

Clinical Review
 Joette M. Meyer, Pharm.D.
 NDA 21-744
 Proquin XR™ (ciprofloxacin extended-release) tablets

TABLE 11
Adverse Events:
Non-Caucasian Patients in Clinical Studies 81-0005 and 81-0015

	Treatment Group		Total	p-value
	Ciprofloxacin	Ciprofloxacin		
	GR	IR		
Number of Patients Randomized in the Study	132	104	236	
Number (%) of Patients Received Treatment	129 (100%)	104 (100%)	233 (100%)	
Number (%) of Patients without Any Adverse Event in the Study	82 (63.6%)	64 (61.5%)	146 (62.7%)	
Number (%) of Patients with at Least One Adverse Event in the Study	47 (36.4%)	40 (38.5%)	87 (37.3%)	NS
<u>Number (%) of Patients Who Reported Adverse Events by System Organ Class</u>				
Ear and labyrinth disorders	0	2 (1.9%)	2 (0.9%)	NS
Vertigo	0	2 (1.9%)	2 (0.9%)	NS
Gastrointestinal disorders	6 (4.7%)	9 (8.7%)	15 (6.4%)	NS
Nausea / Nausea aggravated	1 (0.8%)	3 (2.9%)	4 (1.7%)	NS
Abdominal pain NOS	2 (1.6%)	1 (1.0%)	3 (1.3%)	NS
Abdominal distension	2 (1.6%)	0	2 (0.9%)	NS
Constipation	1 (0.8%)	1 (1.0%)	2 (0.9%)	NS
Vomiting NOS	0	2 (1.9%)	2 (0.9%)	NS
Abdominal pain lower	1 (0.8%)	0	1 (0.4%)	NS
Abdominal pain upper	0	1 (1.0%)	1 (0.4%)	NS
Abdominal tenderness	1 (0.8%)	0	1 (0.4%)	NS
Dyspepsia	0	1 (1.0%)	1 (0.4%)	NS
Flatulence	0	1 (1.0%)	1 (0.4%)	NS
Irritable bowel syndrome aggravated	1 (0.8%)	0	1 (0.4%)	NS
General disorders and administration site conditions	2 (1.6%)	1 (1.0%)	3 (1.3%)	NS
Pain NOS	1 (0.8%)	0	1 (0.4%)	NS
Rigors	0	1 (1.0%)	1 (0.4%)	NS
Tenderness NOS	1 (0.8%)	0	1 (0.4%)	NS
Immune system disorders	0	1 (1.0%)	1 (0.4%)	NS
Hypersensitivity NOS	0	1 (1.0%)	1 (0.4%)	NS
Infections and infestations	22 (17.1%)	14 (13.5%)	36 (15.5%)	NS
Urinary tract infection NOS	16 (12.4%)	7 (6.7%)	23 (9.9%)	NS
Sinusitis NOS	1 (0.8%)	4 (3.8%)	5 (2.1%)	NS
Upper respiratory tract infection NOS	1 (0.8%)	2 (1.9%)	3 (1.3%)	NS
Vaginitis bacterial NOS	1 (0.8%)	2 (1.9%)	3 (1.3%)	NS
Vaginosis fungal NOS	1 (0.8%)	2 (1.9%)	3 (1.3%)	NS

Note: Adverse event mapping was based on the MedDRA Version 5.1 thesaurus.

A patient may be reported in more than one category.

The p-values were obtained from the Fisher's Exact test and were presented if they are less than 0.10.

NS = Not statistically significant at 0.10 level.

Source: Table 34 in the applicant's submission dated May 4, 2005

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TABLE 11 (continued)
Adverse Events:
Non-Caucasian Patients in Clinical Studies 81-0005 and 81-0015

	Treatment Group		Total	p-value
	Ciprofloxacin	Ciprofloxacin		
	GR	IR		
Number (%) of Patients Received Treatment	129 (100%)	104 (100%)	233 (100%)	
<u>Number (%) of Patients Who Reported Adverse Events by System Organ Class</u>				
Infections and infestations (Continued)				
Escherichia infection NOS	2 (1.6%)	0	2 (0.9%)	NS
Influenza	0	1 (1.0%)	1 (0.4%)	NS
Otitis media NOS	0	1 (1.0%)	1 (0.4%)	NS
Pyelonephritis NOS	1 (0.8%)	0	1 (0.4%)	NS
Vaginal candidiasis	1 (0.8%)	0	1 (0.4%)	NS
Injury, poisoning and procedural complications				
Alcohol poisoning	0	1 (1.0%)	1 (0.4%)	NS
Muscle strain	1 (0.8%)	0	1 (0.4%)	NS
Periorbital haematoma	0	1 (1.0%)	1 (0.4%)	NS
Investigations				
Alanine aminotransferase increased	1 (0.8%)	0	1 (0.4%)	NS
Aspartate aminotransferase increased	1 (0.8%)	0	1 (0.4%)	NS
Blood potassium increased	0	1 (1.0%)	1 (0.4%)	NS
Gamma-glutamyltransferase increased	0	1 (1.0%)	1 (0.4%)	NS
White blood cell count decreased	0	1 (1.0%)	1 (0.4%)	NS
Metabolism and nutrition disorders				
Hypercalcaemia	0	4 (3.8%)	4 (1.7%)	0.038
Hyperglycaemia NOS	0	1 (1.0%)	1 (0.4%)	NS
Hyperlipidaemia NOS	0	1 (1.0%)	1 (0.4%)	NS
Hypernatraemia	0	1 (1.0%)	1 (0.4%)	NS
Musculoskeletal and connective tissue disorders				
Back pain	7 (5.4%)	6 (5.8%)	13 (5.6%)	NS
Arthralgia	3 (2.3%)	2 (1.9%)	5 (2.1%)	NS
Flank pain	1 (0.8%)	1 (1.0%)	2 (0.9%)	NS
Muscle spasms	1 (0.8%)	0	2 (0.9%)	NS
Musculoskeletal stiffness	1 (0.8%)	0	1 (0.4%)	NS
Neck pain	1 (0.8%)	1 (1.0%)	1 (0.4%)	NS

Note: Adverse event mapping was based on the MedDRA Version 5.1 thesaurus.
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TABLE 11 (continued)
Adverse Events:
Non-Caucasian Patients in Clinical Studies 81-0005 and 81-0015

	Treatment Group		Total	p-value
	Ciprofloxacin	Ciprofloxacin		
	GR	IR		
Number (%) of Patients Received Treatment	129 (100%)	104 (100%)	233 (100%)	
<u>Number (%) of Patients Who Reported Adverse Events by System Organ Class</u>				
Musculoskeletal and connective tissue disorders (Continued)				
Pain in jaw	0	1 (1.0%)	1 (0.4%)	NS
Pain in limb	1 (0.8%)	0	1 (0.4%)	NS
Nervous system disorders	3 (2.3%)	8 (7.7%)	11 (4.7%)	0.067
Headache	3 (2.3%)	5 (4.8%)	8 (3.4%)	NS
Dizziness	0	1 (1.0%)	1 (0.4%)	NS
Migraine NOS	0	1 (1.0%)	1 (0.4%)	NS
Sciatica	0	1 (1.0%)	1 (0.4%)	NS
Tension headaches	0	1 (1.0%)	1 (0.4%)	NS
Psychiatric disorders	0	4 (3.8%)	4 (1.7%)	0.038
Anxiety	0	2 (1.9%)	2 (0.9%)	NS
Insomnia	0	1 (1.0%)	1 (0.4%)	NS
Panic attack	0	1 (1.0%)	1 (0.4%)	NS
Renal and urinary disorders	9 (7.0%)	3 (2.9%)	12 (5.2%)	NS
Micturition urgency	3 (2.3%)	1 (1.0%)	4 (1.7%)	NS
Haematuria	2 (1.6%)	0	2 (0.9%)	NS
Chromaturia	1 (0.8%)	0	1 (0.4%)	NS
Cystitis NOS	1 (0.8%)	0	1 (0.4%)	NS
Cystitis interstitial	0	1 (1.0%)	1 (0.4%)	NS
Urethral spasm	1 (0.8%)	0	1 (0.4%)	NS
Urinary frequency	1 (0.8%)	0	1 (0.4%)	NS
Urine odour abnormal	0	1 (1.0%)	1 (0.4%)	NS
Reproductive system and breast disorders	2 (1.6%)	3 (2.9%)	5 (2.1%)	NS
Vaginal discharge	2 (1.6%)	1 (1.0%)	3 (1.3%)	NS
Amenorrhoea NOS	0	1 (1.0%)	1 (0.4%)	NS
Menstruation irregular	0	1 (1.0%)	1 (0.4%)	NS

Note: Adverse event mapping was based on the MedDRA Version 5.1 thesaurus.

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NS = Not statistically significant at 0.10 level.

Source: Table 34 in the applicant's submission dated May 4, 2005

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TABLE 11 (continued)
Adverse Events:
Non-Caucasian Patients in Clinical Studies 81-0005 and 81-0015

	Treatment Group		Total	p-value
	Ciprofloxacin	Ciprofloxacin		
	GR	IR		
Number (%) of Patients Received Treatment	129 (100%)	104 (100%)	233 (100%)	
<u>Number (%) of Patients Who Reported Adverse Events by System Organ Class</u>				
Respiratory, thoracic and mediastinal disorders	10 (7.8%)	8 (7.7%)	18 (7.7%)	NS
Nasopharyngitis	4 (3.1%)	2 (1.9%)	6 (2.6%)	NS
Pharyngitis	2 (1.6%)	2 (1.9%)	4 (1.7%)	NS
Bronchitis NOS	0	3 (2.9%)	3 (1.3%)	0.088
Cough	2 (1.6%)	1 (1.0%)	3 (1.3%)	NS
Nasal congestion	2 (1.6%)	0	2 (0.9%)	NS
Rhinitis allergic NOS	1 (0.8%)	1 (1.0%)	2 (0.9%)	NS
Allergic sinusitis	0	1 (1.0%)	1 (0.4%)	NS
Skin and subcutaneous tissue disorders	6 (4.7%)	0	6 (2.6%)	0.035
Urticaria NOS	2 (1.6%)	0	2 (0.9%)	NS
Contusion	1 (0.8%)	0	1 (0.4%)	NS
Erythema	1 (0.8%)	0	1 (0.4%)	NS
Pruritus	1 (0.8%)	0	1 (0.4%)	NS
Rash NOS	1 (0.8%)	0	1 (0.4%)	NS
Swelling face	1 (0.8%)	0	1 (0.4%)	NS
Vascular disorders	1 (0.8%)	1 (1.0%)	2 (0.9%)	NS
Hot flushes NOS	1 (0.8%)	0	1 (0.4%)	NS
Hypertension aggravated	0	1 (1.0%)	1 (0.4%)	NS

Note: Adverse event mapping was based on the MedDRA Version 5.1 thesaurus.

A patient may be reported in more than one category.

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Source: Table 34 in the applicant's submission dated May 4, 2005

7.1.5 Common Adverse Events

One or more treatment-emergent AEs during the 5-week study period occurred in 230 (42.0%) patients in the Proquin XR group and 231 (42.9%) patients in the Cipro IR group, as shown in Table 12.

The incidence of common adverse events (reported for at least 1% of patients treated with Proquin XR) is: fungal infection (2.6%), nasopharyngitis (2.6%), headache (2.4%), micturition urgency (2.0%), abdominal pain (1.6%), back pain (1.6%), dysuria (1.6%), upper respiratory tract infection (1.6%), suprapubic pain (1.5%), nausea (1.3%), pharyngitis (1.3%), urinary frequency (1.3%), hematuria (1.1%), dizziness (1.1%), nasal congestion (1.1%), and vaginosis fungal (1.1%).

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There was no significant difference between treatment groups for the proportion of patients with AEs. The types of AEs were generally similar for the two treatment groups. However, the applicant notes that the proportion of patients with diarrhea was significantly lower in the Proquin XR group (2/547, 0.4%) than in the Cipro IR group (10/538, 1.9%) ($p=0.021$). The proportion of patients with nausea/nausea aggravated was lower, but not statistically different, in the Proquin XR group (7/547, 1.3%) than in the Cipro IR group (15/538, 2.8%) ($p=0.088$).

Clinical Reviewer's Comment: Although the incidence of diarrhea and nausea were numerically lower in the Proquin XR group, the incidence of all gastrointestinal adverse events was not significantly different in the Proquin XR group (6.2%) compared to the Cipro IR group (8.9%), nor was the incidence of adverse events overall (42% and 42.9%, respectively). The rate of discontinuations due to adverse events was also higher in the Proquin XR group (1.3%) compared to the Cipro IR group (0.6%). Finally, the incidence of renal and urinary disorders (Proquin XR 6.4%; Cipro IR 2.8%) and dysuria (Proquin XR 1.6%; Cipro IR 0.2%) were higher in the Proquin XR group than in the Cipro IR group ($p=0.006$ and $p=0.021$, respectively). The higher incidence of urinary adverse events may signify lower efficacy in the Proquin XR group.

Therefore, the Reviewer does not feel that the "gastric retentive" formulation of the Proquin XR tablet is responsible for less clinically relevant gastrointestinal adverse events

(See Section 8.1: "Dosing Regimen and Administration" and Section 9.4: "Labeling Review").

**APPEARS THIS WAY
ON ORIGINAL**

Clinical Review
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TABLE 12
Adverse Events Occurring During the Study
Safety Population of Clinical Studies 81-0005 and 81-0015

	Treatment Group		Total	p-value
	Ciprofloxacin GR	Ciprofloxacin IR		
Number of Patients Randomized in the Study	553	542	1095	
Number (%) of Patients Received Treatment	547 (100%)	538 (100%)	1085 (100%)	
Number (%) of Patients without Any Adverse Event in the Study	317 (58.0%)	307 (57.1%)	624 (57.5%)	
Number (%) of Patients with at Least One Adverse Event in the Study	230 (42.0%)	231 (42.9%)	461 (42.5%)	NS
<u>Number (%) of Patients Who Reported Adverse Events by System Organ Class</u>				
Blood and lymphatic system disorders	4 (0.7%)	3 (0.6%)	7 (0.6%)	NS
Lymphadenopathy	3 (0.5%)	1 (0.2%)	4 (0.4%)	NS
Leukopenia NOS	0	2 (0.4%)	2 (0.2%)	NS
Anaemia NOS	1 (0.2%)	0	1 (0.1%)	NS
Cardiac disorders	1 (0.2%)	0	1 (0.1%)	NS
Ventricular bigeminy	1 (0.2%)	0	1 (0.1%)	NS
Ear and labyrinth disorders	3 (0.5%)	5 (0.9%)	8 (0.7%)	NS
Ear pain	0	2 (0.4%)	2 (0.2%)	NS
Fluid in middle ear	2 (0.4%)	0	2 (0.2%)	NS
Vertigo	0	2 (0.4%)	2 (0.2%)	NS
Cerumen impaction	1 (0.2%)	0	1 (0.1%)	NS
Deafness NOS	0	1 (0.2%)	1 (0.1%)	NS
Endocrine disorders	1 (0.2%)	0	1 (0.1%)	NS
Goitre	1 (0.2%)	0	1 (0.1%)	NS
Eye disorders	0	3 (0.6%)	3 (0.3%)	NS
Conjunctivitis	0	2 (0.4%)	2 (0.2%)	NS
Eye swelling	0	1 (0.2%)	1 (0.1%)	NS
Vision blurred	0	1 (0.2%)	1 (0.1%)	NS
Gastrointestinal disorders	34 (6.2%)	48 (8.9%)	82 (7.6%)	NS
Nausea	7 (1.3%)	14 (2.6%)	21 (1.9%)	NS
Abdominal pain NOS	9 (1.6%)	6 (1.1%)	15 (1.4%)	NS
Diarhoea NOS	2 (0.4%)	10 (1.9%)	12 (1.1%)	0.021
Abdominal pain lower	1 (0.2%)	4 (0.7%)	5 (0.5%)	NS
Dyspepsia	2 (0.4%)	3 (0.6%)	5 (0.5%)	NS
Abdominal pain upper	1 (0.2%)	3 (0.6%)	4 (0.4%)	NS

Note: Adverse event mapping was based on the MedDRA Version 5.1 thesaurus.

A patient may be reported in more than one category.

Source: Table 11 in the applicant's Summary of Clinical Safety in the NDA submission

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TABLE 12 (continued)
Adverse Events Occurring During the Study
Safety Population of Clinical Studies 81-0005 and 81-0015

	Treatment Group		Total	p-value
	Ciprofloxacin GR	Ciprofloxacin IR		
Number (%) of Patients Received Treatment	547 (100%)	538 (100%)	1085 (100%)	
<u>Number (%) of Patients Who Reported Adverse Events by System Organ Class</u>				
<u>Gastrointestinal disorders (Continued)</u>				
Constipation	2 (0.4%)	2 (0.4%)	4 (0.4%)	NS
Abdominal tenderness	3 (0.5%)	0	3 (0.3%)	NS
Gastroesophageal reflux disease	2 (0.4%)	1 (0.2%)	3 (0.3%)	NS
Vomiting NOS	1 (0.2%)	2 (0.4%)	3 (0.3%)	NS
Abdominal distension	2 (0.4%)	0	2 (0.2%)	NS
Flatulence	0	2 (0.4%)	2 (0.2%)	NS
Haemorrhoids	1 (0.2%)	1 (0.2%)	2 (0.2%)	NS
Intractable bowel syndrome aggravated	2 (0.4%)	0	2 (0.2%)	NS
Abdominal discomfort	1 (0.2%)	0	1 (0.1%)	NS
Anal discomfort	0	1 (0.2%)	1 (0.1%)	NS
Diverticulum NOS	1 (0.2%)	0	1 (0.1%)	NS
Gastritis NOS	1 (0.2%)	0	1 (0.1%)	NS
Gastroenteritis NOS	1 (0.2%)	0	1 (0.1%)	NS
Gingivitis	0	1 (0.2%)	1 (0.1%)	NS
Haemorrhoidal haemorrhage	1 (0.2%)	0	1 (0.1%)	NS
Intestinal obstruction NOS	0	1 (0.2%)	1 (0.1%)	NS
Lip ulceration	0	1 (0.2%)	1 (0.1%)	NS
Melaena	1 (0.2%)	0	1 (0.1%)	NS
Nausea aggravated	0	1 (0.2%)	1 (0.1%)	NS
Oesophageal spasm	1 (0.2%)	0	1 (0.1%)	NS
Oral mucosal discolouration	1 (0.2%)	0	1 (0.1%)	NS
Pruritus ani	0	1 (0.2%)	1 (0.1%)	NS
Rectal discharge	0	1 (0.2%)	1 (0.1%)	NS
Toothache	0	1 (0.2%)	1 (0.1%)	NS
<u>General disorders and administration site conditions</u>				
Suprapubic pain	8 (1.5%)	4 (0.7%)	12 (1.1%)	NS
Chest pain	3 (0.5%)	5 (0.9%)	8 (0.7%)	NS
Fatigue	3 (0.5%)	4 (0.7%)	7 (0.6%)	NS
Pyrexia	3 (0.5%)	3 (0.6%)	6 (0.6%)	NS
Pain NOS	3 (0.5%)	2 (0.4%)	5 (0.5%)	NS

Note: Adverse event mapping was based on the MedDRA Version 5.1 thesaurus.

A patient may be reported in more than one category.

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TABLE 12 (continued)
Adverse Events Occurring During the Study
Safety Population of Clinical Studies 81-0005 and 81-0015

	Treatment Group		Total	p-value
	Ciprofloxacin GR	Ciprofloxacin IR		
Number (%) of Patients Received Treatment	547 (100%)	538 (100%)	1085 (100%)	
<u>Number (%) of Patients Who Reported Adverse Events by System Organ Class</u>				
General disorders and administration site conditions (Continued)				
Rigors	1 (0.2%)	2 (0.4%)	3 (0.3%)	NS
Asthenia	1 (0.2%)	0	1 (0.1%)	NS
Axillary pain	1 (0.2%)	0	1 (0.1%)	NS
Discomfort NOS	0	1 (0.2%)	1 (0.1%)	NS
Feeling cold	0	1 (0.2%)	1 (0.1%)	NS
Feeling hot	0	1 (0.2%)	1 (0.1%)	NS
Inflammation NOS	0	1 (0.2%)	1 (0.1%)	NS
Lethargy	1 (0.2%)	0	1 (0.1%)	NS
Malaise	0	1 (0.2%)	1 (0.1%)	NS
Oedema peripheral	0	1 (0.2%)	1 (0.1%)	NS
Tenderness NOS	1 (0.2%)	0	1 (0.1%)	NS
Thirst	1 (0.2%)	0	1 (0.1%)	NS
Hepatobiliary disorders	1 (0.2%)	1 (0.2%)	2 (0.2%)	NS
Cholelithiasis	1 (0.2%)	1 (0.2%)	2 (0.2%)	NS
Immune system disorders	2 (0.4%)	6 (1.1%)	8 (0.7%)	NS
Seasonal allergy	0	3 (0.6%)	3 (0.3%)	NS
Drug hypersensitivity	0	2 (0.4%)	2 (0.2%)	NS
Hypersensitivity NOS	1 (0.2%)	1 (0.2%)	2 (0.2%)	NS
Allergy to arthropod sting	1 (0.2%)	0	1 (0.1%)	NS
Infections and infestations	106 (19.4%)	107 (19.9%)	213 (19.6%)	NS
Urinary tract infection NOS	59 (10.8%)	55 (10.2%)	114 (10.5%)	NS
Upper respiratory tract infection NOS	9 (1.6%)	17 (3.2%)	26 (2.4%)	NS
Fungal infection NOS	14 (2.6%)	10 (1.9%)	24 (2.2%)	NS
Vaginosis fungal NOS	6 (1.1%)	11 (2.0%)	17 (1.6%)	NS
Syngnitis NOS	4 (0.7%)	8 (1.5%)	12 (1.1%)	NS
Vaginitis bacterial NOS	3 (0.5%)	4 (0.7%)	7 (0.6%)	NS
Vaginal candidiasis	2 (0.4%)	3 (0.6%)	5 (0.5%)	NS
Gastroenteritis viral NOS	2 (0.4%)	2 (0.4%)	4 (0.4%)	NS

Note: Adverse event mapping was based on the MedDRA Version 5.1 thesaurus.

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TABLE 12 (continued)
Adverse Events Occurring During the Study
Safety Population of Clinical Studies 81-0005 and 81-0015

	Treatment Group		Total	p-value
	Ciprofloxacin GR	Ciprofloxacin IR		
Number (%) of Patients Received Treatment	547 (100%)	538 (100%)	1085 (100%)	
<u>Number (%) of Patients Who Reported Adverse Events by System Organ Class</u>				
<u>Infections and infestations (Continued)</u>				
Herpes simplex	1 (0.2%)	3 (0.6%)	4 (0.4%)	NS
Tooth abscess	1 (0.2%)	3 (0.6%)	4 (0.4%)	NS
Beta haemolytic streptococcal infection	2 (0.4%)	1 (0.2%)	3 (0.3%)	NS
Pyelonephritis NOS	1 (0.2%)	2 (0.4%)	3 (0.3%)	NS
Vaginal infection NOS	2 (0.4%)	1 (0.2%)	3 (0.3%)	NS
Vaginitis	1 (0.2%)	2 (0.4%)	3 (0.3%)	NS
Candidal infection NOS	0	2 (0.4%)	2 (0.2%)	NS
Escherichia infection NOS	2 (0.4%)	0	2 (0.2%)	NS
Influenza	1 (0.2%)	1 (0.2%)	2 (0.2%)	NS
Otitis media NOS	1 (0.2%)	1 (0.2%)	2 (0.2%)	NS
Klebsiella infection NOS	1 (0.2%)	0	1 (0.1%)	NS
Lyme disease	0	1 (0.2%)	1 (0.1%)	NS
Oral candidiasis	1 (0.2%)	0	1 (0.1%)	NS
Otitis externa NOS	0	1 (0.2%)	1 (0.1%)	NS
Otitis media serous acute NOS	0	1 (0.2%)	1 (0.1%)	NS
Pharyngitis streptococcal	1 (0.2%)	0	1 (0.1%)	NS
Pharyngitis viral NOS	0	1 (0.2%)	1 (0.1%)	NS
Pharyngotonsillitis	1 (0.2%)	0	1 (0.1%)	NS
Pneumonia NOS	1 (0.2%)	0	1 (0.1%)	NS
Streptococcal infection NOS	1 (0.2%)	0	1 (0.1%)	NS
Upper respiratory tract infection viral NOS	1 (0.2%)	0	1 (0.1%)	NS
Viral infection NOS	1 (0.2%)	0	1 (0.1%)	NS
<u>Injury, poisoning and procedural complications</u>				
Muscle strain	5 (0.9%)	8 (1.5%)	13 (1.2%)	NS
Thermal burn	2 (0.4%)	2 (0.4%)	4 (0.4%)	NS
Thermal burn	0	2 (0.4%)	2 (0.2%)	NS
Abrasion NOS	1 (0.2%)	0	1 (0.1%)	NS
Alcohol poisoning	0	1 (0.2%)	1 (0.1%)	NS
Arthropod bite	0	1 (0.2%)	1 (0.1%)	NS
Heat exhaustion	1 (0.2%)	0	1 (0.1%)	NS
Joint sprain	0	1 (0.2%)	1 (0.1%)	NS

Note: Adverse event mapping was based on the MedDRA Version 5.1 thesaurus.

