this study were female. In general, the Microbiologic Eradication rates and the by-treatment group comparisons within each demographic subcategory are similar to the results observed for the primary efficacy analysis in the overall group.

Table 4: Microbiologic Eradication (with or without New Infection) at the TOC Visit by Age and Race (PP Analysis Group)			
	Proquin™	Cipro®	95% Confidence Interval for Difference in Proportions
Age			
<65 years	242 / 258 (93.8%)	207 / 232 (89.2%)	(-0.4%, 9.5%)
≥65 years	12 / 14 (85.7%)	18 / 19 (94.7%)	(-29.9%, 11.9%)
Race			
Caucasian	204 / 216 (94.4%)	188 / 209 (90.0%)	(-0.6%, 9.6%)
Non-Caucasian	50 / 56 (89.3%)	37 / 42 (88.1%)	(-11.5%, 13.9%)

4.2 Other Special/Subgroup Populations

Table 5 displays the Microbiological Eradication rates at the TOC visit by organism. Organisms included in Table 5 were specified by the clinical review team as being of interest.

Table 5: Microbiologic Eradication of the Indicated Pathogen at the TOC Visit by Organism (PP Analysis Group)			
	Proquin™	Cipro®	95% Confidence Interval for Difference in Proportions
<i>E. coli</i>	211 / 222 (95.0%)	184 / 202 (91.1%)	(-0.9%, 8.8%)
<i>K. pneumoniae</i>	11 / 12 (91.7%)	10 / 13 (76.9%)	(-13.0%, 42.5%)

5. SUMMARY AND CONCLUSIONS

5.1 Statistical Issues and Collective Evidence

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

- A sensitivity analysis is presented utilizing the original protocol-defined **TOC window of 5 to 9 days post-treatment** and confirms that the non-inferiority of the primary endpoint is not sensitive to the change in the TOC window. (Refer to *Section 3.1, Table 3*)
- A sensitivity analysis is presented utilizing a definition for Microbiological Eradication that requires subjects to be free of new infection(s) to be considered successes and confirms that the non-inferiority in terms of the **primary endpoint without new infection** is still achieved. The success rates for both treatment groups using this endpoint are substantially lower than the success rates utilizing the sponsor's original definition of Microbiological Eradication. (Refer to *Section 3.1, Table 3*)
- A sensitivity analysis is presented including the patients with a **uropathogen that was not susceptible to the study drugs** who had previously been excluded and confirms that the non-inferiority in the primary endpoint is not sensitive to the inclusion/exclusion of subjects whose baseline pathogen was not susceptible to the study drugs. (Refer to *Section 3.1, Table 3*)
- Although the sponsor defines an intent-to-treat group and efficacy population which are the same as the reviewer's MITT and PP groups, for a given analysis of a particular endpoint at a particular time point the sponsor excluded subjects for whom that particular endpoint at that particular time point was missing. Reviews of similar products within the Division in the recent past have utilized consistent analysis groups for all endpoints and time points. In the opinion of this reviewer, this approach would likely provide a more appropriate and clear quantification of the data. This review includes development of the analysis groups based on the evaluable nature of the primary efficacy endpoint and for analyses of the secondary efficacy endpoints, the same patient groups are utilized by imputing the missing secondary endpoints as failures. One qualitative by-treatment group conclusion was changed from the sponsor's analyses as a result of utilizing **consistent analysis groups**. (Refer to *Section 3, Figure 1 and Table 2*)
- The reasons for a subject having missing microbiological data at TOC and thus being excluded from the PP group were not clearly summarized by the sponsor in the study report. Attempts to identify the **reason for a subject not having evaluable microbiological data at TOC** were made by this reviewer. (Refer to *Section 3, Figure 1*)

5.2 Conclusions and Recommendations

From a statistical perspective, the results of this study indicate that Proquin™ is non-inferior to Cipro® in terms of the following endpoints.

- Microbiological Eradication at the TOC Visit (primary efficacy endpoint)
- Clinical Outcome at the TOC Visit
- Microbiological Eradication at the Follow-Up Visit
- Clinical Outcome at the Follow-Up Visit

These results remain consistent across both the PP and mITT analysis groups. In addition, the conclusions for the primary endpoint results are not dependent on the use of the amended TOC window rather than the window defined in the original protocol or the requirement that baseline pathogens be susceptible to the study drugs. Although the non-inferiority criterion is satisfied when considering Microbiological Eradication **without new infection**, the success rates for both treatment groups using this endpoint are substantially lower than the success rates utilizing the sponsor's original definition of Microbiological Eradication.

Examination of the primary efficacy endpoint by age, race, and baseline pathogen did not reveal any problematic subgroup differences.

It is the opinion of this reviewer that Proquin™ 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. However, careful consideration should be given to the clinical importance of the method for classifying subjects with New Infections for the analysis of the Microbiological Eradication endpoint since the within treatment group success rates are substantially different depending on how subjects with New Infections are classified.

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