A patient may be reported in more than one category.

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 Proquin XR™ (ciprofloxacin extended-release) tablets

TABLE 12 (continued)
Adverse Events Occurring During the Study
Safety Population of Clinical Studies 81-0005 and 81-0015

	Treatment Group		Total	p-value
	Ciprofloxacin GR	Ciprofloxacin IR		
Number (%) of Patients Received Treatment	547 (100%)	538 (100%)	1085 (100%)	
<u>Number (%) of Patients Who Reported Adverse Events by System Organ Class</u>				
<u>Injury, poisoning and procedural complications</u> (Continued)				
Periorbital haematoma	0	1 (0.2%)	1 (0.1%)	NS
Skin laceration	1 (0.2%)	0	1 (0.1%)	NS
<u>Investigations</u>				
Gamma-glutamyltransferase increased	7 (1.3%)	8 (1.5%)	15 (1.4%)	NS
Blood bilirubin increased	0	4 (0.7%)	4 (0.4%)	0.060
Blood potassium increased	3 (0.5%)	0	3 (0.3%)	NS
Alanine aminotransferase increased	0	3 (0.6%)	3 (0.3%)	NS
Abdominal aortic bruit	2 (0.4%)	0	2 (0.2%)	NS
Aspartate aminotransferase increased	1 (0.2%)	0	1 (0.1%)	NS
Body temperature increased	1 (0.2%)	0	1 (0.1%)	NS
Culture urine positive	1 (0.2%)	0	1 (0.1%)	NS
Haematocrit decreased	0	1 (0.2%)	1 (0.1%)	NS
Haemoglobin decreased	0	1 (0.2%)	1 (0.1%)	NS
Platelet count decreased	1 (0.2%)	0	1 (0.1%)	NS
Red blood cell count decreased	0	1 (0.2%)	1 (0.1%)	NS
White blood cell count decreased	0	1 (0.2%)	1 (0.1%)	NS
<u>Metabolism and nutrition disorders</u>				
Anorexia	1 (0.2%)	5 (0.9%)	6 (0.6%)	NS
Appetite increased NOS	1 (0.2%)	0	1 (0.1%)	NS
Hypercalcaemia	0	1 (0.2%)	1 (0.1%)	NS
Hyperglycaemia NOS	0	1 (0.2%)	1 (0.1%)	NS
Hyperlipidaemia NOS	0	1 (0.2%)	1 (0.1%)	NS
Hypematraemia	0	1 (0.2%)	1 (0.1%)	NS
<u>Musculoskeletal and connective tissue disorders</u>				
Back pain	21 (3.8%)	23 (4.3%)	44 (4.1%)	NS
Arthralgia	9 (1.6%)	9 (1.7%)	18 (1.7%)	NS
Flank pain	2 (0.4%)	2 (0.4%)	4 (0.4%)	NS
Joint swelling	1 (0.2%)	2 (0.4%)	3 (0.3%)	NS

Note: Adverse event mapping was based on the MedDRA Version 5.1 thesaurus.

A patient may be reported in more than one category.

Source: Table 11 in the applicant's Summary of Clinical Safety in the NDA submission

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TABLE 12 (continued)
Adverse Events Occurring During the Study
Safety Population of Clinical Studies 81-0005 and 81-0015

	Treatment Group		Total	p-value
	Ciprofloxacin GR	Ciprofloxacin IR		
Number (%) of Patients Received Treatment	547 (100%)	538 (100%)	1085 (100%)	
<u>Number (%) of Patients Who Reported Adverse Events by System Organ Class</u>				
Musculoskeletal and connective tissue disorders (Continued)				
Chest wall pain	1 (0.2%)	1 (0.2%)	2 (0.2%)	NS
Myalgia	1 (0.2%)	1 (0.2%)	2 (0.2%)	NS
Pain in limb	2 (0.4%)	0	2 (0.2%)	NS
Back pain aggravated	1 (0.2%)	0	1 (0.1%)	NS
Bursitis	0	1 (0.2%)	1 (0.1%)	NS
Costochondritis	0	1 (0.2%)	1 (0.1%)	NS
Facial pain	1 (0.2%)	0	1 (0.1%)	NS
Groin pain	0	1 (0.2%)	1 (0.1%)	NS
Muscle cramp	0	1 (0.2%)	1 (0.1%)	NS
Muscle spasms	1 (0.2%)	0	1 (0.1%)	NS
Musculoskeletal stiffness	0	1 (0.2%)	1 (0.1%)	NS
Neck pain	1 (0.2%)	0	1 (0.1%)	NS
Night cramps	1 (0.2%)	0	1 (0.1%)	NS
Pain in jaw	0	1 (0.2%)	1 (0.1%)	NS
Scoliosis	1 (0.2%)	0	1 (0.1%)	NS
Spinal osteoarthritis	0	1 (0.2%)	1 (0.1%)	NS
Tendonitis	0	1 (0.2%)	1 (0.1%)	NS
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	2 (0.4%)	0	2 (0.2%)	NS
Non-Hodgkin's lymphoma NOS	1 (0.2%)	0	1 (0.1%)	NS
Papillary thyroid cancer	1 (0.2%)	0	1 (0.1%)	NS
Nervous system disorders	23 (4.2%)	33 (6.1%)	56 (5.2%)	NS
Headache	13 (2.4%)	21 (3.9%)	34 (3.1%)	NS
Dizziness	6 (1.1%)	4 (0.7%)	10 (0.9%)	NS
Migraine NOS	2 (0.4%)	1 (0.2%)	3 (0.3%)	NS
Dysgeusia	0	2 (0.4%)	2 (0.2%)	NS
Sciatica	1 (0.2%)	1 (0.2%)	2 (0.2%)	NS
Syncope	0	2 (0.4%)	2 (0.2%)	NS
Tension headaches	0	2 (0.4%)	2 (0.2%)	NS
Disturbance in attention	1 (0.2%)	0	1 (0.1%)	NS

Note: Adverse event mapping was based on the MedDRA Version 5.1 thesaurus.

A patient may be reported in more than one category.

Source: Table 11 in the applicant's Summary of Clinical Safety in the NDA submission

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TABLE 12 (continued)
Adverse Events Occurring During the Study
Safety Population of Clinical Studies 81-0005 and 81-0015

	Treatment Group		Total	p-value
	Ciprofloxacin GR	Ciprofloxacin IR		
Number (%) of Patients Received Treatment	547 (100%)	538 (100%)	1085 (100%)	
<u>Number (%) of Patients Who Reported Adverse Events by System Organ Class</u>				
Nervous system disorders (Continued)				
Hypoaesthesia	0	1 (0.2%)	1 (0.1%)	NS
Paraesthesia	1 (0.2%)	0	1 (0.1%)	NS
Radiculopathy NOS	1 (0.2%)	0	1 (0.1%)	NS
Sinus headache	1 (0.2%)	0	1 (0.1%)	NS
Pregnancy, puerperium and perinatal conditions	1 (0.2%)	0	1 (0.1%)	NS
Pregnancy NOS	1 (0.2%)	0	1 (0.1%)	NS
Psychiatric disorders	1 (0.2%)	10 (1.9%)	11 (1.0%)	0.006
Insomnia	0	3 (0.6%)	3 (0.3%)	NS
Anxiety	0	2 (0.4%)	2 (0.2%)	NS
Depression	0	2 (0.4%)	2 (0.2%)	NS
Depression aggravated	0	1 (0.2%)	1 (0.1%)	NS
Disorientation	0	1 (0.2%)	1 (0.1%)	NS
Mood swings	1 (0.2%)	0	1 (0.1%)	NS
Panic attack	0	1 (0.2%)	1 (0.1%)	NS
Renal and urinary disorders	35 (6.4%)	15 (2.8%)	50 (4.6%)	0.006
Micturition urgency	11 (2.0%)	5 (0.9%)	16 (1.5%)	NS
Urinary frequency	7 (1.3%)	5 (0.9%)	12 (1.1%)	NS
Dysuria	9 (1.6%)	1 (0.2%)	10 (0.9%)	0.021
Haematuria	6 (1.1%)	1 (0.2%)	7 (0.6%)	NS
Cystitis NOS	3 (0.5%)	1 (0.2%)	4 (0.4%)	NS
Nephrolithiasis	2 (0.4%)	1 (0.2%)	3 (0.3%)	NS
Urine odour abnormal	1 (0.2%)	2 (0.4%)	3 (0.3%)	NS
Chromaturia	2 (0.4%)	0	2 (0.2%)	NS
Bladder pain	1 (0.2%)	0	1 (0.1%)	NS
Bladder spasm	0	1 (0.2%)	1 (0.1%)	NS
Costovertebral angle tenderness	1 (0.2%)	0	1 (0.1%)	NS
Cystitis interstitial	0	1 (0.2%)	1 (0.1%)	NS
Cystocele	1 (0.2%)	0	1 (0.1%)	NS

Note: Adverse event mapping was based on the MedDRA Version 5.1 thesaurus.

A patient may be reported in more than one category.

Source: Table 11 in the applicant's Summary of Clinical Safety in the NDA submission

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TABLE 12 (continued)
Adverse Events Occurring During the Study
Safety Population of Clinical Studies 81-0005 and 81-0015

	Treatment Group		Total	p-value
	Ciprofloxacin GR	Ciprofloxacin IR		
Number (%) of Patients Received Treatment	547 (100%)	538 (100%)	1085 (100%)	
<u>Number (%) of Patients Who Reported Adverse Events by System Organ Class</u>				
Renal and urinary disorders (Continued)				
Incontinence NOS	1 (0.2%)	0	1 (0.1%)	NS
Urethral cyst	1 (0.2%)	0	1 (0.1%)	NS
Urethral pain	1 (0.2%)	0	1 (0.1%)	NS
Urethral spasm	1 (0.2%)	0	1 (0.1%)	NS
Urethral syndrome	0	1 (0.2%)	1 (0.1%)	NS
Reproductive system and breast disorders				
Genital pruritus female	2 (0.4%)	4 (0.7%)	6 (0.6%)	NS
Ovarian cyst	1 (0.2%)	3 (0.6%)	4 (0.4%)	NS
Vaginal discharge	3 (0.5%)	1 (0.2%)	4 (0.4%)	NS
Adnexa uteri pain	0	2 (0.4%)	2 (0.2%)	NS
Dysmenorrhoea	2 (0.4%)	0	2 (0.2%)	NS
Vaginal burning sensation	0	2 (0.4%)	2 (0.2%)	NS
Vaginal haemorrhage	2 (0.4%)	0	2 (0.2%)	NS
Amenorrhoea NOS	0	1 (0.2%)	1 (0.1%)	NS
Dyspareunia NOS	1 (0.2%)	0	1 (0.1%)	NS
Endometrial hypertrophy	1 (0.2%)	0	1 (0.1%)	NS
Menstruation irregular	0	1 (0.2%)	1 (0.1%)	NS
Metrorrhagia	1 (0.2%)	0	1 (0.1%)	NS
Pelvic pain NOS	0	1 (0.2%)	1 (0.1%)	NS
Uterine pain	1 (0.2%)	0	1 (0.1%)	NS
Vaginal disorder NOS	1 (0.2%)	0	1 (0.1%)	NS
Vaginal irritation	1 (0.2%)	0	1 (0.1%)	NS
Vulvovaginal dryness	1 (0.2%)	0	1 (0.1%)	NS
Respiratory, thoracic and mediastinal disorders				
Nasopharyngitis	14 (2.6%)	7 (1.3%)	21 (1.9%)	NS
Pharyngitis	7 (1.3%)	6 (1.1%)	13 (1.2%)	NS
Nasal congestion	6 (1.1%)	1 (0.2%)	7 (0.6%)	NS
Bronchitis NOS	1 (0.2%)	5 (0.9%)	6 (0.6%)	NS
Cough	2 (0.4%)	4 (0.7%)	6 (0.6%)	NS

Note: Adverse event mapping was based on the MedDRA Version 5.1 thesaurus.

A patient may be reported in more than one category.

Source: Table 11 in the applicant's Summary of Clinical Safety in the NDA submission

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TABLE 12 (continued)
Adverse Events Occurring During the Study
Safety Population of Clinical Studies 81-0005 and 81-0015

	Treatment Group		Total	p-value
	Ciprofloxacin GR	Ciprofloxacin IR		
Number (%) of Patients Received Treatment	547 (100%)	538 (100%)	1085 (100%)	
<u>Number (%) of Patients Who Reported Adverse Events by System Organ Class</u>				
Respiratory, thoracic and mediastinal disorders (Continued)				
Dyspnoea NOS	1 (0.2%)	2 (0.4%)	3 (0.3%)	NS
Rhinitis allergic NOS	2 (0.4%)	1 (0.2%)	3 (0.3%)	NS
Sinus congestion	2 (0.4%)	1 (0.2%)	3 (0.3%)	NS
Postnasal drip	1 (0.2%)	1 (0.2%)	2 (0.2%)	NS
Rhinitis seasonal	2 (0.4%)	0	2 (0.2%)	NS
Rhinorrhoea	2 (0.4%)	0	2 (0.2%)	NS
Allergic sinusitis	0	1 (0.2%)	1 (0.1%)	NS
Emphysema	0	1 (0.2%)	1 (0.1%)	NS
Epistaxis	1 (0.2%)	0	1 (0.1%)	NS
Haemoptysis	0	1 (0.2%)	1 (0.1%)	NS
Laryngitis NOS	1 (0.2%)	0	1 (0.1%)	NS
Pleurisy	0	1 (0.2%)	1 (0.1%)	NS
Pleuritic pain	0	1 (0.2%)	1 (0.1%)	NS
Rhonchi	1 (0.2%)	0	1 (0.1%)	NS
Sinus pain	1 (0.2%)	0	1 (0.1%)	NS
Wheezing	1 (0.2%)	0	1 (0.1%)	NS
Skin and subcutaneous tissue disorders				
Rash NOS	3 (0.5%)	2 (0.4%)	5 (0.5%)	NS
Confusion	3 (0.5%)	1 (0.2%)	4 (0.4%)	NS
Erythema	1 (0.2%)	2 (0.4%)	3 (0.3%)	NS
Acne NOS	1 (0.2%)	1 (0.2%)	2 (0.2%)	NS
Pruritus	2 (0.4%)	0	2 (0.2%)	NS
Urticaria NOS	2 (0.4%)	0	2 (0.2%)	NS
Dermatitis contact	0	1 (0.2%)	1 (0.1%)	NS
Eczema	1 (0.2%)	0	1 (0.1%)	NS
Parapsoriasis	0	1 (0.2%)	1 (0.1%)	NS
Rash maculo-papular	0	1 (0.2%)	1 (0.1%)	NS
Sweating increased	0	1 (0.2%)	1 (0.1%)	NS
Swelling face	1 (0.2%)	0	1 (0.1%)	NS

Note: Adverse event mapping was based on the MedDRA Version 5.1 thesaurus.

A patient may be reported in more than one category.

Source: Table 11 in the applicant's Summary of Clinical Safety in the NDA submission

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TABLE 12 (continued)
Adverse Events Occurring During the Study
Safety Population of Clinical Studies 81-0005 and 81-0015

	Treatment Group		Total	p-value
	Ciprofloxacin GR	Ciprofloxacin IR		
Number (%) of Patients Received Treatment	547 (100%)	538 (100%)	1085 (100%)	
<u>Number (%) of Patients Who Reported Adverse Events by System Organ Class</u>				
Surgical and medical procedures	1 (0.2%)	0	1 (0.1%)	NS
Nasal cyst removal	1 (0.2%)	0	1 (0.1%)	NS
Vascular disorders	1 (0.2%)	5 (0.9%)	6 (0.6%)	NS
Hot flashes NOS	1 (0.2%)	1 (0.2%)	2 (0.2%)	NS
Hypertension aggravated	0	2 (0.4%)	2 (0.2%)	NS
Aortic aneurysm	0	1 (0.2%)	1 (0.1%)	NS
Hypertension NOS	0	1 (0.2%)	1 (0.1%)	NS

Note: Adverse event mapping was based on the MedDRA Version 5.1 thesaurus.

A patient may be reported in more than one category.

Source: Table 11 in the applicant's Summary of Clinical Safety in the NDA submission

7.1.6 Treatment Related Adverse Events

The incidence of adverse events, judged by investigators to be at least possibly drug-related, occurring any time during the study in at least 1% of Proquin XR-treated patients was fungal infection (1.6%).

7.1.7 Laboratory Findings

Within each of the Phase II and Phase III studies, all clinical laboratory samples were analyzed at a central laboratory to ensure consistent interpretation of results. Clinical laboratory results for these studies were not pooled; therefore the results for each study are described separately.

7.1.7.1 Phase III Study (81-0015)

There were no clinically significant differences between treatment groups for changes from baseline to final visit for any hematology, chemistry, or urinalysis parameter.

7.1.7.2 Phase II Study (81-0005)

One patient in the Proquin XR group had an AE of anemia that led to discontinuation of study drug; this event was considered severe but unrelated to study drug and was resolved after 4 days. There were no other clinically important changes in laboratory abnormalities or laboratory values (hematology, chemistry, or urinalysis).

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7.1.7.3 Phase I Studies

Clinical laboratory results in the Phase I studies during Proquin XR treatment that were considered to be AEs included increased eosinophil count; increased blood creatinine, glucose, LDH, AST, ALT, and alkaline phosphatase; WBCs in urine, glucose in urine, blood in urine, and urine ketone bodies present. None of the events caused discontinuation of study drug.

7.1.8 Vital Signs

Vital signs data for the Phase II and Phase III studies were not pooled; therefore the results for each study are described separately.

7.1.8.1 Phase III Study (81-0015)

There were no significant differences in vital signs between treatment groups at baseline or at final visit. Although there were some statistically significant mean changes from baseline to final visit in vital signs in both treatment groups, these changes were small and not clinically significant.

There were no individual clinically important abnormalities in vital signs or AEs related to vital signs that caused discontinuation of study drug.

7.1.8.2 Phase II Study (81-0005)

In the Phase II study, there were no statistically significant/notable changes from baseline to final visit in vital signs for patients who received either treatment. In addition, there were no statistically significant differences between treatment groups for changes from baseline for vital signs.

There were no individual clinically important abnormalities in vital signs or AEs related to vital signs that caused discontinuation of study drug.

7.1.9 Electrocardiograms (ECGs)

Electrocardiograms were not routinely performed in clinical trials.

7.1.10 Immunogenicity

No information on immunogenicity was included in the NDA submission.

7.1.11 Human Carcinogenicity

No information on human carcinogenicity was included in the NDA submission.

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7.1.12 Special Safety Studies

No special safety studies were included in the NDA submission.

7.1.13 Withdrawal Phenomena and/or Abuse Potential

Ciprofloxacin is not considered to have the potential for psychological dependence. Therefore, studies to evaluate Proquin XR withdrawal and/or rebound have not been conducted.

Ciprofloxacin, like other fluoroquinolones, does not have the potential for psychological or physiological dependence. Therefore, Proquin XR is not considered a drug of abuse.

7.1.14 Human Reproduction and Pregnancy Data

No adequate, well-controlled clinical trials were conducted in pregnant women or nursing mothers using Proquin XR in this clinical program.

In the pivotal Phase III clinical trial conducted with Proquin XR, two patients became pregnant during the study. Patient 2719 was randomized to the Proquin XR treatment group, completed study drug dosing, and had a positive pregnancy test at the test-of-cure visit. The patient elected to keep the pregnancy, the pregnancy progressed to term and the patient delivered a normal healthy baby at term (see narrative in the individual study review of Study 81-0015, Section 10: *Appendices*). The second case was a patient (4124) who was randomized to the Cipro IR treatment group, also completed study drug dosing, and had a positive pregnancy test. The patient elected to keep the pregnancy and the pregnancy was reported to be progressing well without any complications at the time of the study report.

7.1.15 Assessment of Effect on Growth

No information on the effect of Proquin XR on growth was contained in the NDA submission. Ciprofloxacin is not known to inhibit growth.

7.1.16 Overdose Experience

There are only a few reported cases of ciprofloxacin overdose in humans in the literature.

In the toxicology program conducted by the applicant, single doses of ciprofloxacin were relatively non-toxic via the oral route of administration in rat. No deaths occurred during the post treatment observation period at the highest oral doses of 2,000 mg/kg tested. Clinical signs observed included clear oral discharge and gasping 10 minutes after dosing. These animals were normal at all other observations intervals (Study 80-0006).

In the event of an acute overdosage with Proquin XR, the stomach should be emptied by inducing vomiting or by gastric lavage. The patient should be carefully observed and given supportive treatment. Adequate hydration must be maintained. Only a small amount of ciprofloxacin (<10%) is removed from the body after hemodialysis or peritoneal dialysis.

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7.1.17 Postmarketing Experience

Proquin XR has not been marketed previously. For a summary of post-marketing AEs occurring with other oral formulations of ciprofloxacin, see the labels for Cipro® and Cipro XR®.

7.2 Adequacy of Patient Exposure and Safety Assessments

7.2.1 Description of Primary Clinical Data Sources (Populations Exposed and Extent of Exposure) Used to Evaluate Safety

The safety of Proquin XR for the treatment of acute, uncomplicated urinary tract infections (uUTIs) in female patients was evaluated in two similarly-designed, active-controlled, clinical safety and efficacy studies (Phase II study 81-0005 and Phase III study 81-0015). A total of 1,095 patients were enrolled in these studies. Both studies were multicenter, randomized, double-blind, parallel-group studies that compared the safety and efficacy of Proquin XR to Cipro IR. Patients received either Proquin XR 500 mg once daily (qd) or Cipro IR 250 mg twice daily (bid). The duration of treatment was 3 days and the study duration was approximately 5.5 weeks. The total daily dose of ciprofloxacin and the duration of treatment were chosen to be consistent with the approved regimen of Cipro® for the treatment of acute, uncomplicated UTIs.

The average duration of exposure to Proquin XR in the Phase II and III studies was 3 days (range 1 to 3 days) and all patients received the same dose. The average duration of exposure to Cipro IR was 4 days (range 1 to 4 days). (Note: the average duration of exposure to active study drug appears longer for Cipro IR-treated patients because the final dose was taken on the morning of the 4th day, whereas the final dose for Proquin XR-treated patients was taken on the evening of the 3rd day). Study drug exposure for patients in the safety and efficacy studies is presented in Table 13.

TABLE 13
Extent of Exposure to Study Drug
Safety Population of Clinical Studies 81-0005 and 81-0015

Length of Exposure	Treatment Group		Total (N=1085)
	C-GR (n=547)	C-IR (n=538)	
n	545	538	1083
Mean (SD)	3 (0.4)	4 (0.4)	3 (0.6)
Median	3	4	3
(Min, Max)	(1, 3)	(1, 4)	(1, 4)

C-GR = Proquin XR tablets; C-IR = Cipro® immediate release tablets

Safety population included all randomized patients who received study drug

Source: Table 2 in the applicant's Summary of Clinical Safety in the NDA submission

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In addition, safety was evaluated in nine open-label pharmacokinetic (PK) studies that included 216 healthy adult volunteers; four of the PK studies included treatment with Proquin XR and Cipro IR and five included treatment with Proquin XR only.

A summary of drug exposure during the PK studies is presented in Table 14.

TABLE 14
Summary of Study Drug Exposure in Phase I Pharmacokinetic Studies

Study No.	C-GR			C-IR		
	No. of Subjects who Received Study Drug	Dose	Duration	No. of Subjects who Received Study Drug	Dose	Duration
00-07	15	500 mg qd	3 x 1 day	15	500 mg	1 day
81-0024	28 ^a	500 mg qd	2 x 1 day	0	n/a	n/a
81-0025	28	500 mg qd	1 day	27	250 mg bid	1 day
81-0026	28	500 mg qd	3 days	27	250 mg bid	3 days
81-0027	27	2x500 mg qd	2 x 1 day	0	n/a	n/a
81-0028	28 ^a	2x500 mg qd	3 x 1 day	0	n/a	n/a
81-0029	16	500 mg qd	3 x 1 day	16	500 mg qd	1 day
81-0032	16	500 mg qd	1 day	0	n/a	n/a
81-0033	30	2x500 mg qd	3 x 1 day	0	n/a	n/a
Total	216	--	--	98	--	--

Source: Table 3 in the applicant's Summary of Clinical Safety in the NDA submission

7.2.2 Description of Secondary Clinical Data Sources Used to Evaluate Safety

Ciprofloxacin has been marketed since 1989. Proquin XR is a 505(b)1 application, but safety data is very well known in the scientific community, and may be viewed as common or general scientific knowledge. Inclusion of such information is permitted in a 505(b)(1) NDA. Therefore, both the Cipro® and Cipro (XR) tablet labels were used to obtain additional safety information on Proquin XR.

7.2.3 Adequacy of Overall Clinical Experience

The applicant followed recommendations in the draft Guidance for Industry (July 1998): "Uncomplicated Urinary Tract Infections – Developing Antimicrobial Drugs for Treatment" with regard to the study design of Study 81-0005 and 81-0015, including inclusion/exclusion

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criteria, timing of evaluation visits, assessments performed, definition outcome, and statistical analyses.

Study 81-0015 was adequately powered to detect a 95% two-sided confidence interval for the difference in microbiological outcome between treatment groups (Proquin XR minus Cipro IR) with a lower bound of at least -15%, which was the primary endpoint of the study.

7.2.4 Adequacy of Special Animal and/or In Vitro Testing

No special animal or in vitro testing was performed by the applicant for inclusion in this NDA submission.

7.2.5 Adequacy of Routine Clinical Testing

Routine clinical testing performed in the clinical studies was adequate.

7.2.6 Adequacy of Metabolic, Clearance, and Interaction Workup

The pharmacokinetics, including metabolism; and drug-drug interactions of ciprofloxacin have previously been determined. However, since this is a 505(b)1 submission, the applicant performed additional clinical pharmacology studies, as deemed necessary by the FDA, using Proquin XR. For a complete listing of these studies, see the Clinical Pharmacology/Biopharmaceutics Review filed with this NDA.

7.2.7 Adequacy of Evaluation for Potential Adverse Events for Any New Drug and Particularly for Drugs in the Class Represented by the New Drug; Recommendations for Further Study

The adverse event profile for Proquin XR has been adequately addressed. There are no recommendations for further study.

7.2.8 Assessment of Quality and Completeness of Data

The data from Studies 81-0005 and 81-0015 are considered to be acceptable quality and completeness.

7.2.9 Additional Submissions, Including Safety Update

The applicant has no on-going clinical trials with Proquin XR; therefore, no additional safety data were submitted.

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7.3 Summary of Selected Drug-Related Adverse Events, Important Limitations of Data, and Conclusions

7.4 General Methodology

7.4.1 Pooling Data Across Studies to Estimate and Compare Incidence

Safety data from Studies 81-0005 and 81-0015 were pooled for an analysis of safety, as the study design for both studies was similar. See Section 7.1: “*Methods and Findings*” for a discussion of the pooled results.

7.4.2 Explorations for Predictive Factors

No additional exploratory analyses were performed.

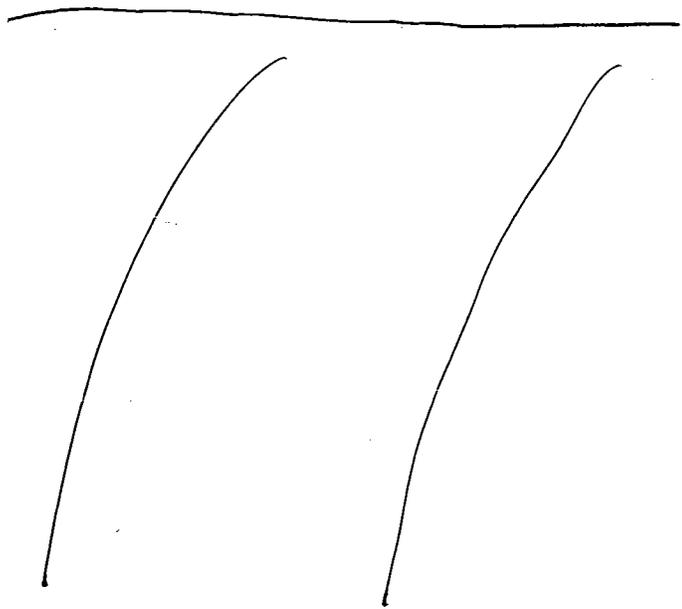
7.4.3 Causality Determination

Additional assessments of causality were not performed.

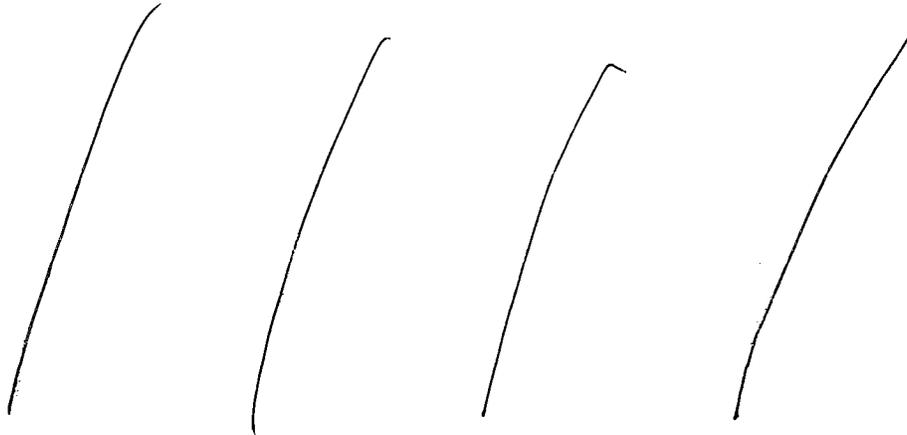
8 ADDITIONAL CLINICAL ISSUES

8.1 Dosing Regimen and Administration

The applicant has requested :



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Upon review of the data provided by the applicant, the Division has concluded that there is not sufficient data to support

As discussed in Section 7.1.5: "*Common Adverse Events*", the incidence of nausea in the clinical studies was lower in the Proquin XR group, but not significantly different from the Cipro IR group (1.3% and 2.8%, respectively; $p = 0.088$). The incidence of diarrhea was statistically lower in the Proquin XR group (0.4%) compared to Cipro IR (1.9%) ($p=0.021$). However, the overall incidence of any type of gastrointestinal adverse event was not statistically different between the two products (6.2% and 8.9%, respectively, nor was the overall incidence of adverse events (42.0% and 42.9%, respectively). The rate of discontinuation from study drug was numerically higher in the Proquin XR group (1.3%) compared to the Cipro IR group (0.6%).

8.2 Drug-Drug Interactions

Ciprofloxacin is involved in drug-food and drug-drug interactions. These are summarized below.

8.2.1 Drug-Food Interactions

Several published studies have shown that oral multivitamin and mineral supplements fortified with multivalent cations such as calcium, iron or zinc, calcium-fortified orange juice, and dairy products like milk and yogurt, interact with the fluoroquinolones, including other formulations of ciprofloxacin, by chemical complexation with the multivalent cations thereby reducing the serum and urine concentrations of ciprofloxacin.

Therefore, fortified oral multivitamins and mineral supplements should not be administered concomitantly with Proquin XR. Proquin XR should not be taken alone with dairy products (like milk or yogurt) or calcium-fortified juices, since the absorption of ciprofloxacin may be significantly reduced. However, Proquin XR may be taken with a meal that contains these products.

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8.2.2 Drug-Drug Interactions

8.2.2.1 Caffeine

Some quinolones, including ciprofloxacin, have also been shown to interfere with the metabolism of caffeine. This may lead to reduced clearance of caffeine and a prolongation of its serum half-life.

8.2.2.2 Cyclosporine

Concomitant administration of other formulations of ciprofloxacin to patients receiving cyclosporine maintenance therapy has resulted in increased risk of nephrotoxicity including acute renal failure with transient elevations in serum creatinine. The mechanism of this interaction is not known but is thought could involve synergistic effects of the drug and/or interference by ciprofloxacin with cyclosporine metabolism. Therefore, Proquin XR should be administered cautiously to patients on cyclosporine maintenance therapy.

8.2.2.3 Glyburide

There are published case reports that concomitant administration of other formulations of ciprofloxacin with glyburide therapy has, on rare occasions, resulted in severe hypoglycemia. Therefore, concomitant administration of Proquin XR and glyburide should be avoided or blood glucose levels should be monitored very closely.

8.2.2.4 Methotrexate

Concomitant administration of other formulations of ciprofloxacin and methotrexate has been reported to result in inhibition of renal tubular transport of methotrexate potentially resulting in increased plasma levels and associated toxic reactions. Therefore, patients on methotrexate therapy should be carefully monitored when concomitant Proquin XR is required.

8.2.2.5 Multivalent Cation-Containing Products

Concurrent administration of oral quinolones, including other oral formulations of ciprofloxacin, with multivalent cation-containing products such as magnesium or aluminum antacids, sucralfate, VIDEX chewable/buffered tablets or pediatric powder, or products containing calcium, iron, or zinc may substantially decrease the absorption of ciprofloxacin, resulting in serum and urine levels considerably lower than desired.

The interaction of Proquin XR and magnesium/aluminum-containing antacids was evaluated in healthy volunteers. To minimize the effect of antacids on the absorption of ciprofloxacin, Proquin XR should be given either 2 hours after or at least 4 hours before antacids. This time window for Proquin XR is different than for other oral formulations of ciprofloxacin.

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8.2.2.6 Non-steroidal anti-inflammatory drugs (but not aspirin)

Published studies in animals have reported that fluoroquinolones decrease the receptor binding of gamma-amino-butyric acid (GABA) leading to CNS excitation. This decreased binding may be potentiated by simultaneous administration of certain non-steroidal anti-inflammatory drugs (NSAIDs). There have been recent reports from Japan of convulsions in patients receiving the NSAID, fenbufen, and the fluoroquinolone, enoxacin. Therefore, concomitant administration of Proquin XR with a NSAID could result in increased risk of CNS stimulation (e.g., seizures).

8.2.2.7 Omeprazole

The rate and extent of absorption of ciprofloxacin was not substantially different when Proquin XR was given alone or when Proquin XR was given 2 hours after omeprazole at the dose that maximally suppresses gastric acid secretion. Proquin XR should be taken with the main meal of the day, preferably the evening meal, and should be taken at least 2 hours after omeprazole

8.2.2.8 Phenytoin

There are reports in the literature that other formulations of ciprofloxacin interacted with phenytoin in rare instances resulting in altered (increase or decrease) serum levels of phenytoin. Therefore, the concomitant administration of Proquin XR with phenytoin should be avoided and if it must be given concomitantly, plasma phenytoin concentrations should be monitored.

8.2.2.9 Probenecid

Concomitant administration of probenecid has been reported in the literature to interfere with renal tubular secretion of other formulations of ciprofloxacin resulting in a reduction in renal clearance, an increase in systemic concentration, and a prolonged serum half-life of ciprofloxacin. Therefore, patients should be monitored for an increased incidence of adverse events if Proquin XR and probenecid are to be administered concomitantly.

8.2.2.10 Theophylline

As with some other quinolones, concurrent administration of ciprofloxacin with theophylline may lead to elevated serum concentrations of theophylline and prolongation of its elimination half-life. This may result in increased risk of theophylline-related adverse reactions. If concomitant use of Proquin XR and theophylline cannot be avoided, serum levels of theophylline should be monitored and dosage adjustments made as appropriate.

8.2.2.11 Warfarin

Administration of fluoroquinolones, including other formulations of ciprofloxacin, to patients on the oral anticoagulant, warfarin, or its derivatives, has resulted in published reports of an increased anticoagulant effect and an increased risk of bleeding.

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The co-administration of single doses of Proquin XR and Coumadin® (7.5 mg) did not result in significant changes in the pharmacokinetics of ciprofloxacin nor did it significantly affect the pharmacodynamics of S-warfarin and R-warfarin. Although the C_{max} and AUC of the two warfarin enantiomers and the elimination $t_{1/2}$ of S-warfarin were not significantly altered by ciprofloxacin co-administration, the $t_{1/2}$ of R-warfarin was statistically significantly prolonged ($P=0.029$). Therefore, Proquin XR should be administered with caution in patients receiving coumarin anticoagulant therapy and prothrombin time and international normalized ratio (INR) should be monitored very closely.

8.3 Special Populations

The patient populations studied in the clinical trials did not include pregnant or nursing women, pediatric patients, or patients with renal or hepatic impairment.

8.3.1.1 Pregnant Women or Nursing Mothers

There are no adequate and well-controlled studies of Proquin XR in pregnant women or nursing mothers. An expert review of published data on experiences with ciprofloxacin use during pregnancy by TERIS – the Teratogen Information System – concluded that therapeutic doses during pregnancy are unlikely to pose a substantial teratogenic risk (quantity and quality of data = fair), but the data are insufficient to state that there is no risk.

Ciprofloxacin is excreted into breast milk and could result in the potential for serious adverse effects of ciprofloxacin in the nursing infant. Therefore, in lactating mothers, if Proquin XR treatment is indicated, a decision should be made either to discontinue the drug or discontinue breastfeeding.

8.3.1.2 Renal Impairment

In severe renally impaired patients ($CL_{Cr} < 30$ mL/min); the recommended maximum daily dose of ciprofloxacin has been determined to be 400 mg IV or 500 mg orally once daily. Since the maximum daily dose of ciprofloxacin for uncomplicated UTI is 500 mg orally, no dosage adjustment is required for patients with severe renal impairment with uncomplicated UTI receiving Proquin XR.

8.3.1.3 Hepatic Impairment

No dosage adjustment is required for patients with stable chronic cirrhosis, since hepatic dysfunction appears to have little effect on the disposition and elimination of ciprofloxacin. Thus, the exclusion of these patients from the clinical studies should not impact the predicted safety of this product in the marketplace. Other formulations of ciprofloxacin have been marketed worldwide for over 15 years, and the safety profile of ciprofloxacin is well established.

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8.3.1.4 Age (< 65 years or ≥ 65 Years)

Microbiological eradication rates were similar for patients 65 years or older and younger patients in the Phase III study. No clinically relevant differences in safety were observed between older patients and patients less than 65 years old. Dosage adjustments based upon age are not warranted.

8.3.1.5 Race (Caucasian and non-Caucasian)

Microbiological eradication rates were similar for Caucasian and non-Caucasian patients. No clinically relevant differences in safety were observed between Caucasian and non-Caucasian patients. Dosage adjustments race are not warranted.

8.4 Pediatrics

No data are available in pediatric patients in the current NDA submission. Clinical studies were conducted in adult women. Uncomplicated urinary tract infection is not considered to be a disease affecting children, with the exception of young, sexually active women.

8.5 Advisory Committee Meeting

No Advisory Committee Meeting was held to discuss this NDA submission.

8.6 Literature Review

Cipro® and Cipro (XR) tablet labels were used to obtain additional safety information on other formulations of ciprofloxacin.

8.7 Postmarketing Risk Management Plan

The Office of Drug Safety (ODS) was consulted on the applicant's Risk Management Plan (submitted with the NDA on July 18, 2004). ODS concluded that the proposed plan did not differ substantially from typical new product labeling and routine passive post-marketing safety surveillance. The complete review (dated March 24, 2005) can be found in DFS.

No additional post-marketing risk management is planned.

8.8 Other Relevant Materials

The applicant submitted a position paper with the NDA which outlines their justification that Proquin XR (referred to in the paper as Ciprofloxacin GR™) should be considered by the Agency as a 505(b)1, as opposed to 505(b)2 application. The Division agrees with a 505(b)1 designation.

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Executive Summary

Depomed Inc.'s ("DEPO's") New Drug Application ("NDA") for Ciprofloxacin GR™ for the treatment of uncomplicated urinary tract infections ("UTIs") in women meets the requirements of a 505(b)(1) or "stand-alone" NDA. DEPO's application contains full reports of investigations of the product's safety and effectiveness that were conducted by DEPO.¹ DEPO has successfully completed the necessary pivotal clinical trial and has adequately studied the clinical pharmacology, toxicology, and microbiology of Ciprofloxacin GR.² As the Food and Drug Administration ("FDA") has specifically stated in draft guidance on the subject, referring to scientific literature, e.g., in proposed product labeling, does not automatically change a 505(b)(1) NDA to a 505(b)(2) application.³ Appendix 1 of this document summarizes several precedents to support this conclusion.⁴ Moreover, to the extent that this NDA includes information from the scientific literature, Depomed is including such information in part because it is required to do so. In addition to reports of its investigations of the drug product, an applicant is required to include in the NDA "all other information about the drug pertinent to an evaluation of the application that is received or otherwise obtained by the applicant from any source." 21 C.F.R. § 314.50 (first paragraph) (emphasis added).

There are four specific grounds upon which the Division can conclude that this application meets the requirements of a 505(b)(1) NDA. First, to the extent that DEPO has referred to information in the scientific literature, the information is so well known in the scientific community (including Division reviewers) that it amounts to common or general scientific knowledge. Second, to the extent that DEPO has referred to information in the scientific literature, the information is not essential for approval of the application. Rather, it provides helpful information to the reviewer and the prescriber.

FDA has clarified that such references to published studies do not convert a full NDA to a 505(b)(2) application.⁵ Such references are useful to support the application and to provide information helpful to the reviewer and to the prescriber.

Third, DEPO has complied fully with the applicable FDA guidance for developing antimicrobial drugs for the treatment of uncomplicated UTIs, which calls for the applicant to conduct one statistically adequate and well-controlled clinical trial that establishes safety and effectiveness of the product, and to submit adequate microbiologic and human pharmacokinetic/pharmacodynamic ("PK/PD") data supportive of the product's effectiveness.⁶

Finally, this application includes data from studies conducted by or for DEPO that are sufficient for the Division to conclude that there exists substantial evidence of the safety and effectiveness of Ciprofloxacin GR.⁷ As the Division is aware, the Food and Drug Administration Modernization Act of 1997 ("FDAMA"), Section 115(a), codified at 21 U.S.C. § 355(d), clarified that the substantial evidence standard can be met with a single clinical trial ("SCT") plus confirmatory evidence ("CE"). DEPO has completed a clinical development program that fits the SCT plus CE paradigm: one adequate and well-controlled multicenter clinical study that establishes the product's safety and effectiveness, plus microbiologic and PK/PD studies that provide confirmatory evidence of that finding.

¹ Federal Food Drug and Cosmetic Act ("FDC Act") Sec. 505(b)(1)(a); 21 U.S.C. § 355(b)(1)(a).

² DEPO has also completed the appropriate non clinical. Our understanding is that the Division is in agreement. Therefore, this position paper discusses clinical studies only.

³ Draft Guidance for Industry, Applications Covered by Section 505(b)(2), 2 (Oct. 1999) ("FDA's 505(b)(2) Guidance") (noting that references to "published general information" or "general knowledge" does not cause the application to be a 505(b)(2) application) (copy provided as Attachment A).

⁴ Appendix 1 summarizes seven examples of products approved under a full 505(b)(1) NDA, each of which relied on published studies in the product labeling or in the FDA's summary basis of approval ("SBA"). We have not done an exhaustive search. There are likely more examples.

⁵ FDA's 505(b)(2) Guidance, 2.

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9 OVERALL ASSESSMENT

9.1 Conclusions

Proquin XR (ciprofloxacin extended-release 500 mg tablets) was found to be safe and effective for the treatment of uncomplicated urinary tract infection in adult women.

9.2 Recommendation on Regulatory Action

Proquin XR (ciprofloxacin extended-release 500 mg tablets) should be approved for the treatment of uncomplicated urinary tract infection in adult women. The recommended dose is 500 mg orally once daily for 3 days. Proquin XR should be given with a main meal of the day, preferably the evening meal.

9.3 Recommendation on Postmarketing Actions

There are no recommendations for risk management activity. The Division requests two Phase 4 commitments from the applicant.

9.3.1 Risk Management Activity

None.

9.3.2 Required Phase 4 Commitments

1. Track ciprofloxacin-resistance to baseline and treatment emergent isolates of *E. coli* prospectively in patients with uncomplicated urinary tract infection for the first two years of Proquin XR availability:
Protocol Submission: January 1, 2006
Study Start: July 1, 2006
Final Report Submission: December 31, 2008
2. Provide an annual update on Proquin XR usage patterns, noting patient demographics, setting of practice, indication for use, and treatment regimen prescribed for the first two years of product availability; with the submission dates being no later than _____, respectively.

9.3.3 Other Phase 4 Requests

None.

4 Page(s) Withheld

 Trade Secret / Confidential

✓ Draft Labeling

 Deliberative Process

10 APPENDICES

10.1 Review of Study 81-0005

Randomized, Double Blind (Double Dummy), Parallel Group Pilot Study to Assess the Comparative Efficacy, Safety, and Tolerability of Once Daily Extended Release (GR) and Twice Daily Immediate Release (IR) Ciprofloxacin Formulations in Female Patients with Uncomplicated Urinary Tract Infections (UTI)

Phase II Study

Study Initiation Date: October 16, 2001

Study Report Date: June 29, 2004

Clinical Reviewer's Comments: Unless otherwise noted, all tables in this review are reproduced from the applicant's study report.

Abbreviations defined:

C-GR: ciprofloxacin gastric-release (GR) tablets also known as ciprofloxacin extended-release tablets or Proquin XR

C-IR: ciprofloxacin immediate-release tablets (Cipro IR)

10.1.1 Study Objectives

The objectives of the study were as follows:

- To compare the efficacy of once daily C-GR with twice daily C-IR at equal total daily doses in achieving clinical and microbiological cure at 7 (± 2) days after treatment.
- To compare the efficacy of C-GR once daily with C-IR twice daily at equal total daily doses in achieving clinical and microbiological cure at 5 weeks (± 7 days) after treatment.
- To compare the incidence and severity of side effects with C-GR once daily and C-IR twice daily at equal total daily doses.

10.1.2 Study Design

This was a pilot, multicenter, randomized, double-blind (double-dummy), active-controlled, parallel-group clinical study designed to compare the efficacy and safety of ciprofloxacin extended- or gastric-release, one 500 mg tablet once daily for 3 days, and ciprofloxacin immediate release (Cipro®, Bayer Corporation), one 250 mg tablet twice daily for 3 days, in the treatment of acute, uncomplicated urinary tract infection (UTI). Adult female patients with an onset of clinical signs and symptoms of acute, uncomplicated UTI within the previous 72 hours were eligible for screening after providing informed consent.

Patients were randomly assigned to treatment with either ciprofloxacin gastric-release (C-GR) once daily or ciprofloxacin immediate release (C-IR) twice daily, and instructed to take their first

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dose of study medication on the evening of study enrollment, following dinner. Dosing continued through the morning and evening of the next 2 days, and into the morning of the fourth day. Patients returned to the clinic for a post-treatment Test-of-Cure Visit at 7 days (± 2 days) after completing medication. Patients returned for a Late Post-Treatment visit at 5 weeks (± 7 days) following treatment.

This study was planned to be conducted in 50 adult female patients who had a primary diagnosis of acute, symptomatic, uncomplicated lower UTI and who had qualified for enrollment on the basis of the following inclusion and exclusion criteria. Fifty-eight patients were actually enrolled in the study.

10.1.3 Inclusion Criteria

1. Female patients were at least 18 years of age.
2. Patients of childbearing potential had a negative urine pregnancy test at screening and randomization, and used medically acceptable methods of birth control throughout the study. Acceptable methods of birth control included abstinence, oral contraceptives, condom and foam, intrauterine device (IUD), vaginal spermicidal suppository, progestin implant or injection. The reason for non-childbearing 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 (CRF).
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 or ≥ 10 white blood cells (WBCs)/mm³ (unspun urine).
4. At least one positive pretreatment clean catch mid-stream urine culture within 48 hours of enrollment in the study, defined as $\geq 10^5$ colony forming units (CFU)/mL.
5. Demonstrated susceptibility of uropathogen to both the test drug and the control drug by *in vitro* testing (NCCLS criteria).
6. Patient was willing and able to comply with the study procedures and provided written informed consent to participate in the study.

10.1.4 Exclusion Criteria

1. Patient was pregnant or nursing or not using acceptable birth control as defined in Inclusion Criteria number 2 above.
2. Patient had three or more episodes of acute uncomplicated UTI in the past 12 months.

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3. Patient had evidence of factors predisposing her to the development of UTIs, including calculi, stricture, primary renal disease (e.g., polycystic renal disease), or neurogenic bladder.
4. Patient had a history of gastric or duodenal ulcers, upper gastrointestinal or bowel surgery (excluding appendectomy) within 2 years, or active gastrointestinal disease (pancreatitis, biliary tract disease, hepatitis, colitis) within 2 years.
5. Patient had chronic gastroparesis or severe gastrointestinal symptoms, including diarrhea, dyspepsia, constipation, and weight loss.
6. Patient had a temperature $\geq 101^{\circ}$ F, flank pain, chills, or any other manifestations suggestive of upper UTI.
7. Patient had known hypersensitivity to ciprofloxacin.
8. Patient had received treatment with other antimicrobials within 48 hours prior to study entry.
9. Patient had received any cation-containing products such as magnesium/aluminum antacids, sucralfate, Videx® (didanosine) chewable/buffered tablets, or any products containing calcium, iron, or zinc within 48 hours prior to entry.
10. Patient was taking theophylline.
11. Patient had history of impaired renal function (creatinine clearance < 30 mL/min or serum creatinine > 3.0 mg/dL).
12. Patient had participated in a clinical trial of an investigational drug or device within 30 days of the screening visit.
13. Patient had any condition that, in the opinion of the Investigator, jeopardized the safety of the patient or affected the validity of the trial results.

10.1.5 Study Drug Administration

Patients assigned to the C-GR group received

- one tablet of C-GR 500 mg once daily (in the evening) x 3 days
- one tablet of C-IR placebo twice daily (one C-IR placebo tablet in the morning and one C-IR placebo tablet in the evening) x 3 days

Patients assigned to the C-IR group received

- one tablet of C-IR 250 mg twice daily (one C-IR tablet in the morning and one C-IR tablet in the evening) x 3 days
- one tablet of C-GR placebo once daily (in the evening) x 3 days

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The first dose of study drug was to be taken after dinner on the day of screening/randomization. If a patient was enrolled in the morning and the investigator determined that the patient could not wait until evening to start study drug, the patient was permitted to take the first dose of medication following lunch. The timing of subsequent doses remained unchanged.

Dosing continued through the morning and evening of the next 2 days, and the last dose was taken on the morning of the fourth day. Patients were instructed to take study medication following breakfast in the morning and following dinner in the evenings. Patients were instructed to swallow each of the tablets whole, and not to cut, crush, chew, or otherwise modify the tablets.

Patient compliance was estimated by tablet count of any returned, unused medication.

10.1.6 Prior and Concomitant Medications

Prior treatment with other antimicrobials, with any cation-containing products such as magnesium/aluminum antacids, sucralfate, Videx® (didanosine) chewable/buffered tablets, or with any products containing calcium, iron, or zinc, within 48 hours prior to study entry were not permitted.

The following medications were not allowed as concomitant therapy during the course of the study:

- Concomitant antimicrobial and urinary antiseptic drugs.
- Theophylline.
- Any cation-containing products such as magnesium/aluminum antacids, sucralfate, Videx® (didanosine) chewable/buffered tablets.
- Any products containing calcium, iron, or zinc.
- The urinary analgesic phenazopyridine may have been administered up to 24 hours following study enrollment.
- All prescription and over-the-counter concomitant medications used at the time of enrollment or during 30 days prior to study enrollment were documented on the appropriate page of the CRF. Use of concomitant medications was documented at each visit.

10.1.7 Study Assessments

The efficacy and safety assessments performed during the study are shown in Table 1.

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TABLE 1
Study Assessments

Study Period	Screening/ Randomization	Test-of-Cure Visit	Late Post-Treatment Visit
Visit/Study Day	Visit 1 Day 1	Visit 2 Day 11 (± 2)	Visit 3 Day 39 (± 7)
Informed consent	X		
Medical history	X		
Physical examination	X	X	X
Clinical signs/symptoms	X	X	X
Vital signs	X	X	X
Chemistry*/hematology**	X	X	
Clean catch urine sample	X	X	X
Dipstick	X	X	X
Urine pregnancy test	X		
Urinalysis***	X	X	X
Microbiological culture/susceptibility	X	X	X
Dispense medication	X		
Return unused medication		X	
Prior/concomitant medications	X	X	X
Adverse events		X	X

* Hematology: Hemoglobin, hematocrit, red blood cell (RBC) count, WBC including differential leukocyte count, platelet count, prothrombin time (PT), and partial thromboplastin time (PTT).

** Chemistry: Albumin, total protein, blood glucose, sodium, potassium, blood urea nitrogen (BUN), creatinine, serum glutamic oxaloacetic transaminase (SGOT [aspartate transaminase; AST]), serum glutamate pyruvate transaminase (SGPT [alanine transaminase; ALT]), alkaline phosphatase, gamma glutamyl transferase, total bilirubin, triglyceride, total cholesterol, lactate dehydrogenase (LDH), calcium, and uric acid.

*** Urinalysis: Urine specific gravity, pH, protein, glucose, ketones, urobilinogen, bilirubin, blood, and microscopy.

Source: Table 2 in applicant's study report

10.1.8 Efficacy Evaluation

10.1.8.1 Primary Efficacy Parameter

The primary efficacy parameter was microbiological outcome at Test-of-Cure Visit (7 ± 2 days following treatment). Microbiological outcomes were defined as:

- *Eradication*: Urine culture showed that all uropathogens present at study enrollment at $\geq 10^5$ CFU/mL were reduced to $<10^4$ CFU/mL.

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- *Persistence*: Urine culture taken any time after completion of therapy showed $\geq 10^4$ CFU/mL of uropathogens present at study enrollment.
- *New Infection*: Urine culture taken any time after completion of therapy showed $\geq 10^5$ CFU/mL of uropathogens not present at study enrollment.
- *Superinfection*: Urine culture taken for any reason during therapy showed growth of $\geq 10^5$ CFU/mL of an uropathogen other than those detected at study enrollment.

Clinical Reviewer's Comment: Routine urine cultures were not obtained during therapy, therefore the applicant did not assess the development of superinfections in this study.

10.1.8.2 Secondary Efficacy Parameters

The secondary efficacy parameters were

1. clinical outcome at the Test-of-Cure Visit (7 ± 2 days following treatment)
2. clinical outcome at the Late Post-Treatment Visit (5 weeks \pm 7 days following treatment)
3. microbiological outcome at the Late Post-Treatment Visit (5 weeks \pm 7 days) following treatment)

Clinical outcome was defined at the Test-of-Cure Visit as:

- *Clinical Cure*: Signs and symptoms of acute UTI were resolved and the patient had not used any additional antimicrobial therapy for the current UTI since completion of study treatment.
- *Clinical Failure*: Signs or symptoms of acute UTI persisted or had recurred, or additional antimicrobial therapy had been used for the current UTI since completion of study medication.

Clinical outcome at the Late Post-Treatment Visit was defined as:

- *Sustained Cure*: No evidence of resurgence of signs or symptoms of acute UTI.
- *Relapse*: Signs and symptoms of acute UTI that were absent at the Test-of-Cure Visit had re-appeared.
- *Failure*: Patients classified as *Clinical Failure* at Test-of-Cure Visit were carried forward.

Microbiological outcome at the Late Post-Treatment Visit was defined as:

- *Long-term, Sustained Eradication*: Urine culture at the Late Post-Treatment Visit showed that all uropathogens present at $\geq 10^5$ CFU/mL at study entry still remained at $< 10^4$ CFU/mL.

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- *Persistence*: Urine culture taken any time after completion of therapy showed $\geq 10^4$ CFU/mL of uropathogens present at study enrollment.
- *Recurrence*: Urine culture showed $\geq 10^4$ CFU/mL of the original uropathogen after documentation of eradication at the Test-of-Cure Visit, up to and including the Late Post-Treatment Visit.
- *New Infection*: A pathogen other than the original microorganism found at baseline at a level of $\leq 10^5$ CFU/mL was present at the level of $\geq 10^5$ CFU/mL any time after treatment was finished.

10.1.9 Efficacy Analysis

The primary efficacy analysis was the construction of the 90% confidence interval of the one-week clinical cure rate or one-week microbiological eradication rate within each treatment group. No formal hypothesis testing was performed to examine efficacy difference between two treatment groups.

All statistical tests used for the analysis of baseline variables and efficacy parameters were performed at the $\alpha = 0.05$ significance level. All tests were two-sided.

Clinical Reviewer's Comment: A 90% confidence interval was used for this small pilot study, which is acceptable as a 95% confidence interval calculated using this small sample size would be too large to yield a useful estimate of efficacy.

10.1.10 Analysis Populations

The intent-to-treat (ITT) population included evaluable patients randomized in this study. The evaluable patients are randomized patients who met the enrollment criteria for positive urine microbiology and uropathogen susceptibility (Inclusion Criteria 4 and 5).

The efficacy population included evaluable patients who were randomized in this study and had microbiological data at the Test-of-Cure Visit. The efficacy population was used for the analysis of primary and secondary efficacy parameters.

The ITT population was used for the analysis of microbiological eradication data and clinical cure data at Test-of-Cure Visit.

All randomized patients including non-evaluable patients were used for the analysis of selected efficacy endpoint. The safety population included all patients who received treatment.

10.1.11 Sample Size

This Phase II clinical study was designed to provide comparative information on the efficacy and safety of C-GR relative to C-IR. A sample size of 20 patients per treatment group was not

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expected to show statistically significant treatment differences, but would allow a general comparison of the two treatments, as well as provide useful information for planning a Phase III trial.

For each treatment group, a sample size of 20 patients has 80% power to demonstrate that the one-week clinical cure rate at 7 days post-treatment Test-of-Cure Visit evaluation following 3-day treatment is non-inferior to a target of 85% clinical cure rate. This is based on the criteria that the lower limit of a 90% confidence interval of the one-week clinical cure rate is not less than 65%.

10.1.12 Changes to the Efficacy Analysis

The primary efficacy parameter is one-week microbiological eradication rate based on the evaluation outcomes obtained at the Test-of-Cure Visit, with visit window of 4 to 11 days after the completion of study treatment. In order 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 (i.e., 7 to 14 days after the randomization date). The change to the evaluable window for the Test-of-Cure Visit was made after unblinding of this study to maintain consistency of the analysis for this study with the analysis of the Phase 3 study (Study 81-0015).

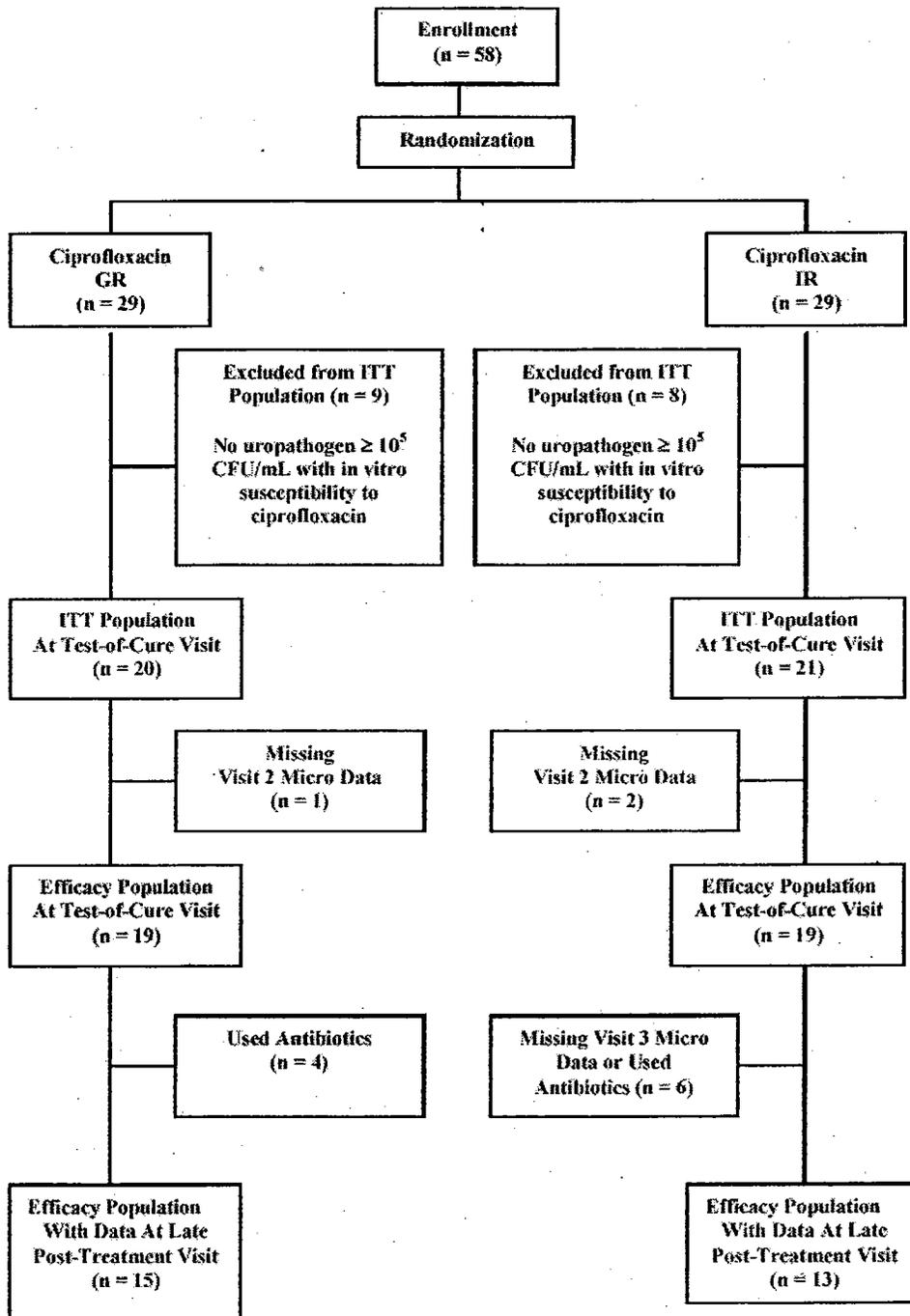
10.1.13 Patient Disposition

A total of 58 adult female patients were enrolled from six investigational sites across the US. The number of patients enrolled in each site ranged from 1 to 22. Twenty-nine patients were enrolled in each of the two treatment groups. All 29 patients (100.0%) in the C-GR group and 27 of 29 patients (93.1%) in the C-IR group completed the study. Two of 29 patients (6.9%) in the C-IR group discontinued from the study due to withdrawal of consent (Patient 308 and 511).

The applicant's Test-of-Cure ITT population included 20 of 29 patients in the C-GR group and 21 of 29 patients in the C-IR group. Nineteen of 29 patients in the C-GR group and 19 of 29 patients in the C-IR group were included in the applicant's Test-of-Cure Efficacy population.

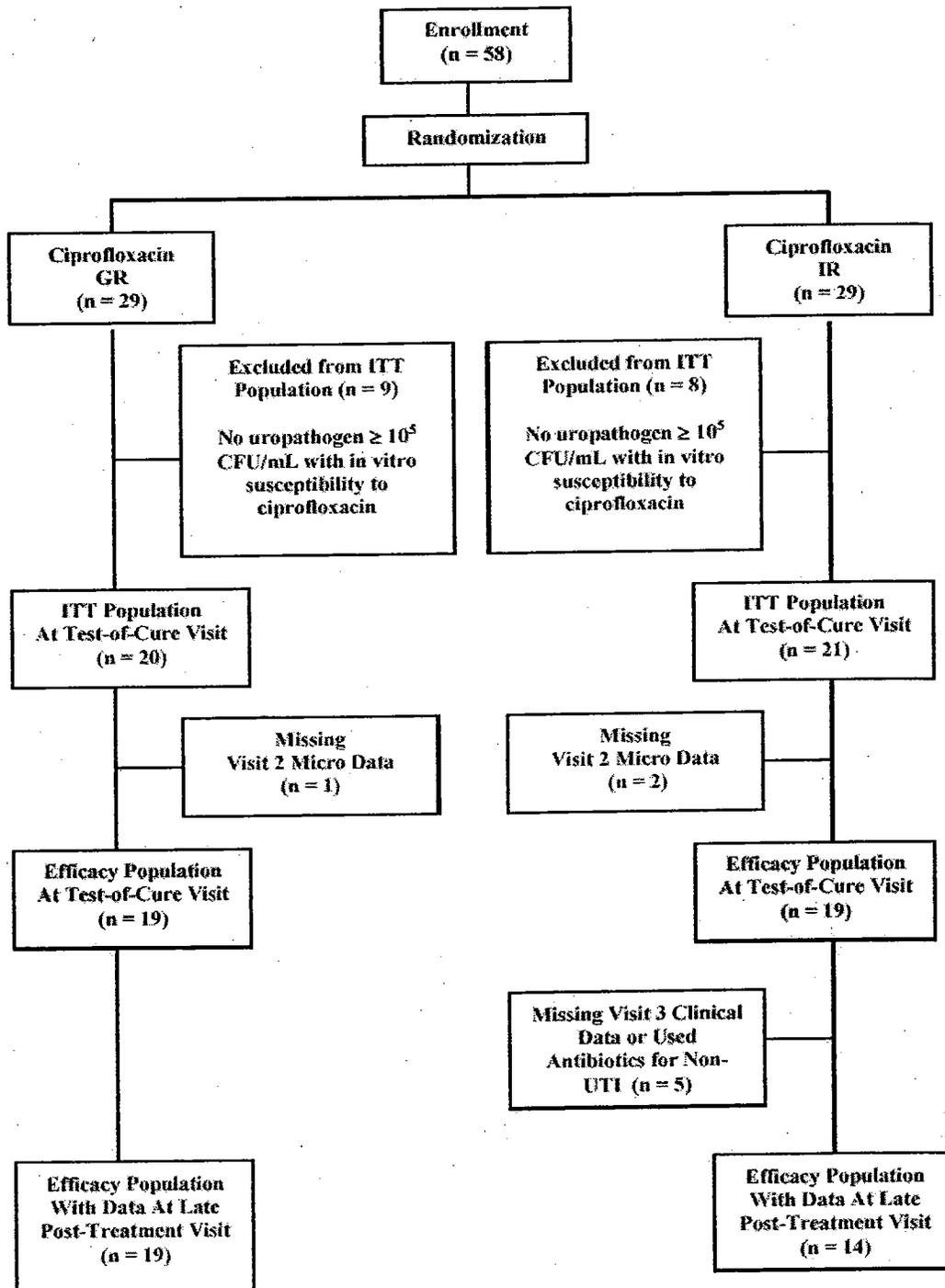
The applicant's microbiological and efficacy populations were defined as shown in Figures 1 and 2.

FIGURE 1
Applicant's Population for Microbiological Data Analysis



Source: Figure 3 in the applicant's study report

FIGURE 2
Population for Clinical Data Analysis



Source: Figure 4 in the applicant's study report

Clinical Reviewer's Comment: The applicant defined different populations for the microbiologic and clinical efficacy endpoints, as well as different populations for the Test-of-Cure Visit and Follow-up Visits, which is not considered acceptable by the Division. Instead, a consistent population should be used for all endpoints and visits. The applicant's populations were redefined by the Clinical and Statistical Reviewers as shown in Table 2 (created by the Reviewer). The applicant's defined intent-to-treat (ITT) and Efficacy Populations are similar to the FDA's modified intent-to-treat (MITT) and Per Protocol (PP) populations, respectively. In the FDA's PP population in the C-GR group, 4 patients who used antibacterials between the TOC and late post-treatment visit have been removed, reducing the number of evaluable patients from 19 (applicant's Efficacy population) to 15. In the C-IR group, there was one patient without microbiologic data at the TOC visit, one patient with a TOC visit outside the window, and 5 patients who used antibacterial during the study; reducing the number of evaluable patients from 19 (applicant's population) to 14.

TABLE 2
FDA Analysis of Patient Evaluability

	C-GR	C-IR
Safety Population	29	29
Modified Intent-to-Treat Population	22	22
<i>No pathogen $\geq 10^5$ CFU/mL at baseline¹</i>	7	7
Intent-to-Treat Population	20	21
<i>Baseline pathogen was not susceptible to ciprofloxacin²</i>	2	1
Per Protocol Population	15	13
<i>No microbiologic data at the TOC visit³</i>	0	1
<i>TOC visit outside 7-14 day window⁴</i>	1	1
<i>Used antibacterials during the study⁵</i>	4	5
<i>Lost to follow-up⁶</i>	0	1

¹ C-GR patients 204, 212, 322, 402, 405, 506, 507; C-IR patients 206, 308, 311, 319, 504, 508, 509

² C-GR patients 307, 510; C-IR patient 601

³ C-IR patient 511

⁴ C-GR patient 210; C-IR patients 312

⁵ C-GR patients 202, 302, 305, 320; C-IR patients 201, 203, 208, 317, 404

⁶ C-IR patient 303

10.1.14 Study Medication Compliance

Compliance with the study medication dosing was 100% in both the C-GR (29/29) and C-IR (29/29) groups for all randomized patients.

10.1.15 Demographics and Baseline Characteristics

Demographic and baseline data for all randomized patients are summarized in Table 3. The patients assigned to each treatment group were similar with respect to demographics and baseline

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characteristics. All patients were female with no statistically significant differences in age, weight, height, ethnicity, or childbearing potential.

TABLE 3
Demographics and Baseline Characteristics
All Randomized Patients

Characteristics	Statistics	Treatment Group		Total (n = 58)	p-value
		C-GR (n = 29)	C-IR (n = 29)		
Age (year)	Mean (SD)	41 (16.3)	46 (19.1)	44 (17.8)	0.287
	(Min, Max)	(19, 81)	(19, 78)	(19, 81)	
Female	n (%)	29 (100%)	29 (100%)	58 (100%)	NA
Caucasian	n (%)	20 (69.0%)	23 (79.3%)	43 (74.1%)	0.594
Height (in)	Mean (SD)	64 (2.6)	65 (3.2)	64 (2.9)	0.395
	(Min, Max)	(59, 69)	(59, 74)	(59, 74)	
Weight (lb)	Mean (SD)	150 (30.7)	158 (45.6)	154 (38.6)	0.410
	(Min, Max)	(114, 257)	(102, 305)	(102, 305)	

Note: The p-value for the test of treatment effect between two treatment groups was based on the two-sample t-test for numeric data or the Fisher's Exact test for categorical data.

NA=Not applicable

Source: Table 3 in applicant's study report

10.1.16 Efficacy Results

10.1.16.1 Microbiological Outcomes at the Test-of-Cure Visit

In the applicant's ITT population, eradication of baseline uropathogens was achieved for 15 of 20 patients (75.0%) in the C-GR group and 18 of 21 patients (85.7%) in the C-IR group, as shown in Table 3.

TABLE 3
Microbiological Outcomes at Test of Cure Visit
Applicant's ITT Population

One-Week Microbiological Eradication	Statistics	Treatment Group		Difference (C-GR - C-IR)	p-value
		C-GR (n = 20)	C-IR (n = 21)		
Microbiological Eradication.	Event / Sample Size*	15/20	18/21		0.454
	Eradication Rate	75.0%	85.7%	-10.70%	
	95% CI of Rate	(59.07%, 90.93%)	(73.13%, 98.27%)	(-30.99%, 9.59%)	

Note: The p-value for the test of treatment effect between two treatment groups was based on the Fisher's Exact test.

Source: Table 5 in the applicant's study report

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TABLE 4
Microbiological Outcomes at Test of Cure Visit
Applicant's Efficacy Population

One-Week Microbiological Outcomes	Statistics	Treatment Group		Difference (C-GR -C-IR)	p-value
		C-GR (n = 19)	C-IR (n = 19)		
Microbiological Eradication	Event / Sample Size	15 / 19	18 / 19		0.340
	Eradication Rate	78.9%	94.7%	-15.80%	
	90% CI of Rate	(63.50%, 4.30%)	(86.25%, 100.00%)	(-33.37%, 1.77%)	
Microbiological Persistence	Event / Sample Size	4 / 19	1 / 19		0.340
	Cure Rate	21.1%	5.3%	15.80%	
	90% CI of Rate	(5.70%, 36.50%)	(-3.15%, 13.75%)	(-1.77%, 33.37%)	
New Infection	Event / Sample Size	4 / 19	5 / 19		1.000
	New Infection Rate	21.1%	26.3%	-5.20%	
	90% CI of Rate	(5.70%, 36.5%)	(9.69%, 42.91%)	(-27.85%, 17.45%)	

Note: The p-value for the test of treatment effect between two treatment groups was based on the Fisher's Exact test.
 Source: Table 4 in the applicant's study report

In the applicant's efficacy population at the TOC visit, eradication of baseline uropathogens was achieved for 15 of 19 patients (78.9%) in the C-GR group and 18 of 19 patients (94.7%) in the C-IR group, as shown in Table 4. Eradication of the baseline uropathogen with no new infection was seen 11 of 19 evaluable patients (57.9%) in the C-GR group and 13 of 19 evaluable patients (68.4%) in the C-IR group. Eradication of the baseline uropathogen combined with a new infection was observed in 4 of 19 patients (21.1%) in the C-GR group and in 5 of 19 patients (26.3%) in the C-IR group. Persistence of baseline uropathogen without new infection was observed in 4 of 19 patients (21.1%) in the C-GR group and in 1 of 19 patients (5.3%) in the C-IR group. No patients in either treatment group experienced persistence combined with new infection.

Clinical Reviewer's Comments: In Table 3 and Table 4, the applicant has counted patients with eradication of the baseline uropathogen as a success, even if the patient developed a new infection. For other uUTI studies the Division has defined microbiological success as that all uropathogens present at study enrollment at $\geq 10^5$ CFU/mL were reduced to $<10^4$ CFU/mL AND no new infections. Therefore, for this application the Clinical and Statistical Reviewers have redefined eradication in both the FDA's MITT and PP populations to include only patients with no new infections. Outcomes in the redefined FDA's MITT and PP populations are shown in Table 5 (created by the Reviewer).

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TABLE 5
FDA Analysis of Microbiologic Outcome at the Test-of-Cure Visit

Outcome	MITT Population		PP Population	
	C-GR (N=22)	C-IR (N=22)	C-GR (n=15)	C-IR (N=13)
Eradication*	13/22 (59.1%)	14/22 (63.6%)	10/15 (66.6%)	8/13 (61.5%)
Persistence	4 (#s 202, 310, 314, had <i>E. coli</i> persist; 318 had <i>P. mirabilis</i> persist)	1 (107 had <i>E. coli</i> persist)	3 (#s 310, 314, 318)	1 (#107)
New Infection (> 10 ⁵ CFU/mL)	4 (#s 305, 320, 512 with new <i>Enterococcus</i> species; 503 with new <i>Hafnia alvei</i>)	5 (#s 201, 211, 316, 501, and 603 all had new <i>Enterococcus</i> species)	2 (#s 512, 503)	4 (#s 211, 316, 501, 603)
Missing Data	1 (# 210 TOC visit was late)	2 (#511 did not return for TOC visit; #312 TOC visit was late)	--	--
Superinfection**	0	0	0	0

* Eradication = Urine culture showed that all uropathogens present at study enrollment at $\geq 10^5$ CFU/mL were reduced to $<10^4$ CFU/mL AND no new infections

** No superinfections because no urine cultures obtained during therapy

10.1.16.2 Microbiological Outcome by Organism at the Test-of-Cure Visit

The microbiological response at the TOC visit by baseline organism for the applicant's Efficacy population is shown in Table 6.

Clinical Reviewer's Comment: Table 6 was adapted for clarity by the Reviewer from Table 14 in the applicant's submission.

TABLE 6
Microbiological Response at Test-of-Cure Visit by Baseline Organism
Applicant's Efficacy Population

Microbiological Response at Test-of-Cure Visit by Baseline Organism	n/N (%) Eradication	
	C-GR (n = 19)	C-IR (n = 19)
<i>Escherichia coli</i>	13/16 (81.3%)	15/16 (93.8%)
<i>Proteus mirabilis</i>	1/2 (50.0%)	1/1 (100%)
<i>Klebsiella pneumoniae</i>	1/1 (100%)	1/1 (100%)
<i>Pseudomonas aeruginosa</i>	1/1 (100%)	0/0
<i>Acinetobacter baumannii</i>	0/0	1/1 (100%)

Note: Baseline organisms at concentrations >100,000 cfu/mL and that are susceptible to ciprofloxacin are included in this data analysis.

Source: Table 14 in the applicant's study report

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Clinical Reviewer's Comment: Table 7 was created by the Reviewer using data listings in the applicant's study report for the FDA's PP Population.

TABLE 7
FDA Analysis of Microbiological Response at Test-of-Cure Visit by Baseline Organism
FDA's Per Protocol Population

Microbiological Response by Baseline Organism	n/N (%) Eradication	
	C-GR (n = 15)	C-IR (n = 13)
<i>Escherichia coli</i>	8/10 (80.0%)	11/12 (93.8%)
<i>Proteus mirabilis</i>	1/2 (50.0%)	0
<i>Pseudomonas aeruginosa.</i>	1/1 (100%)	0
<i>Klebsiella pneumoniae</i>	0	1/1 (100%)

Note: Baseline organisms at concentrations >100,000 cfu/mL and that are susceptible to ciprofloxacin are included in this data analysis.

10.1.16.3 Clinical Outcomes at the Test-of-Cure Visit

In the applicant's ITT population, clinical cure was experienced by 12 of 20 patients (60.0%) in the C-GR group and by 16 of 21 patients (76.2%) in the C-IR group, as shown in Table 8.

For the applicant's efficacy population at the Test-of-Cure Visit, clinical cure was experienced by 12 of 19 patients (63.2%) in the C-GR group and by 16 of 19 patients (84.2%) in the C-IR group, as shown in Table 9.

TABLE 8
Clinical Cure Rate at the Test-of-Cure Visit
Applicant's ITT Population

One-Week Clinical Outcome	Statistics	Treatment Group		Difference (C-GR - C-IR)	p-value
		C-GR (n = 19)	C-IR (n = 19)		
Clinical Cure	Event / Sample Size	12 / 19	16 / 19	-21.00%	0.269
	Clinical Cure Rate	63.2%	84.2%		
	90% CI of Rate	(45.00%, 81.40%)	(70.44%, 97.96%)		

Note: The p-value for the test of treatment effect between two treatment groups was based on the Fisher's Exact test.
 Source: Table 8 in the applicant's study report

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TABLE 9
Clinical Cure Rate at the Test-of-Cure Visit
Applicant's Efficacy Population

One-Week Clinical Outcome	Statistics	Treatment Group		Difference (C-GR - C-IR)	p-value
		C-GR (n = 19)	C-IR (n = 19)		
Clinical Cure	Event / Sample Size	12 / 19	16 / 19	-21.00%	0.269
	Clinical Cure Rate	63.2%	84.2%		
	90% CI of Rate	(45.00%, 81.40%)	(70.44%, 97.96%)		

Note: The p-value for the test of treatment effect between two treatment groups was based on the Fisher's Exact test.
 Source: Table 7 in the applicant's study report

Clinical Reviewer's Comments: The Clinical Reviewer recalculated clinical cure for patients in the FDA's MITT and PP populations in Table 10 (created by the Reviewer). The patients included in each population are the same as used in the assessment of microbiologic eradication at the TOC visit.

TABLE 10
FDA's Analysis of Clinical Cure Rate at the Test-of-Cure Visit

Outcome	MITT Population		Efficacy Population	
	C-GR (N=22)	C-IR (N=22)	C-GR (n=15)	C-IR (N=13)
Clinical Cure	14/22 (63.6%)	16/22 (72.7%)	10/15 (66.7%)	11/13 (84.6%)

Source: Listing 16.2.12 in the applicant's study report

10.1.16.4 Correlation Between Microbiological and Clinical Outcomes at the Test-of-Cure Visit

In the applicant's efficacy population at the Test-of-Cure Visit, both clinical cure and microbiological eradication were reported for 10 of 19 patients (52.6%) in the C-GR group and in 16 of 19 patients (84.2%) in the C-IR group. Two of 19 patients (10.5%) in the C-GR group and none of the 19 patients in the C-IR group were asymptomatic without eradication; 5 of 19 patients (26.3%) in the C-GR group and 2 of 19 patients (10.5%) in the C-IR group were symptomatic but had eradication of baseline uropathogen; and 2 of 19 patients (10.5%) in the C-GR group and 1 of 19 patients (5.3%) had neither clinical cure nor eradication.

The correlation between clinical cure and microbiological eradication in the applicant's efficacy population at the Test-of-Cure visit was not statistically significant after stratified by treatment factor in this study.

Clinical Reviewer's Comment: The correlation between microbiological and clinical outcome in both the FDA's ITT and Efficacy populations are shown in Tables 11 and 12, which were created by the Reviewer.

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TABLE 11
C-GR Correlation Between Microbiological and Clinical Outcome

Microbiological Outcome	Clinical Outcome			
	Clinical Cure		Clinical Failure	
	MITT Population	Efficacy Population	MITT Population	Efficacy Population
Eradication/No new infection	9	7	4	3
Persistence/New infection/Missing	5	3	4	2

Source: Listing 16.2.12 in the applicant's study report

TABLE 12
C-IR Correlation Between Microbiological and Clinical Outcome

Microbiological Outcome	Clinical Outcome			
	Clinical Cure		Clinical Failure	
	MITT Population	Efficacy Population	MITT Population	Efficacy Population
Eradication/No new infection	12	9	2	0
Persistence/New infection/Missing	4	4	4	1

Source: Listing 16.2.12 in the applicant's study report

10.1.16.5 Summary of Test-of-Cure Visit Results

Ciprofloxacin GR (C-GR) was evaluated for the treatment of uncomplicated urinary tract infections (acute cystitis) in a randomized, double-blind, controlled clinical trial conducted in the US. This study compared C-GR (500 mg once daily for three days) with ciprofloxacin immediate-release tablets (CIPRO® 250 mg BID for three days). Of the 58 patients enrolled, 29 were randomly assigned to the C-GR treatment group and 29 were randomly assigned to the ciprofloxacin immediate-release (C-IR) group. The primary efficacy variable was microbiological eradication of the baseline organism(s) with no new infection at test-of-cure (Day 4 - 11 Post-therapy).

The microbiological eradication and clinical success rates were similar between the C-GR group and the C-IR group. The eradication and clinical success rates and their corresponding 95% confidence intervals for the differences between rates (C-GR minus C-IR) are given in Table 13.

Clinical Reviewer's Comment: Table 13 was created by the Reviewer.

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TABLE 13
Summary of Microbiological and Clinical Outcomes at Test-of-Cure Visit
FDA's Per Protocol Population

	C-GR	C-IR
Randomized Patients	29	29
Efficacy Patients	15	13
Microbiological Eradication*	10/15 (66.6%)	8/13 (61.5%)
Microbiological Eradication by Organism**		
<i>Escherichia coli</i>	8/10 (80.0%)	11/12 (93.8%)
<i>Proteus mirabilis</i>	1/2 (50.0%)	0
<i>Pseudomonas aeruginosa</i>	1/1 (100%)	0
<i>Klebsiella pneumoniae</i>	0	1/1 (100%)
Clinical Response	10/15 (66.7%)	11/13 (84.6%)

* n/N patients with baseline uropathogen eradicated and no new infections/number of patients in the Efficacy population

** n/N organisms eradicated; one organism per patient; regardless of whether a new infection occurred in a particular patient

10.1.16.6 Microbiologic Outcomes at the Late Post-Treatment Visit

For the microbiological endpoints at the Late Post-Treatment Visit, the applicant's efficacy population included 15 patients in the C-GR group and 13 patients in the C-IR group and the results are shown in Table 14.

TABLE 14
Microbiological Response at Late Post-Treatment Visit
Applicant's Efficacy Population

	Treatment Group		Difference (C-GR - C-IR)	p-value
	C-GR (n = 19)	C-IR (n = 19)		
Microbiologic Response - n (%)	15 (100%)	13 (100%)	--	0.755
Sustained Eradication	9 (60.0%)	8 (61.5%)	-1.54%	
Recurrence	3 (20.0%)	4 (30.8%)	-10.77%	
Persistence	3 (20.0%)	1 (7.7%)	12.31%	

Note: The p-value for the test of treatment effect between two treatment groups was based on the Fisher's Exact test.

Source: Table 9 in the applicant's study report

New infections with an *Enterococcus* species were observed in the applicant's efficacy population in 2 of 15 patients (13.3%) in the C-GR group and in 4 of 13 patients (30.8%) in the C-IR group at the Late Post-Treatment Visit. New infections were also observed with *Enterobacter cloacae* (one patient in the C-IR group); and *Streptococcus agalactiae* (one patient in the C-GR group) at the Late Post-Treatment Visit.

Clinical Reviewer's Comment: Table 15 was created by the reviewer and includes the results for the FDA's MITT and PP populations.

TABLE 15
FDA's Analysis of Microbiologic Outcome at Late Post-Treatment Visit
MITT and Per Protocol Populations

Outcome	MITT Population		PP Population	
	C-GR (N=22)	C-IR (N=22)	C-GR (n=15)	C-IR (N=14)
Sustained Eradication*	4/22 (18.2%)	4/22 (18.2%)	4/15 (26.7%)	3/14 (21.4%)
Persistence	3	1	3	1
Recurrence**	4	4	3	4
New Infection	6	4	5	4
Missing Data	5	9	--	2
Superinfection***	0	0	0	0

* Urine culture at the Late Post-Treatment Visit showed that all uropathogens present at $\geq 10^3$ CFU/mL at study entry still remained at $< 10^4$ CFU/mL AND no new infections

** Urine culture showed $\geq 10^4$ CFU/mL of the original uropathogen after documentation of eradication at the Test-of-Cure Visit, up to and including the Late Post-Treatment Visit; including those with a new infection

*** No superinfections because no urine cultures were obtained during therapy

Source: Listing 16.2.12 in the applicant's study report

10.1.16.7 Clinical Outcomes at the Late Post-Treatment Visit

The applicant's efficacy population for clinical endpoints at the Late Post-Treatment Visit included 19 patients in the C-GR group and 14 patients in C-IR group and the results are shown in Table 16.

TABLE 16
Clinical Response at Late Post-Treatment Visit
Applicant's Efficacy Population

	Treatment Group		Difference (C-GR - C-IR)	p-value
	C-GR (n = 19)	C-IR (n = 19)		
Clinical Response - n (%)	19 (100%)	14 (100%)	--	0.731
Sustained Eradication	8 (42.1%)	7 (50.0%)	-7.89%	
Recurrence	4 (21.1%)	4 (28.6%)	-7.52%	
Persistence	7 (36.8%)	3 (21.4%)	15.41%	

Note: The p-value for the test of treatment effect between two treatment groups was based on the Fisher's Exact test.
 Source: Table 12 in the applicant's study report

Clinical Reviewer's Comment: Table 17 was created by the reviewer and includes the results for the FDA's MITT and PP populations.

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TABLE 17
FDA's Analysis of Clinical Outcome at Late Post-Treatment Visit
MITT and Per Protocol Populations

Outcome	MITT Population		Per Protocol Population	
	C-GR (N=22)	C-IR (N=22)	C-GR (n=15)	C-IR (N=14)
Sustained Clinical Cure	9/22 (40.9%)	7/22 (31.8%)	7/15 (46.7%)	7/14 (50.0%)
Relapse	4	4	2	4
Failure	8	4	6	2
Missing Data	1	7	--	1

Note: The p-value for the test of treatment effect between two treatment groups was based on the Fisher's Exact test.
 Source: Listing 16.2.12 in the applicant's study report

10.1.16.8 Clinical Response by Baseline Organism

In the applicant's efficacy population at the Test-of-Cure Visit, the clinical cure rate for *E. coli* infections was 75.0% (12 of 16 patients) in C-GR-treated patients. Clinical cure was not observed in C-GR-treated patients for other organisms present at baseline: *P. mirabilis* (2 patients); *K. pneumoniae* (1 patient); and *P. aeruginosa* (1 patient). For C-IR-treated patients, the clinical cure rate for *E. coli* was 87.5% (14 of 16 patients). Clinical cure was also observed for the following organisms in C-IR-treated patients: *K. pneumoniae* (1 patient); and *A. baumannii* (1 patient). Clinical cure was not observed for one C-IR-treated patient with a *P. mirabilis* infection.

In the applicant's efficacy population at the Late Post-Treatment Visit, sustained cure was experienced by 50% (8 of 16) of C-GR-treated patients who had *E. coli* infections at baseline. Among C-GR-treated patients who had *E. coli* infections, four (25%) had relapse and four (25%) had clinical failure at the Late Post-Treatment Visit. Clinical failure was observed for two C-GR-treated patients who had *P. mirabilis* infections and for one C-GR-treated patient each who had *K. pneumoniae* and *P. aeruginosa* infections at baseline. For the C-IR group, sustained cure was experienced by 58.7% (7 of 12) of patients who had *E. coli* infections at baseline (Table 14.1.2-26). Among C-IR-treated patients who had *E. coli* infections, three (25.0%) had relapse and two (16.7%) had clinical failure at the Late Post-Treatment Visit. Clinical failure was observed for one C-IR-treated patient who had a *P. mirabilis* infection at baseline and relapse was experienced by one C-IR-treated patient who had a *K. pneumoniae* infection.

10.1.16.9 Clinical Response for Patients with Persistent Baseline or New Infecting Pathogens

Clinical response at both the TOC and Late Post-Treatment Visits of individual patients who either had a persistent baseline or new infecting pathogens at the TOC visit are shown in Tables 18 and 19 for the C-GR and C-IR patients, respectively.

Clinical Reviewer's Comment: Tables 18 and 19 were created by the Reviewer using the FDA's MITT population.

TABLE 18
C-GR Patients Clinical Outcome for Persistent Baseline or New Infecting Pathogens
MITT Population

Patient #	Organism	Clinical Outcome at TOC	Clinical Outcome at Late Visit
Persistent Baseline Organism			
107	<i>E. coli</i>	Failure	Failure
310	<i>E. coli</i>	Cure	Sustained Cure
314	<i>E. coli</i>	Cure	Sustained Cure
318	<i>P. mirabilis</i>	Failure	Failure
New Infection			
305	<i>Enterococcus</i>	Cure	Relapse
320	<i>Enterococcus</i>	Cure	Relapse
512	<i>Enterococcus</i>	Failure	Failure
503	<i>Hafnia alvei</i>	Cure	Sustained Cure

TABLE 19
C-IR Patients Clinical Outcome for Persistent Baseline or New Infecting Pathogens
MITT Population

Patient #	Organism	Clinical Outcome at TOC	Clinical Outcome at Late Visit
Persistent Baseline Organism			
107	<i>E. coli</i>	Failure	Failure
New Infection			
201	<i>Enterococcus</i>	Cure	Missing
211	<i>Enterococcus</i>	Cure	Sustained Cure
316	<i>Enterococcus</i>	Cure	Sustained Cure
501	<i>Enterococcus</i>	Failure	Failure
603	<i>Enterococcus</i>	Cure	Relapse

10.1.16.10 Individual Patient Data for Microbiologic and Clinical Response Status

Individual microbiological and clinical response data at the TOC and Late Post-Treatment Visits are shown in Tables 20 and 21.

Clinical Reviewer's Comment: Tables 20 and 21 were created by the reviewer using the FDA's MITT population.

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TABLE 20
Ciprofloxacin GR – Microbiologic and Clinical Response Status
MITT Population*

Patient #	Status of Baseline Pathogen/New Infection? at TOC	Clinical Response	Status of Baseline Pathogen/New Infection? at Late Visit	Clinical Response at Late Visit	Comment
202	Persistence/No	Failure	--	Failure	Used abx
205	<i>E. coli</i> Erad/No	Failure	Sustained erad/Yes	Failure	
207	<i>E. coli</i> Erad/No	Cure	Sustained erad/Yes	Failure	
210	Persistence/--	Failure	--	--	TOC visit outside window
302	Erad/No	Failure	--	Failure	Used abx
304	<i>E. coli</i> Erad/No	Cure	Sustained erad/Yes	Sustained cure	
305	Erad/Yes	Cure	--	Relapse	Used abx
307	Erad/No	Cure	Recurrence/No	Sustained cure	Baseline org R to cipro
309	<i>E. coli</i> Erad/No	Cure	Sustained erad/No	Sustained cure	
310	<i>E. coli</i> Persistence/No	Cure	Persistence/No	Sustained cure	
314	<i>E. coli</i> Persistence/No	Cure	Persistence/No	Sustained cure	
315	<i>E. coli</i> Erad/No	Failure	Recurrence/No	Failure	
318	<i>P. mirabilis</i> Persistence/No	Failure	Persistence/No	Failure	
320	Erad/Yes	Cure	--	Relapse	Used abx
401	<i>E. coli</i> Erad/No	Failure	Sustained erad/No	Failure	
407	<i>E. coli</i> Erad/No	Cure	Sustained erad/No	Relapse	
502	<i>E. coli</i> Erad/No	Cure	Sustained erad/No	Sustained cure	
503	<i>E. coli</i> Erad/Yes	Cure	Recurrence/Yes	Sustained cure	
510	Erad/No	Cure	Sustained erad/Yes	Sustained cure	Baseline org R to cipro
512	<i>P. aeruginosa</i> Erad/Yes	Failure	Sustained erad/Yes	Failure	
602	<i>E. coli</i> Erad/No	Cure	Sustained erad/Yes	Sustained Cure	
604	<i>E. coli</i> Erad/No	Cure	Recurrence/No	Relapse	

*includes all patients who received one dose of study medication and who had a baseline pathogen

Excluded from the MITT Population, Excluded from the Efficacy Population

Source: Listing 16.2.12 in the applicant's study report

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TABLE 21
Ciprofloxacin IR – Microbiologic and Clinical Response Status
MITT Population*

Patient #	Status of Baseline Pathogen/New Infection? at TOC	Clinical Response	Status of Baseline Pathogen/New Infection? at Late Visit	Clinical Response at Late Visit	Comment
107	<i>E. coli</i> Persistence/No	Failure	Persistence/No	Failure	
201	Erad/Yes	Cure	---	---	Used abx
203	Erad/No	Cure	---	---	Used abx
208	Erad/No	Cure	---	---	Used abx
209	<i>K. pneumoniae</i> Erad/No	Cure	--	Relapse	
211	<i>E. coli</i> Erad/Yes	Cure	Sustained erad/Yes	Sustained cure	
301	<i>E. coli</i> Erad/No	Cure	Sustained erad/No	Sustained cure	
303	Erad/No	Cure	---	---	
306	<i>E. coli</i> Erad/No	Cure	Recurrence/No	Sustained cure	
312	Persistence/No	Failure	---	---	TOC visit outside of window
313	<i>E. coli</i> Erad/No	Cure	Recurrence/No	Relapse	
316	<i>E. coli</i> Erad/Yes	Cure	Sustained erad/Yes	Sustained cure	
317	Erad/No	Cure	---	---	Used abx
321	<i>E. coli</i> Erad/No	Cure	Recurrence/No	Sustained cure	
403	<i>E. coli</i> Erad/No	Cure	Sustained erad/No	Sustained cure	
404	Erad/No	Failure	Sustained erad/no	Failure	Used abx
406	<i>E. coli</i> Erad/No	Cure	Sustained erad/Yes	Relapse	
501	<i>E. coli</i> Erad/Yes	Failure	Recurrence/Yes	Failure	
505	<i>E. coli</i> Erad/No	Cure	Sustained erad/No	Sustained cure	
511	Persistence/--	Failure	---	---	No TOC visit
601	Erad/No	Failure	---	Failure	Baseline org R to cipro
603	<i>E. coli</i> Erad/Yes	Cure	Sustained erad/Yes	Relapse	

*includes all patients who received one dose of study medication and who had a baseline pathogen

~~Excluded from the MITT Population; Excluded from the Per Protocol Population~~

Source: Listing 16.2.12 in the applicant's study report

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10.1.17 Safety Results

All patients in both treatment groups were 100% compliant with the prescribed treatment regimen, as determined by return of unused tablets, and received study drug for 3 days as described in the protocol.

10.1.17.1 Deaths, Discontinuations, and Severe Adverse Events

No patients died or experienced AEs that caused the discontinuation of study medication during the course of the 5-week study. One patient in the C-GR treatment group experienced an SAE of chest pain that was considered by the investigator to be mild in severity and not related to study treatment. A clinical summary prepared by the applicant follows:

Patient 604 was a 61-year-old female with a significant past medical history of cholecystectomy (1988) and hysterectomy (1977). The subject first received treatment with 500 mg of C-GR (one tablet in the evening) once daily on _____. The last dose of C-GR was taken on _____. On _____, one day after taking the final dose of study drug, the patient complained of chest pain and was hospitalized for further evaluation. Her vital signs included a blood pressure of 128/82 mm Hg, a pulse rate of 60 beats/min, a temperature of 97.0F, and a respiratory rate of 20 breaths/min. She was given two doses of sublingual nitroglycerin, which relieved her chest pain. On the following day her chest pain returned, accompanied by vomiting. The patient was subsequently placed on oxygen via nasal cannula and was administered nitro paste (0.5 inch every six hours), enoxaparin (1 mg/kg subcutaneously every 12 hours), and acetylsalicylic acid (1 tablet per day). Diagnostic tests revealed nonspecific T-wave changes from electrocardiogram, normal results from adenosine cardiolute test, and no evidence of acute cardiopulmonary disease from chest x-ray. The patient's symptoms abated after receiving ranitidine hydrochloride therapy, and she was discharged on _____ in good condition.

Concomitant medications taken at the time of the event included acetylsalicylic acid, phenazopyridine, nitroglycerin, enoxaparin and ranitidine hydrochloride.

In the opinion of the investigator, the chest pain was considered mild in severity and not related to study treatment.

Clinical Reviewer's Comment: The Reviewer agrees with the investigator's assessment of this adverse event.

10.1.17.2 All Adverse Events

Adverse events occurring during the study in the all randomized patients population are summarized by treatment group, preferred term, and system organ class in Table 22. For each preferred term, there were no significant differences in the numbers of patients who experienced AEs between the C-GR group and the C-IR group.

During the course of the 5-week study, 17 of 29 patients (58.6%) in the C-GR group and 15 of 29 patients (51.7%) in the C-IR group experienced AEs. The most common AEs during the course of the 5-week study for the all randomized patient population (both treatment groups combined) were urinary tract infection NOS in 8 of 58 patients (13.8%); fungal vaginosis in 5 of 58 patients (8.6%); upper respiratory tract infection NOS in 4 of 58 patients (6.9%); dizziness and nausea each in 3 of 58 patients (5.2%); and bronchitis NOS, cough, headache, hematuria, herpes simplex infection, pharyngitis, and suprapubic pain each in 2 of 58 patients (3.4%).

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TABLE 22
Summary of Adverse Events Occurring During the Study

	Treatment Group		Total	p-value
	Ciprofloxacin GR	Ciprofloxacin IR		
Number of Patients Randomized in the Study	29	29	58	
Number (%) of Patients Received Treatment	29 (100%)	29 (100%)	58 (100%)	
Number (%) of Patients without Any Adverse Event in the Study	12 (41.4%)	14 (48.3%)	26 (44.8%)	
Number (%) of Patients with at Least One Adverse Event in the Study	17 (58.6%)	15 (51.7%)	32 (55.2%)	NS
Number (%) of Patients Who Reported Adverse Events by System Organ Class				
Ear and labyrinth disorders	0	1 (3.4%)	1 (1.7%)	NS
Deafness NOS	0	1 (3.4%)	1 (1.7%)	NS
Gastrointestinal disorders	2 (6.9%)	6 (20.7%)	8 (13.8%)	NS
Nausea	0	3 (10.3%)	3 (5.2%)	NS
Abdominal pain lower	0	1 (3.4%)	1 (1.7%)	NS
Anal discomfort	0	1 (3.4%)	1 (1.7%)	NS
Constipation	1 (3.4%)	0	1 (1.7%)	NS
Diarrhoea NOS	0	1 (3.4%)	1 (1.7%)	NS
Flatulence	0	1 (3.4%)	1 (1.7%)	NS
Gastroesophageal reflux disease	1 (3.4%)	0	1 (1.7%)	NS
Pruritus ani	0	1 (3.4%)	1 (1.7%)	NS
General disorders and administration site conditions	2 (6.9%)	1 (3.4%)	3 (5.2%)	NS
Suprapubic pain	1 (3.4%)	1 (3.4%)	2 (3.4%)	NS
Chest pain	1 (3.4%)	0	1 (1.7%)	NS
Immune system disorders	1 (3.4%)	1 (3.4%)	2 (3.4%)	NS
Allergy to arthropod sting	1 (3.4%)	0	1 (1.7%)	NS
Drug hypersensitivity	0	1 (3.4%)	1 (1.7%)	NS
Infections and infestations	8 (27.6%)	9 (31.0%)	17 (29.3%)	NS
Urinary tract infection NOS	3 (10.3%)	5 (17.2%)	8 (13.8%)	NS
Vaginosis fungal NOS	2 (6.9%)	3 (10.3%)	5 (8.6%)	NS
Upper respiratory tract infection NOS	2 (6.9%)	2 (6.9%)	4 (6.9%)	NS
Herpes simplex	1 (3.4%)	1 (3.4%)	2 (3.4%)	NS
Fungal infection NOS	0	1 (3.4%)	1 (1.7%)	NS
Sinusitis NOS	0	1 (3.4%)	1 (1.7%)	NS
Viral infection NOS	1 (3.4%)	0	1 (1.7%)	NS
Injury, poisoning and procedural complications	1 (3.4%)	0	1 (1.7%)	NS
Muscle strain	1 (3.4%)	0	1 (1.7%)	NS
Musculoskeletal and connective tissue disorders	0	2 (6.9%)	2 (3.4%)	NS
Back pain	0	1 (3.4%)	1 (1.7%)	NS
Flank pain	0	1 (3.4%)	1 (1.7%)	NS

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	Treatment Group		Total	p-value
	Ciprofloxacin GR	Ciprofloxacin IR		
Nervous system disorders	1 (3.4%)	4 (13.8%)	5 (8.6%)	NS
Dizziness	0	3 (10.3%)	3 (5.2%)	NS
Headache	1 (3.4%)	1 (3.4%)	2 (3.4%)	NS
Renal and urinary disorders	4 (13.8%)	0	4 (6.9%)	NS
Haematuria	2 (6.9%)	0	2 (3.4%)	NS
Dysuria	1 (3.4%)	0	1 (1.7%)	NS
Micturition urgency	1 (3.4%)	0	1 (1.7%)	NS
Urethral spasm	1 (3.4%)	0	1 (1.7%)	NS
Reproductive system and breast disorders	3 (10.3%)	1 (3.4%)	4 (6.9%)	NS
Dysmenorrhoea	1 (3.4%)	0	1 (1.7%)	NS
Endometrial hypertrophy	1 (3.4%)	0	1 (1.7%)	NS
Genital pruritus female	0	1 (3.4%)	1 (1.7%)	NS
Ovarian cyst	1 (3.4%)	0	1 (1.7%)	NS
Vaginal discharge	1 (3.4%)	0	1 (1.7%)	NS
Respiratory, thoracic and mediastinal disorders	3 (10.3%)	2 (6.9%)	5 (8.6%)	NS
Bronchitis NOS	0	2 (6.9%)	2 (3.4%)	NS
Cough	1 (3.4%)	1 (3.4%)	2 (3.4%)	NS
Pharyngitis	1 (3.4%)	1 (3.4%)	2 (3.4%)	NS
Rhinitis allergic NOS	1 (3.4%)	0	1 (1.7%)	NS

Note: Adverse event mapping was based on the MedDRA Version 5.1 thesaurus.

A patient may be reported in more than one category.

The p-values were obtained from the Fisher's Exact test and were presented if they are less than 0.10.

NS = Not statistically significant at 0.10 level.

Source: Table 14.1.3-1 in the applicant's study report

10.1.17.3 Treatment-Related Adverse Events

During the course of the 5-week study, treatment-related AEs of fungal vaginosis NOS (in 2 of 29 patients [6.9%]) and urinary tract infection NOS (in 1 of 29 patients [3.4%]) were experienced by patients in the C-GR group. The following treatment-related AEs were experienced by patients in the C-IR group: nausea (in 3 of 29 patients [10.3%]); fungal vaginosis NOS, urinary tract infection NOS, and dizziness (each in 2 of 29 patients [6.9%]); and lower abdominal pain, diarrhea NOS, flank pain, and genital pruritus (each in 1 of 29 patients [3.4%]).

10.1.17.4 Severity of Adverse Events

During the course of the 5-week study, the majority of AEs experienced by patients in the C-GR and C-IR groups were mild or moderate in severity. The following severe AEs were reported: headache, urinary tract infection NOS, and viral infection NOS each in 1 of 29 patients (3.4%) for the C-GR group; and herpes simplex, urinary tract infection NOS, and upper respiratory tract infection NOS each in 1 of 29 patients (3.4%) for the C-IR group. None of the severe AEs experienced by patients in the C-GR and C-IR groups were reported to be related to study drug.

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10.1.17.5 Changes in Laboratory Parameters

There were no significant differences between the C-GR and C-IR groups in the mean changes from baseline to final visit in test results for hematology parameters, blood chemistry parameters, and urinalysis parameters. There were no noteworthy changes in laboratory values between baseline and end of study except for reduction of white blood cells and neutrophils.

10.1.17.6 Changes in Vital Signs

There were no significant differences between the C-GR and C-IR groups in the mean changes from baseline to final study visit in results of vital signs measurements.

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10.2 Review of Study 81-0015

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 in Female Urinary Tract Infections

Phase III Study

Study Initiation Date: June 3, 2003

Study Report Date: June 30, 2004

Clinical Reviewer's Comments: Unless otherwise noted, all tables in this review are reproduced from the applicant's study report.

Abbreviations defined:

C-GR: ciprofloxacin gastric-release tablets also known as extended-release tablets or Proquin XR

C-IR: ciprofloxacin immediate-release tablets (Cipro IR)

10.2.1 Study Objectives

The objectives of the study were as follows:

- To compare the efficacy of C-GR qd with C-IR bid at equal total daily doses (500 mg) in achieving microbiological eradication of pathogens associated with UTIs at 7 (\pm 2) days after the completion of treatment.
- To compare the efficacy of C-GR qd with C-IR bid at equal total daily doses (500 mg) in achieving clinical cure at 7 (\pm 2) days after the completion of treatment.
- To compare the efficacy of C-GR qd with C-IR bid at equal total daily doses (500 mg) in achieving clinical cure and microbiological eradication of pathogens associated with UTIs at 5 weeks (\pm 7 days) after the completion of treatment.
- To compare the incidence and severity of side effects with C-GR qd and C-IR bid at equal total daily doses (500 mg).

10.2.2 Study Design

This was a multicenter, randomized, double-blind (double-dummy), active-controlled, parallel-group, non-inferiority, clinical study designed to compare the efficacy and safety of C-GR, 500 mg once daily for 3 days, and C-IR, 250 mg twice daily for 3 days, in the treatment of acute, uncomplicated UTI. Adult female patients with an onset of clinical signs and symptoms of acute, uncomplicated UTI within the previous 72 hours were eligible for screening after providing written informed consent.

Patients who met eligibility requirements were enrolled in the study. Patients who were enrolled in the study and were later determined not to have met the criteria for positive urine

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microbiology and uropathogen susceptibility testing remained in the study, were included in the safety analyses, but were excluded from the efficacy analyses.

At the screening/randomization visit, patients received instruction on accessing the interactive voice response system (IVRS) to answer questions daily about symptoms until the Test-of-Cure Visit. The first call was made at the study site to record baseline symptoms. Patients were instructed to call IVRS twice daily during drug treatment (i.e., through the morning of Day 4), and once daily after completion of the evening meal until the Test-of-Cure Visit (i.e., through 7 days [± 2 days] after completion of treatment). During drug treatment, the patient responded to questions about compliance with the treatment regimen only in the morning IVRS call, and to questions about symptoms of a UTI and treatment compliance during the evening call.

Patients were randomly assigned to treatment with either C-GR or C-IR and instructed to take their first dose of study drug during the evening of study enrollment, following dinner. If a patient was enrolled in the morning and the investigator determined that the patient could not wait until evening to start study drug, the patient was permitted to take the first dose of medication following lunch. The timing of subsequent doses remained unchanged. Dosing continued through the morning and evening of the next 2 days, and the morning of the fourth day.

Patients returned to the clinic for a Test-of-Cure Visit at 7 days (± 2 days) after completing medication (11 days ± 2 from the enrollment visit) and a Late Post-Treatment Visit at 5 weeks (± 7 days) following treatment.

This study was planned to evaluate 576 adult, female patients who had a primary diagnosis of acute, symptomatic, uncomplicated lower UTI and who had qualified for enrollment on the basis of the following inclusion and exclusion criteria. A total of 1037 patients were actually enrolled in the study.

10.2.3 Inclusion Criteria

Inclusion criteria were identical to those in Study 81-0005 (see Section 10.1.3 *Inclusion Criteria*), with the exception of the clean catch mid-stream urine culture, which had to be obtained on the day of enrollment in (as opposed to within 48 hours of enrollment) in the study.

10.2.4 Exclusion Criteria

Inclusion criteria were identical to those in Study 81-0005 (see Section 10.1.4 *Exclusion Criteria*), with the addition of the following three criteria:

- Patient had signs and symptoms of a vaginal infection.
- Patient had gastric reduction surgery
- Patient was taking the anticoagulant warfarin or its derivatives (such as Coumadin®).

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10.2.5 Study Drug Administration

Same as Study 81-0005 (See Section 10.1.5 *Study Drug Administration*).

10.2.6 Prior and Concomitant Medications

Same as Study 81-0005 (See Section 10.1.6 *Prior and Concomitant Medications*), with the addition of warfarin as a prohibited concomitant medication.

10.2.7 Study Assessments

The efficacy and safety assessments performed during the study are shown in Table 1.

TABLE 1
Study Assessments

Study Period	Screening/ Randomization	Test-of-Cure Visit	Late Post- Treatment Visit	Optional Unscheduled Visit
Visit/Study Day	Visit 1 Day 1	Visit 2 Day 11 (± 2)	Visit 3 Day 39 (± 7)	Unscheduled Visit
Informed consent	X			
Medical history	X			
Physical examination	X	X	X	X
Clinical signs/symptoms	X	X	X	X
Vital signs	X	X	X	X
Chemistry/hematology	X	X	X	X
Clean catch urine sample	X	X	X	X
Dipstick	X			
Urine pregnancy test	X	X		
Urinalysis/microscopy	X	X	X	X
Microbiological culture/susceptibility	X	X	X	X
Global assessments		X		
Dispense medication	X			
Access IVRS in office	X			
Return unused medication		X		
Prior/concomitant medications	X	X	X	X
Adverse events		X	X	X

Source: Table 2 in applicant's study report

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10.2.8 Efficacy Evaluation

10.2.8.1 Primary Efficacy Parameter

The primary efficacy parameter was microbiological outcome at Test-of-Cure Visit (4 to 11 days following treatment). Microbiological outcome was defined the same as in Study 81-0005 (see Section 10.2.8.1 Primary Efficacy Parameter)

- *Eradication*: Urine culture showed that all uropathogens present at study enrollment at $\geq 10^5$ CFU/mL were reduced to $<10^4$ CFU/mL.
- *Persistence*: Urine culture taken any time after completion of therapy showed $\geq 10^4$ CFU/mL of uropathogens present at study enrollment.
- *New Infection*: Urine culture taken any time after completion of therapy showed $\geq 10^5$ CFU/mL of uropathogens not present at study enrollment.
- *Superinfection*: Urine culture taken for any reason during therapy showed growth of $\geq 10^5$ CFU/mL of an uropathogen other than those detected at study enrollment.

Clinical Reviewer's Comment: Routine urine cultures were not obtained during therapy, therefore the applicant did not assess the development of superinfections in this study.

10.2.8.2 Secondary Efficacy Parameters

The secondary efficacy parameters were:

1. Clinical outcome at the Test-of-Cure Visit (4 to 11 days following treatment)
2. Global evaluation at the Test-of-Cure Visit (4 to 11 days following treatment)
 - *Investigator Evaluation*: The investigator responded "Yes" or "No" to the following question: "Do you feel that the patient's UTI has satisfactorily resolved?"
 - *Patient Evaluation*: The patient responded "Yes" or "No" to the following question: "Do you feel that your UTI has been successfully treated?"
3. Clinical symptom data collected by the IVRS from baseline through the Test-of-Cure Visit
4. Clinical outcomes at the Late Post-Treatment Visit (5 weeks \pm 7 days) following treatment)
5. Microbiological outcome at the Late Post-Treatment Visit (5 weeks \pm 7 days) following treatment)

Clinical outcome at the Test-of-Cure Visit and Late Post-Treatment Visit, as well as microbiological outcome at the Late Post-Treatment Visit was defined the same as in Study 81-0005 (see Section 10.1.8.2 *Secondary Efficacy Parameters*)

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10.2.9 Efficacy Analysis

10.2.9.1 Primary Efficacy Analysis

For the analysis of the primary efficacy parameter, a 95% confidence interval of the microbiological eradication rate of each treatment group was constructed. A 95% confidence interval of the difference in this event rate between two treatment groups (C-GR - C-IR) was also constructed. A lower boundary of the confidence interval of the difference in the microbiological eradication rate at Test-of-Cure Visit of not less than -10% was necessary for the C-GR treatment to be considered non-inferior to the C-IR treatment.

In addition, a two-sample one-sided Z test on proportions was performed. This Z test was used for testing the null hypothesis that the treatment difference (C-GR minus C-IR) in the microbiological eradication rate at the Test-of-Cure Visit is equal to the lower equivalence margin (-10%) versus the alternative that the treatment difference is greater than the lower equivalence margin.

The data collected from all study centers were pooled for data analysis.

10.2.9.2 Secondary Efficacy Analyses

The Fisher's Exact test was used for the analysis of secondary categorical efficacy parameters. These are event rates for the microbiological and clinical outcomes at the Test-of-Cure Visit and at the Late Post-Treatment Visit. The data collected from all study centers were pooled.

A 95% confidence interval of the event rates of each treatment group was constructed for the secondary dichotomous efficacy parameters. In addition, a 95% confidence interval of the difference in event rates between two treatment groups (C-GR minus C-IR) was constructed.

The Cochran-Mantel-Haenszel (CMH) test for general association with treatment as a stratification factor was employed to examine the correlation between bacterial eradication (yes/no) and clinical cure status (yes/no) at the Test-of-Cure Visit.

Fisher's Exact test was used for the test of microbiological response rates by baseline organism between treatment groups, clinical response rates by baseline clinical signs and symptoms between treatment groups, analysis of dichotomous global evaluation data collected at Test-of-Cure Visit, and analysis of categorical clinical symptom data collected by IVRS.

10.2.9.3 Intermediate Data Analysis

An intermediate data analysis was planned for this study based on study data collected for approximately 100 patients who completed the Test-of-Cure Visit. The microbiological eradication rate for all patients combined was calculated based on this intermediate data set without unblinding the randomization treatment codes. This intermediate data analysis was used to validate those assumptions used for the original sample size calculation of the study. Since

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there would be no unblinded treatment comparison performed, there was no adjustment of significance level for the final treatment comparisons.

Clinical Reviewer's Comment: The planned intermediate data analysis was not performed. However, based on a higher than expected non-evaluable rate observed during the study recruitment period, the applicant made an adjustment to the sample size in order to provide sufficient power for this study (see Section 10.2.11 below).

10.2.10 Analysis Populations

The "all randomized patients" population included those who were randomized and received a study patient number and treatment assignment. Three patients (i.e., 2401, 6009, and 6012) were randomized through IVRS in study 81-0015 in error and were excluded from the all randomized patient population for data analysis. There were also patients who were randomized through IVRS, but did not receive study drug. These patients are considered part of the all randomized patient population.

All randomized patients also included non-evaluable patients for the analysis of selected efficacy endpoints. Patients who used additional antimicrobial agents to treat UTI were included and classified as clinical failures after the treatment. Patients who used additional antimicrobial agents were excluded at the visits occurring after antimicrobial treatment.

The safety population included all patients who received treatment.

The intent-to-treat (ITT) population included evaluable patients randomized in this study. The evaluable patients are randomized patients who met the enrollment criteria for positive urine microbiology and uropathogen susceptibility (Inclusion Criteria 4 and 5). The ITT population was used for the analysis of microbiological eradication data and clinical cure data at Test-of-Cure Visit.

The efficacy population included evaluable patients who were randomized in this study and had microbiological data at the Test-of-Cure Visit. The efficacy population was used for the analysis of primary and secondary efficacy parameters.

Clinical Reviewer's Comment: The applicant defined different populations for the microbiologic and clinical efficacy endpoints, as well as different populations for the Test-of-Cure Visit and Follow-up Visits, which is not considered acceptable by the Division. Instead, a consistent population should be used for all endpoints and visits. For further discussion, see Results.

10.2.11 Sample Size

A sample size of approximately 720 patients (360 patients per treatment group) was planned for this study to ensure at least 504 evaluable patients (252 patients per treatment group) to have available primary efficacy data for data analysis. To meet the evaluable criteria, patients must have had one positive pre-treatment clean catch mid-stream urine culture within 48 hours of

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enrollment in the study (defined as $\leq 10^5$ CFU/mL), as well as *in vitro* susceptibility testing of uropathogens to both the test drug and the control drug. A sample size of at least 504 patients (252 patients per treatment group) would provide 80% power to demonstrate therapeutic non-inferiority of the C-GR treatment versus C-IR treatment in microbiological eradication rate at the Test-of-Cure Visit. A 95% confidence interval of the difference in microbiological eradication rate at the Test-of-Cure Visit between two treatment groups (C-GR minus C-IR) was constructed for this dichotomous outcome. If the lower boundary of this confidence interval of the difference in the primary microbiological eradication rate at Test-of-Cure Visit is not less than -10%, the C-GR treatment would be considered non-inferior to the C-IR treatment.

Assuming a microbiological eradication rate of 80% for both C-GR and C-IR treatment groups, a sample size of 252 patients was needed for each treatment group. This calculation was based on a one-sided test with $\alpha=0.025$ and a maximum acceptable difference of 10%. To allow up to a 30% non-evaluable rate, an enrollment of approximately 720 patients for this study was planned.

The planned intermediate data analysis was not performed. However, based on a higher than expected non-evaluable rate observed during the study recruitment period, an adjustment was made to the sample size in order to provide sufficient power for this study.

To calculate the adjusted sample size for this study, the assumption for the nonevaluable rate was modified from 30% to 40%, and the power was modified from 80% to 85% by the applicant. All other assumptions used for the original sample size calculation remained the same. Based on this adjustment, a sample of 960 patients (480 patients per treatment group) was required for this study to ensure at least 576 patients (288 patients per treatment group) who have available primary efficacy data for data analysis. The original sample size assumption for this study was to enroll 720 patients in order to ensure at least 504 patients who have available primary efficacy data for data analysis. As a result of this sample size adjustment, the original sample size for this study was increased by about 34%.

10.2.12 Changes in Conduct of the Study

The original protocol was issued April 1, 2003. The protocol was amended twice: Amendment 1 was issued on July 21, 2003 and Amendment 2 was issued on October 14, 2003. Significant changes to the protocol contained in each Amendment are summarized below.

Amendment 1 (July 21, 2003)

- The number of planned investigators and study sites was changed from 50 to 60-70.
- In the Synopsis (Trial Design) and Section 3.2 of the protocol (Dose and Administration), the following phrase was added: "If a patient is enrolled in the morning and the investigator feels the patient cannot wait until evening to start study drug, she (the patient) may take her first dose of medication following lunch. Timing of subsequent doses remains unchanged."

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- For inclusion criterion 3, the last sentence is modified to delete the following test: “or \geq 10 WBC/mm³ (unspun urine).” Patients must have a positive urine dipstick at the study site to be eligible for inclusion.
- Inclusion criterion 4 was reworded for clarity as shown: “At least one positive, pre-treatment clean-catch mid-stream urine culture collected on the day patient enrolls in the study, defined as $\geq 10^5$ CFU/mL”
- In the Synopsis and Section 4.2 of the protocol (Exclusion Criteria) Exclusion criterion 6 was added: “Patient has had gastric reduction surgery.”
- In Section 5.5.2 (Concomitant Medications), the statement on phenazopyridine was reworded for clarification to the following text: “Patients who are taking the urinary analgesic phenazopyridine (Pyridium®, Urostat®, Azo-Standard®, etc.) at the time of screening may participate in the study. Patients may take (continue to take) phenazopyridine, but *only* for the first 24 hours after study enrollment.”
- The following statement was added immediately after the sentence above: “Patients should be instructed to refrain from use of herbal and other natural supplements that may reduce symptoms of UTI during the study drug treatment period.”
- The first sentence of Section 6.1.3 of the protocol was changed to the following: “If a patient experiences a worsening of symptoms during the period between the start of treatment and the Test-of-Cure Visit, she may return to the clinic for an unscheduled visit.”

Amendment 2 (October 14, 2003)

- Protocol 81-0015 was amended to increase the sample size of the study and to clarify a point in the statistical analysis. At the time of this protocol amendment an unexpectedly high number of non-evaluable patients were observed. To provide sufficient power for statistical analyses, the planned sample size was increased by approximately 34% from 720 patients to 960 patients.
- To calculate the adjusted sample size for this study, the assumed rate of non-evaluable patients was increased from 30% to 40%, and the power was changed from 80% to 85%. All other assumptions used for the original sample size calculation remained the same. Based on this adjustment, a sample of 960 patients (480 patients per treatment group) was required for this study to ensure that primary efficacy data would be available for at least 576 evaluable patients (288 patients per treatment group) who have available primary efficacy data for data analysis (see Section 9.1 of the protocol).
- In the Synopsis and Section 9.5.2 of the protocol (Analysis Population and Handling of Dropouts), the definition of evaluable patients for efficacy endpoints was changed as shown:

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- The main analysis of the primary efficacy parameters and secondary efficacy parameters will include all randomized patients who met the enrollment criteria for positive urine microbiology and uropathogen susceptibility (inclusion criteria 4 and 5) with available data.

Applicant's Correction of error in Protocol

The applicant noted that there was a consistent error in the protocol that specified the time of the Late Post-Treatment Visit as 5 weeks (± 3 days) after the completion of study treatment rather than 5 weeks (± 7 days) as specified in the draft Guidance. The final study report corrected the error.

10.2.13 Changes to the Efficacy Analysis

As per the draft Guidance for Industry (July 1998): "*Uncomplicated Urinary Tract Infection -- Developing Antimicrobial Drugs for Treatment*", the original protocol defined the timing of the test-of-cure (TOC) visit to be 7 (± 2) days after the completion of treatment. However, without amending the protocol, the applicant's final 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".

Clinical Reviewer's Comment: The Clinical and Statistical Reviewers conducted a sensitivity analysis to confirm that the change in the timing of the test-of-cure visit does not affect the results of the primary endpoint of the study. For further information, see Results section.

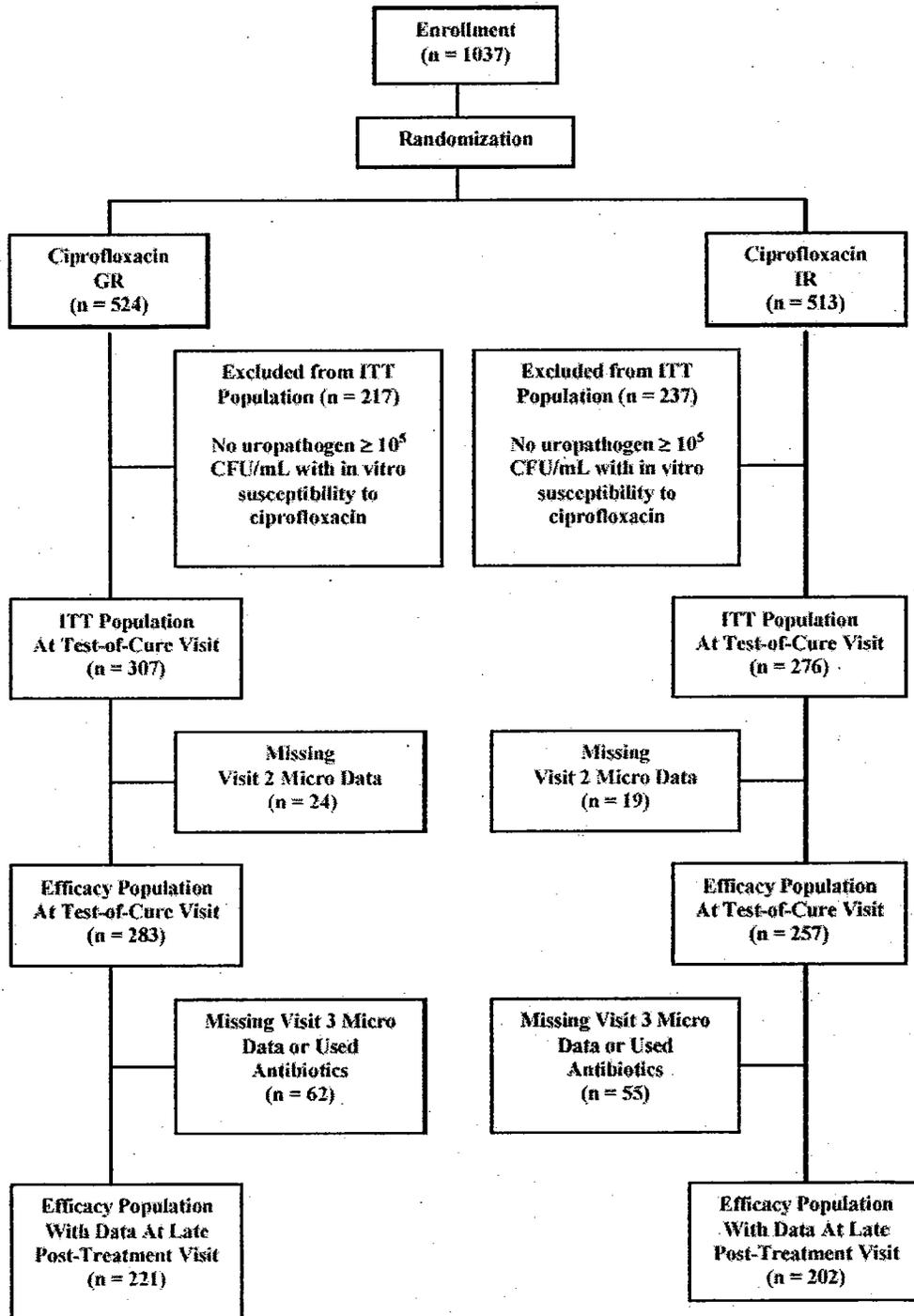
10.2.14 Enrollment by Study Center

Patient enrollment by study center can be found in Section 10.3: "*Enrollment by Study Center, Study 81-0015*"

10.2.15 Patient Disposition

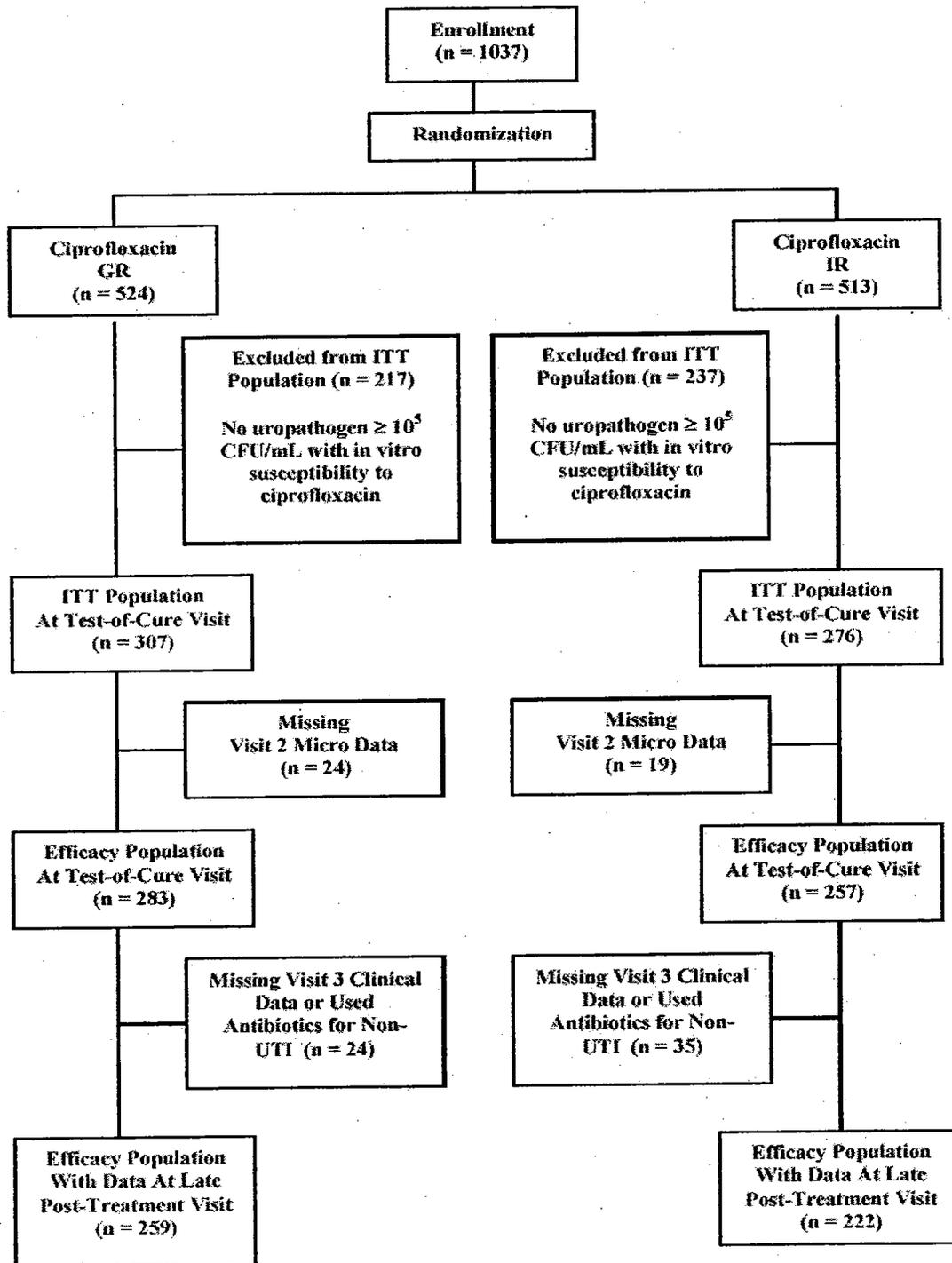
The applicant's microbiological and efficacy populations were defined as shown in Figures 1 and 2.

FIGURE 1
Applicant's Population for Microbiological Data Analysis



Source: Figure 3 in the applicant's study report

FIGURE 2
Population for Clinical Data Analysis



Source: Figure 3 in the applicant's study report

Clinical Reviewer's Comments: The applicant's defined intent-to-treat (ITT) and Efficacy Populations in Figures 1 and 2 are identical to the FDA's modified intent-to-treat (MITT) and Per Protocol (PP) populations, respectively, in Table 2 (created by the Reviewer). However, the applicant defined different populations for the microbiologic and clinical efficacy endpoints, as well as different populations for the Test-of-Cure Visit and Follow-up Visits, which is not considered acceptable by the Division. Instead, a consistent population should be used for all endpoints and visits. In the FDA analyses that follow, a consistent population is used for all endpoints and time points.

In the FDA's MITT population, patients with ciprofloxacin-resistant baseline isolates were excluded, which is consistent with the applicant's protocol and their ITT population. However, the Division usually includes patients with resistant isolates in the MITT population. There were 11 C-GR patients and 9 C-IR patients who were excluded for having ciprofloxacin-resistant isolates. A sensitivity analysis was performed by the Statistical Reviewer to confirm that exclusion of these patients does not affect the results of the primary endpoint. See Results section.

The reasons for a subject having missing microbiological data at TOC and thus being excluded from the FDA's PP population were not clearly summarized by the applicant in the study report. Attempts to identify the reason for a subject not having evaluable microbiological data at TOC were made by the Clinical and Statistical Reviewers and are indicated in Table 2. These assessments were made through use of the electronic data and the patient listings provided in study report.

TABLE 2
FDA Analysis of Patient Evaluability

	C-GR	C-IR
Enrolled	524	513
Safety Population	519	509
<i>Did not receive study medication</i>	<i>5</i>	<i>3</i>
<i>Received alternate study medication in error</i>	<i>0</i>	<i>1</i>
Modified Intent-to-Treat Population	307	276
<i>No pathogen $\geq 10^3$ CFU/mL at baseline</i>	<i>201</i>	<i>224</i>
<i>Baseline pathogen was not susceptible to ciprofloxacin</i>	<i>11</i>	<i>9</i>
Per Protocol Population*	272	251
<i>TOC visit outside 7-14 day window</i>	<i>5</i>	<i>7</i>
<i>Used antibacterials during the study</i>	<i>11</i>	<i>6</i>
<i>Lost to follow-up</i>	<i>15</i>	<i>7</i>
<i>Consent withdrawn</i>	<i>2</i>	<i>4</i>
<i>Adverse Event</i>	<i>0</i>	<i>1</i>
<i>Other</i>	<i>2</i>	<i>0</i>

*reasons for exclusion were determined by the Reviewer; other factors may also have existed that contributed to exclusion of these patients

10.2.16 Study Medication Compliance

Among patients who received at least one dose of study drug, $\geq 80\%$ compliance with the dosing schedule was observed for 492 of 517 patients (95.2%) in the C-GR group and for 496 of 510 patients (97.3%) in the C-IR group.

In the applicant's ITT population, $\geq 80\%$ compliance was reported for 293 of 307 patients (96.1%) in the C-GR group and for 270 of 276 patients (97.8%) in the C-IR group. In the efficacy population, $\geq 80\%$ compliance was reported for 279 of 283 patients (98.6%) in the C-GR group and for 256 of 257 patients (99.6%) in the C-IR group.

10.2.17 Demographics and Baseline Characteristics

Demographics and baseline characteristics were summarized for all randomized patients (524 patients in the C-GR group and 513 patients in the C-IR group) in Table 3.

TABLE 3
Demographics and Baseline Characteristics
All Randomized Patients

Characteristics	Statistics	Treatment Group		Total (n = 1037)	p-value
		C-GR (n = 524)	C-IR (n = 513)		
Age (year)	Mean (SD)	39 (15.1)	39 (14.8)	39 (15.0)	0.577
	(Min, Max)	(18, 89)	(18, 86)	(18, 89)	
Female	n (%)	524 (100%)	513 (100%)	1037 (100%)	NA
Caucasian	n (%)	401 (76.5%)	415 (80.9%)	816 (78.7%)	0.324
Height (in)	Mean (SD)	65 (2.7)	64 (2.9)	64 (2.8)	0.269
	(Min, Max)	(54, 74)	(50, 72)	(50, 74)	
Weight (lb)	Mean (SD)	156 (41.5)	159 (41.8)	158 (41.6)	0.222
	(Min, Max)	(93, 437)	(85, 385)	(85, 437)	

Note: The p-value for the test of treatment effect between two treatment groups was based on the two-sample t-test for numeric data or the Fisher's Exact test for categorical data.

SD=Standard deviation

NA=Not applicable

Source: Table 3 in the applicant's study report

10.2.18 Efficacy Results

10.2.18.1 Microbiological Outcomes at the Test-of-Cure Visit

Microbiological eradication of the baseline pathogen (the protocol-definition of the primary endpoint) is shown for the applicant's ITT population in Table 3 and Efficacy population in Table 4. C-GR was shown to be non-inferior to C-IR as the lower bound of the 95% confidence interval of the treatment difference (C-GR minus C-IR) is above -10% (95% CI for the Efficacy population [-0.99%, 8.59%]).

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TABLE 3
Microbiological Outcomes at Test of Cure Visit
Applicant's ITT Population

One-Week Microbiological Outcomes	Statistics	Treatment Group		Difference (C-GR – C-IR)	p-value
		C-GR (n = 307)	C-IR (n = 276)		
Microbiological Eradication	Event / Sample Size*	254/293	225/268	2.70%	< 0.001
	Eradication Rate	86.7%	84.0%		
	95% CI of Rate	(82.81%, 90.59%)	(79.61%, 88.39%)		

Note: The p-value for the test of non-inferiority of C-GR compared to C-IR in microbiological eradication was based on the two-sample, one-sided Z test of two proportions using delta = -0.10. In the Test-of-Cure Visit efficacy population, 293 patients in the C-GR group and 268 patients in the C-IR group did not receive other antibiotics for the treatment of non-UTI conditions or an UTI prior to the Test-of-Cure Visit. Source: Table 5 in the applicant's study report

TABLE 4
Microbiological Outcomes at Test of Cure Visit
Applicant's Efficacy Population

One-Week Microbiological Outcomes	Statistics	Treatment Group		Difference (C-GR – C-IR)	p-value
		C-GR (n = 283)	C-IR (n = 257)		
Microbiological Eradication	Event / Sample Size*	254/272	225/251	3.80%	< 0.001
	Eradication Rate	93.4%	89.6%		
	95% CI of Rate	(90.45%, 96.35%)	(85.82%, 93.38%)		

Note: The p-value for the test of non-inferiority of C-GR compared to C-IR in microbiological eradication was based on the two-sample, one-sided Z test of two proportions using delta = -0.10. In the Test-of-Cure Visit efficacy population, 272 patients in the C-GR group and 251 patients in the C-IR group had microbiological data at baseline and at the Test-of-Cure Visit. Source: Table 4 in the applicant's study report

Clinical Reviewer's Comments: In Table 3 and Table 4, the applicant has counted patients with eradication of the baseline uropathogen as a success, even if the patient developed a new infection. The Clinical and Statistical Reviewers have redefined microbiological eradication (primary endpoint) in both the FDA's MITT and Per Protocol populations to include patients with a TOC urine culture which showed that all uropathogens present at study enrollment at $\geq 10^5$ CFU/mL were reduced to $<10^4$ CFU/mL AND no new infections, which is consistent with Division policy. Microbiologic outcome for patients with eradication of the baseline pathogen and no new infection who included in the FDA's PP and MITT populations are shown in Table 5 (created by the Reviewer). C-GR is still considered to be non-inferior to C-IR in this new analysis, although the eradication rates are much lower in both treatment groups.

In the PP population, new infections occurred in 42 of 272 patients (15.4%) in the C-GR group and in 36 of 251 patients (14.3%) in the C-IR group. The organisms responsible for new infections are summarized below for each treatment group. Gram-negative rods were responsible for 10/42 (24%) new infections in the C-GR group and 7/32 (22%) new infections in the C-IR group. A complete listing of patients who developed new infections, along with microbiological (including MIC results) and clinical response data at both the TOC and Late

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Post-Treatment Visits was provided by the applicant, in response to a request by the Division, on May 5, 2005.

Organism	Proquin XR N=32	Cipro IR N=32
<i>Acinetobacter</i>	--	--
<i>Citrobacter</i>	1	1
<i>Enterococcus</i>	24	20
<i>E. coli</i>	4	1
<i>Klebsiella</i>	2	5
Non-fermenting gram-negative bacilli	1	--
<i>Pseudomonas</i>		1
<i>Staphylococcus aureus</i>	1	1
<i>Staphylococcus</i> coagulase-negative	2	--
<i>Streptococcus</i> , beta	3	1
<i>Streptococcus</i> , gamma	1	1
Mixed Infections		
<i>Acinetobacter</i> + <i>Serratia</i>	1	--
<i>Acinetobacter</i> + <i>Klebsiella</i>	1	--
<i>Enterococcus</i> + coagulase negative <i>Streptococcus</i>	--	1
<i>Klebsiella</i> + non-fermenting gram-negative bacilli	1	--

TABLE 5
FDA Analysis of Microbiologic Outcome at the Test-of-Cure Visit

Microbiological Eradication with No New Infection at TOC	C-GR	C-IR
Per Protocol Population	212/272 (78%)	193/251 (77%)
	95% CI of the difference (-6.2%, 8.2%)	
MITT Population	212/307 (69%)	193/276 (70%)
	95% CI of the difference (-8.4%, 6.6%)	

Clinical Reviewer's Comment: Two sensitivity analyses of the primary endpoint were conducted by the Statistical Reviewer are presented in Table 6. These analyses were conducted for the following reasons:

1. *As per the draft Guidance, 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*

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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”. There were an additional 29 C-GR patients and 21 C-IR patients who were added to the efficacy analysis when the window was expanded from 5 to 9 days to 4 to 11 days after study drug. A sensitivity analysis was conducted utilizing the original protocol-defined TOC window of 5 to 9 days posttreatment and confirms that the non-inferiority of the primary endpoint is not sensitive to the change in the TOC window.

2. *The applicant’s protocol excludes patients with a ciprofloxacin-resistant baseline organism from their ITT population. In the FDA’s MITT population these patients were also excluded (11 in the C-GR group and 9 in the C-IR group). However, the Division usually includes such patients with resistant organisms in an MITT population. Therefore, a sensitivity analysis was conducted including patients with resistant organisms 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 ciprofloxacin.*

TABLE 6
FDA Sensitivity Analyses of Microbiological Outcome

Protocol-Defined TOC Window of 5 to 9 Days Post-Treatment	PP Population		MITT Population	
	C-GR	C-IR	C-GR	C-IR
	226/243 (93.0%)	211/231 (91.3%)	226/278 (81.3%)	211/256 (82.4%)
95% CI of the difference	(-3.2%, 6.5%)		(-7.7%, 5.4%)	
Ciprofloxacin-Resistant Organisms Included in MITT population	259/283 (91.5%)	231/260 (88.8%)	259/318 (81.4%)	231/285 (81.1%)
95% CI of the difference	(-2.3%, 7.7%)		(-5.8%, 6.6%)	

The microbiological response at the TOC visit by baseline organism for the applicant’s Efficacy population is shown in Table 7.

Clinical Reviewer’s Comment: Table 7 was adapted for clarity by the Reviewer from Table 15 in the applicant’s submission.

TABLE 7
Microbiological Response at Test-of-Cure Visit by Baseline Organism
Applicant's Efficacy Population

Microbiological Response at Test-of-Cure Visit by Baseline Organism	Treatment Group	
	C-GR (n = 283)	C-IR (n = 257)
<i>Escherichia coli</i>	211/222 (95.0%)	184/202 (91.1%)
<i>Klebsiella pneumoniae</i>	11/12 (91.7%)	10/13 (76.9%)
<i>Enterococcus</i>	6/10 (60.0%)	7/9 (77.8%)
<i>Proteus mirabilis</i>	7/7 (100%)	8/9 (88.9%)
<i>Staphylococcus</i> species, coagulase negative	7/9 (77.8%)	5/7 (71.4%)
Beta <i>Strep</i> , Presumptive Group B	1/1 (100%)	6/6 (100%)
<i>Klebsiella</i> species	3/3 (100%)	1/1 (100%)
<i>Staphylococcus aureus</i>	1/1 (100%)	4/4 (100%)
<i>Enterobacter aerogenes</i>	3/3 (100%)	1/1 (100%)
<i>Enterobacter</i> species	2/2 (100%)	2/2 (100%)
<i>Citrobacter</i> species	1/1 (100%)	0 (0%)
<i>Enterobacter cloacae</i>	1/1 (100%)	1/1 (100%)
<i>Hafnia alvei</i>	1/1 (100%)	1/1 (100%)
<i>Acinetobacter baumannii</i>	1/1 (100%)	0 (0%)
Nonfermenting Gram Negative Bacilli	0 (0%)	1/1 (100%)

Note: Baseline organisms with count >100,000 cfu/mL and susceptible to ciprofloxacin were included in this data analysis.

Source: Table 15 in the applicant's study report

For patients in the applicant's Efficacy population with available microbiological data at the Test-of-Cure Visit, the *E. coli* MIC at baseline was 0.06 µg/mL for the majority of patients (201 of 222 patients [90.5%]) in the C-GR group and 166 of 202 patients [82.2%] in the C-IR group. For *K. pneumoniae*, MIC at baseline was 0.06 for 12 of 12 patients (100%) in the C-GR group and 9/13 patients (69.2%) in the C-IR group.

Infections with *E. coli* (MIC=0.06 µg/mL at baseline) were eradicated in 190 of 201 patients (94.5%) in the C-GR group and in 149 of 166 patients (89.8%) in the C-IR group in the efficacy population at the Test-of-Cure Visit. For patients in the C-GR group who had infections with *E. coli* with at higher baseline MIC levels (0.1 to 1.0 µg/mL), the infections were all eradicated at the Test-of-Cure Visit.

10.2.18.2 Clinical Outcomes at the Test-of-Cure Visit

In the applicant's ITT population, clinical cure was experienced in 76.4% (233 of 305 patients) in the C-GR group and 78.8% (216 of 274 patients) in the C-IR group, as shown in Table 8.

For the applicant's Efficacy population at the Test-of-Cure Visit, clinical cure was experienced in 233 of 281 patients (82.9%) in the C-GR group and in 216 of 255 patients (84.7%) in the C-IR group, as shown in Table 9.

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TABLE 8
Clinical Cure Rate at the Test-of-Cure Visit
Applicant's ITT Population

One-Week Clinical Outcome	Statistics	Treatment Group		Difference (C-GR - C-IR)	p-value
		C-GR (n = 307)	C-IR (n = 276)		
Clinical Cure	Event / Sample Size	233/305	216/274	-2.40%	0.487
	Clinical Cure Rate	76.4%	78.8%		
	95% CI of Rate	(71.63%, 81.17%)	(73.96%, 83.64%)		

Note: The p-value for the test of treatment effect between two treatment groups was based on a two-sided Fisher's Exact test.

Source: Table 9 in the applicant's study report

TABLE 9
Clinical Cure Rate at the Test-of-Cure Visit
Applicant's Efficacy Population

One-Week Clinical Outcome	Statistics	Treatment Group		Difference (C-GR - C-IR)	p-value
		C-GR (n = 283)	C-IR (n = 257)		
Clinical Cure	Event / Sample Size	233/281	216/255	-1.80%	0.639
	Clinical Cure Rate	82.9%	84.7%		
	95% CI of Rate	(78.50%, 87.30%)	(80.28%, 89.12%)		

Note: The p-value for the test of treatment effect between two treatment groups was based on a two-sided Fisher's Exact test.

Source: Table 8 in the applicant's study report

Clinical Reviewer's Comments: The Clinical and Statistical Reviewers have recalculated clinical outcomes using the same population as for microbiological outcomes and the results are shown in Table 10 for the FDA's PP and MITT populations.

TABLE 10
FDA Analysis of Clinical Outcome at the Test-of-Cure Visit

Clinical Cure at TOC	C-GR	C-IR
Per Protocol Population	233/272 (85.7%)	216/251 (86.1%)
	95% CI of the difference (-6.4%, 5.6%)	
MITT Population	233/307 (75.9%)	216/276 (78.3%)
	95% CI of the difference (-9.2%, 4.5%)	

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10.2.18.3 Correlation Between Microbiological and Clinical Outcomes at the Test-of-Cure Visit

In the applicant's efficacy population at the Test-of-Cure Visit, 272 patients in the C-GR group and 251 patients in the C-IR group had both microbiological data and clinical data at baseline and at the Test-of-Cure Visit. Both clinical cure and microbiological eradication were reported for the efficacy population in 222 of 272 patients (81.6%) in the C-GR group and in 195 of 251 patients (77.7%) in the C-IR group (Table 14). Eleven of 272 patients (4.0%) in the C-GR group and 21 of 251 patients (8.4%) in the C-IR group were clinically cured but asymptomatic without microbiological eradication; 32 of 272 patients (11.8%) in the C-GR group and 30 of 251 patients (12.0%) in the C-IR group were symptomatic but had microbiological eradication of baseline uropathogen but without clinical cure; and seven of 272 patients (2.6%) in the C-GR group and five of 251 patients (2.0%) had neither clinical cure nor microbiological eradication.

There was a statistically significant positive correlation between clinical cure and microbiological eradication in the efficacy population at the Test-of-Cure Visit for both treatment groups (p=0.009 using the Cochran-Mantel-Haenszel Method for general association). This significant correlation indicates that the microbiological eradication outcome is consistent with the clinical cure outcome at Test-of-Cure Visit for both treatment groups.

The correlation between clinical cure as assessed by signs and symptoms and microbiological eradication at the Test-of-Cure Visit is presented for the efficacy population in Table 11.

TABLE 11
Correlation between Clinical Cure and Microbiological Eradication at Test-of-Cure Visit
Applicant's Efficacy Population

	Treatment Group		Total (n = 540)	p-value
	C-GR (n = 283)	C-IR (n = 257)		
Clinical Cure / Microbiological Eradication - n (%)	272 (100%)	251 (100%)	523(100%)	0.009
Yes / Yes	222 (81.6%)	195 (77.7%)	417 (79.7%)	
Yes / No	11 (4.0%)	21 (8.4%)	32 (6.1%)	
No / Yes	32 (11.8%)	30 (12.0%)	62 (11.9%)	
No / No	7 (2.6%)	5 (2.0%)	12 (2.3%)	

Note: The overall p-value for the test of general association between clinical cure and bacterial eradication was based on the Cochran-Mantel-Haenszel Method for the general association test stratified by treatment.

Source Table 14 in the applicant's study report.

10.2.18.4 Summary of Test-of-Cure Visit Results

The microbiological eradication and clinical success rates were similar between the C-GR and C-IR groups. The eradication and clinical success rates and their corresponding 95% confidence intervals for the differences between rates (C-GR minus C-IR) are given in Table 12 below.

Clinical Reviewer's Comment: Table 12 was created by the Reviewer.

TABLE 12
Summary of Microbiological and Clinical Outcomes at Test-of-Cure Visit
FDA's PP Population

	C-GR	C-IR
Randomized Patients	524	513
Per Protocol Patients	272 (52%)	251 (49%)
Microbiological Eradication with no new infection at TOC	212/272 (78%) (-6.2%, 8.2%)	193/251 (77%)
Clinical Response at TOC	233/272 (86%) (-6.4%, 5.6%)	216/251 (86%)
Microbiological Eradication by organism*		
<i>E. coli</i>	211/222 (95%)	184/202 (91%)
<i>K. pneumoniae</i>	11/12 (92%)	10/13 (77%)

*Number of patients with specified baseline organism eradicated / Number of per-protocol patients with specified baseline organism.

The microbiological eradication rates for baseline organisms at TOC were 93% (254/272) for the C-GR group and 90% (225/251) for the C-IR group. Of the patients with their baseline pathogen eradicated, new infections were detected in 42/254 (16.5%) C-GR patients and 32/225 (14.2%) C-IR patients at the TOC visit. Of the patients with new infections, gram-negative rods were responsible for new infections in 10/42 (24%) patients in the C-GR group and 7/32 (22%) patients in the C-IR group.

10.2.18.5 Microbiologic Outcomes at the Late Post-Treatment Visit

In the applicant's efficacy population, the C-GR group was non-inferior to the C-IR group with respect to sustained microbiological eradication in the efficacy population at the Late Post-Treatment Visit, as shown in Table 13 (95% CI of the treatment difference [-8.0%, 6.4%]).

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TABLE 13
Microbiological Response at Late Post-Treatment Visit
Applicant's Efficacy Population

Five-Week Microbiological Response	Statistics	Treatment Group		Difference (C-GR - C-IR)	p-value
		C-GR (n = 283)	C-IR (n = 257)		
Sustained Microbiological Eradication Rate	Event / Sample Size	182/221	168/202	-0.80%	0.898
	Eradication Rate	82.4%	83.2%		
	95% CI of Rate	(77.38%, 87.42%)	(78.04%, 88.36%)		
Number of Failures (%)		39 (17.6%)	34 (16.8%)		

Note: The p-value for the test of treatment effect between two treatment groups was based on a two-sided Fisher's Exact test.

Source: Table 10 in the applicant's study report

In the applicant's efficacy population, the C-GR group was non-inferior to the C-IR group for the rate of new infection at the Late Post-Treatment Visit (p=0.810). Forty-six of 220 patients (20.9%) in the C-GR group and 40 of 201 patients (19.9%) in the C-IR group experienced new infections at the Late Post-Treatment Visit.

New infections with Group D *Streptococcus (Enterococcus)* were observed in 14 of 220 patients (6.4%) in the C-GR group and in 10 of 201 patients (5.0%) in the C-IR group in the applicant's Efficacy population. New infections were also observed with *E. coli* (1 patient in the C-GR group and 5 patients in the C-IR group) and *K. pneumoniae* (4 patients in the C-GR group and 2 patients in the C-IR group). Two or fewer patients experienced new infections with other organisms at the Late Post-Treatment Visit.

Clinical Reviewer's Comments: The Clinical and Statistical Reviewers have recalculated microbiological outcomes at the Late Post-Treatment Visit using the same population as for the TOC visit and the results are shown in Table 14 for the FDA's PP and MITT populations.

TABLE 14
FDA Analysis of Microbiologic Outcome at the Late Post-Treatment Visit

Microbiological Eradication at the Late Post-Treatment Visit	C-GR	C-IR
Per Protocol Population	182/272 (66.9%)	168/251 (66.9%)
	95% CI of the difference (-8.1%, 8.1%)	
MITT Population	182/307 (59.3%)	168/276 (60.9%)
	95% CI of the difference (-9.5%, 6.4%)	

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 10.2.18.6 Clinical Outcomes at the Late Post-Treatment Visit

In the applicant's Efficacy population, sustained cure was experienced by 196 of 259 patients (75.7%) in the C-GR group and by 175 of 222 patients (78.8%) in the C-IR group at the Late Post-Treatment Visit, as shown in Table 15.

TABLE 15
Clinical Response at Late Post-Treatment Visit
Applicant's Efficacy Population

Five-Week Clinical Response	Statistics	Treatment Group		Difference (C-GR - C-IR)	p-value
		C-GR (n = 283)	C-IR (n = 257)		
Clinical Sustained Cure	Event / Sample Size	196/259	175/222	-3.10%	0.447
	Clinical Sustained Cure Rate	75.7%	78.8%		
	95% CI of Rate	(70.48%, 80.92%)	(73.42, 84.18%)		
Number of Failures (%)		63 (24.3%)	47 (21.2%)		

Note: The p-value for the test of treatment effect between two treatment groups was based on a two-sided Fisher's Exact test.

Source: Table 13 in the applicant's study report

Clinical Reviewer's Comments: The Clinical and Statistical Reviewers have recalculated clinical outcomes at the Late Post-Treatment Visit using the same population as for the TOC visit and the results are shown in Table 10 for the FDA's PP and MITT populations.

TABLE 17
FDA Analysis of Clinical Outcome at the Late Post-Treatment Visit

Clinical Cure at the Late Post-Treatment Visit	C-GR	C-IR
Per Protocol Population	196/272 (72.1%)	175/251 (69.7%)
	95% CI of the difference (-5.5%, 10.1%)	
MITT Population	196/307 (63.8%)	175/276 (63.4%)
	95% CI of the difference (-7.4%, 8.3%)	

10.2.18.7 Response by Baseline Organism

In the applicant's Efficacy population at the Test-of-Cure Visit, the clinical cure rate in C-GR-treated patients for the five most common infecting organisms were 86.8% (197 of 227) for *E. coli*; 57.1% (8 of 14) for *K. pneumoniae*; 90.0% (9 of 10) for Group D *Streptococcus* (*Enterococcus*), 85.7% (6 of 7) for *P. mirabilis*, and 60.0% (6 of 10) for *Staphylococcus* species, coagulase negative. For the C-IR group, clinical cure rates were 86.3% (176 of 204) for *E. coli*; 85.7% (12 of 14) for *K. pneumoniae*; 88.9% (8 of 9) for Group D *Streptococcus* *Enterococcus*,

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60.0% (6 of 10) for *P. mirabilis*, and 85.7% (6 of 7) for *Staphylococcus* species, coagulase negative.

In the applicant's Efficacy population at the Late Post-Treatment Visit, the sustained clinical cure rate in C-GR-treated patients for the five most common infecting organisms were 79.9% (167 of 209) for *E. coli*; 46.2% (6 of 13) for *K. pneumoniae*; 87.5% (7 of 8) for Group D *Streptococcus Enterococcus*, 50.0% (3 of 6) for *P. mirabilis*, and 60.0% (6 of 10) for *Staphylococcus* species, coagulase negative. For the C-IR group, clinical cure rates were 82.0% (146 of 178) for *E. coli*; 50.0% (7 of 14) for *K. pneumoniae*; 66.7% (4 of 6) for Group D *Streptococcus Enterococcus*, 83.3% (5 of 6) for *P. mirabilis*, and 71.4% (5 of 7) for *Staphylococcus* species, coagulase negative.

10.2.18.8 Microbiologic Response by Age and Race

Analysis of the microbiological eradication rate at the TOC Visit was performed by the applicant for the following subgroups in their Efficacy population: patients < 65 years of age; patients ≥ 65 years of age; patients who were Caucasian; and patients who were not Caucasian.

The differences in the rates of microbiological eradication at the TOC Visit were similar between treatment groups in patients who were < 65 years of age and in patients who were ≥ 65 years of age.

For patients who were <65 years of age, microbiological eradication rates were 93.8% (242 of 258 patients) in the C-GR group and 89.2% (207 of 232 patients) in C-IR group. The difference between groups was 4.60% in patients <65 years of age (95% CI [-0.36%, 9.56%]). C-GR was found to be non-inferior to C-IR in patients <65 years of age at the TOC Visit.

Microbiological eradication rates at the TOC Visit for patients who were ≥ 65 years of age were 85.7% (12 of 14 patients) in the C-GR group and 94.7% (18 of 19 patients) in the C-IR group. The difference between groups was -9.00% in patients ≥ 65 years of age (95% CI [-29.92%, 11.92%]).

The differences in the rates of microbiological eradication at the Test-of-Cure Visit were also similar between treatment groups in Caucasian patients and in non-Caucasian patients in the efficacy population. For Caucasian patients, microbiological eradication rates were 94.4% (204 of 216 patients) in the C-GR group and 90.0% (188 of 209 patients) in C-IR group. The difference between groups was 4.40% in Caucasian patients (95% CI [-0.69%, 9.49%]). For non-Caucasian patients, microbiological eradication rates were 89.3% (50 of 56 patients) in the C-GR group and 88.1% (37 of 42 patients) in the C-IR group. The difference between groups was 1.20% in non-Caucasian patients (95% CI [-11.51%, 13.91%])

Clinical Reviewer's Comment: The study was not powered to be able to detect a difference in microbiological outcome between younger and older or Caucasian and non-Caucasian patients within a ± 10% margin. The small number of older patients and non-Caucasian patients accounts for the wide range in the 95% CIs of the treatment differences. Efficacy differences

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between younger and older patients and Caucasian and non-Caucasian patients are not considered by the Reviewer to be clinically significant.

10.2.19 Safety Results

A total of 518 patients in the C-GR group and 509 patients in the C-IR group received at least one dose of study medication and were included in the safety analyses.

10.2.19.1 Deaths, Discontinuations, and Severe Adverse Events

No patients died during the study. Ten patients experienced AEs leading to discontinuation and 9 patients experienced SAEs during the course of the 5-week study.

Events leading to discontinuation in 7 patients in the C-GR group were: anemia, hypersensitivity, dizziness, cystitis, nephrolithiasis, dyspnea, and urticaria. In the C-IR group, three patients discontinued (one each for suprapubic pain, hypersensitivity, and pyelonephritis). Five patients experienced AEs leading to discontinuation that were considered related to study drug by the investigator (hypersensitivity, dyspnea, and urticaria in the C-GR group and hypersensitivity and suprapubic pain in the C-IR group).

Three patients experienced SAEs in the C-GR group, one each with: anemia NOS, chest pain, and papillary thyroid cancer. Six patients in the C-IR group experienced SAEs: intestinal obstruction NOS, chest pain (2 patients), pyelonephritis NOS, nephrolithiasis, and ovarian cyst. None of the SAEs were reported by the investigator to be related to study drug.

10.2.19.2 All Adverse Events

During the course of the 5-week study, 213 of 518 patients (41.1%) in the C-GR group and 216 of 509 patients (42.4%) in the C-IR group experienced AEs. The incidence of individual adverse events is shown in Table 18. The most common AEs during the course of the 5-week study were urinary tract infection not otherwise specified (NOS) in 106 of 1027 patients (10.3%); headache in 32 of 1027 patients (3.1%); fungal infection NOS in 23 of 1027 patients (2.2%); upper respiratory tract infection NOS in 22 of 1027 patients (2.1%); nasopharyngitis in 21 of 1027 patients (2.0%); and nausea in 19 of 1027 patients (1.9%).

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TABLE 18
Summary of Adverse Events Occurring During the Study

	Treatment Group		Total	p-value
	Ciprofloxacin GR	Ciprofloxacin IR		
Number of Patients Randomized in the Study	524	513	1037	
Number (%) of Patients Received Treatment	518 (100%)	509 (100%)	1027 (100%)	
Number (%) of Patients without Any Adverse Event in the Study	305 (58.9%)	293 (57.6%)	598 (58.2%)	
Number (%) of Patients with at Least One Adverse Event in the Study	213 (41.1%)	216 (42.4%)	429 (41.8%)	NS
Number (%) of Patients Who Reported Adverse Events by System Organ Class				
Blood and lymphatic system disorders	4 (0.8%)	3 (0.6%)	7 (0.7%)	NS
Lymphadenopathy	3 (0.6%)	1 (0.2%)	4 (0.4%)	NS
Leukopenia NOS	0	2 (0.4%)	2 (0.2%)	NS
Anaemia NOS	1 (0.2%)	0	1 (0.1%)	NS
Cardiac disorders	1 (0.2%)	0	1 (0.1%)	NS
Ventricular bigeminy	1 (0.2%)	0	1 (0.1%)	NS
Ear and labyrinth disorders	3 (0.6%)	4 (0.8%)	7 (0.7%)	NS
Ear pain	0	2 (0.4%)	2 (0.2%)	NS
Fluid in middle ear	2 (0.4%)	0	2 (0.2%)	NS
Vertigo	0	2 (0.4%)	2 (0.2%)	NS
Cerumen impaction	1 (0.2%)	0	1 (0.1%)	NS
Endocrine disorders	1 (0.2%)	0	1 (0.1%)	NS
Goitre	1 (0.2%)	0	1 (0.1%)	NS
Eye disorders	0	3 (0.6%)	3 (0.3%)	NS
Conjunctivitis	0	2 (0.4%)	2 (0.2%)	NS
Eye swelling	0	1 (0.2%)	1 (0.1%)	NS
Vision blurred	0	1 (0.2%)	1 (0.1%)	NS
Gastrointestinal disorders	32 (6.2%)	42 (8.3%)	74 (7.2%)	NS
Nausea	7 (1.4%)	11 (2.2%)	18 (1.8%)	NS
Abdominal pain NOS	9 (1.7%)	6 (1.2%)	15 (1.5%)	NS
Diarrhoea NOS	2 (0.4%)	9 (1.8%)	11 (1.1%)	0.036
Dyspepsia	2 (0.4%)	3 (0.6%)	5 (0.5%)	NS
Abdominal pain lower	1 (0.2%)	3 (0.6%)	4 (0.4%)	NS
Abdominal pain upper	1 (0.2%)	3 (0.6%)	4 (0.4%)	NS
Abdominal tenderness	3 (0.6%)	0	3 (0.3%)	NS

Note: Adverse event mapping was based on the MedDRA Version 5.1 thesaurus.

A patient may be reported in more than one category.

The p-values were obtained from the Fisher's Exact test and were presented if they are less than 0.10.

NS = Not statistically significant at 0.10 level.

Source: Table 14.1.3-2 in the applicant's study report

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TABLE 18 (continued)
Summary of Adverse Events Occurring During the Study

	Treatment Group		Total	p-value
	Ciprofloxacin GR	Ciprofloxacin IR		
Number (%) of Patients Received Treatment	518 (100%)	509 (100%)	1027 (100%)	
Number (%) of Patients Who Reported Adverse Events by System Organ Class				
Gastrointestinal disorders (Continued)				
Constipation	1 (0.2%)	2 (0.4%)	3 (0.3%)	NS
Vomiting NOS	1 (0.2%)	2 (0.4%)	3 (0.3%)	NS
Abdominal distension	2 (0.4%)	0	2 (0.2%)	NS
Gastroesophageal reflux disease	1 (0.2%)	1 (0.2%)	2 (0.2%)	NS
Haemorrhoids	1 (0.2%)	1 (0.2%)	2 (0.2%)	NS
Irritable bowel syndrome aggravated	2 (0.4%)	0	2 (0.2%)	NS
Abdominal discomfort	1 (0.2%)	0	1 (0.1%)	NS
Diverticulum NOS	1 (0.2%)	0	1 (0.1%)	NS
Flatulence	0	1 (0.2%)	1 (0.1%)	NS
Gastritis NOS	1 (0.2%)	0	1 (0.1%)	NS
Gastroenteritis NOS	1 (0.2%)	0	1 (0.1%)	NS
Gingivitis	0	1 (0.2%)	1 (0.1%)	NS
Haemorrhoidal haemorrhage	1 (0.2%)	0	1 (0.1%)	NS
Intestinal obstruction NOS	0	1 (0.2%)	1 (0.1%)	NS
Lip ulceration	0	1 (0.2%)	1 (0.1%)	NS
Melaena	1 (0.2%)	0	1 (0.1%)	NS
Nausea aggravated	0	1 (0.2%)	1 (0.1%)	NS
Oesophageal spasm	1 (0.2%)	0	1 (0.1%)	NS
Oral mucosal discolouration	1 (0.2%)	0	1 (0.1%)	NS
Rectal discharge	0	1 (0.2%)	1 (0.1%)	NS
Toothache	0	1 (0.2%)	1 (0.1%)	NS
General disorders and administration site conditions	21 (4.1%)	19 (3.7%)	40 (3.9%)	NS
Suprapubic pain	7 (1.4%)	3 (0.6%)	10 (1.0%)	NS
Chest pain	2 (0.4%)	5 (1.0%)	7 (0.7%)	NS
Fatigue	3 (0.6%)	4 (0.8%)	7 (0.7%)	NS
Pyrexia	3 (0.6%)	3 (0.6%)	6 (0.6%)	NS
Pain NOS	3 (0.6%)	2 (0.4%)	5 (0.5%)	NS
Rigors	1 (0.2%)	2 (0.4%)	3 (0.3%)	NS
Asthenia	1 (0.2%)	0	1 (0.1%)	NS
Axillary pain	1 (0.2%)	0	1 (0.1%)	NS

Note: Adverse event mapping was based on the MedDRA Version 5.1 thesaurus.

A patient may be reported in more than one category.

The p-values were obtained from the Fisher's Exact test and were presented if they are less than 0.10.

NS = Not statistically significant at 0.10 level.

Source: Table 14.1.3-2 in the applicant's study report

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TABLE 18 (continued)
Summary of Adverse Events Occurring During the Study

	Treatment Group		Total	p-value
	Ciprofloxacin GR	Ciprofloxacin IR		
Number (%) of Patients Received Treatment	518 (100%)	509 (100%)	1027 (100%)	
Number (%) of Patients Who Reported Adverse Events by System Organ Class				
General disorders and administration site conditions (Continued)				
Discomfort NOS	0	1 (0.2%)	1 (0.1%)	NS
Feeling cold	0	1 (0.2%)	1 (0.1%)	NS
Feeling hot	0	1 (0.2%)	1 (0.1%)	NS
Inflammation NOS	0	1 (0.2%)	1 (0.1%)	NS
Lethargy	1 (0.2%)	0	1 (0.1%)	NS
Malaise	0	1 (0.2%)	1 (0.1%)	NS
Oedema peripheral	0	1 (0.2%)	1 (0.1%)	NS
Tenderness NOS	1 (0.2%)	0	1 (0.1%)	NS
Thirst	1 (0.2%)	0	1 (0.1%)	NS
Hepatobiliary disorders	1 (0.2%)	1 (0.2%)	2 (0.2%)	NS
Cholelithiasis	1 (0.2%)	1 (0.2%)	2 (0.2%)	NS
Immune system disorders	1 (0.2%)	5 (1.0%)	6 (0.6%)	NS
Seasonal allergy	0	3 (0.6%)	3 (0.3%)	NS
Hypersensitivity NOS	1 (0.2%)	1 (0.2%)	2 (0.2%)	NS
Drug hypersensitivity	0	1 (0.2%)	1 (0.1%)	NS
Infections and infestations	98 (18.9%)	98 (19.3%)	196 (19.1%)	NS
Urinary tract infection NOS	56 (10.8%)	50 (9.8%)	106 (10.3%)	NS
Fungal infection NOS	14 (2.7%)	9 (1.8%)	23 (2.2%)	NS
Upper respiratory tract infection NOS	7 (1.4%)	15 (2.9%)	22 (2.1%)	0.087
Vaginosis fungal NOS	4 (0.8%)	8 (1.6%)	12 (1.2%)	NS
Sinusitis NOS	4 (0.8%)	7 (1.4%)	11 (1.1%)	NS
Vaginitis bacterial NOS	3 (0.6%)	4 (0.8%)	7 (0.7%)	NS
Vaginal candidiasis	2 (0.4%)	3 (0.6%)	5 (0.5%)	NS
Gastroenteritis viral NOS	2 (0.4%)	2 (0.4%)	4 (0.4%)	NS
Tooth abscess	1 (0.2%)	3 (0.6%)	4 (0.4%)	NS
Beta haemolytic streptococcal infection	2 (0.4%)	1 (0.2%)	3 (0.3%)	NS
Pyelonephritis NOS	1 (0.2%)	2 (0.4%)	3 (0.3%)	NS
Vaginal infection NOS	2 (0.4%)	1 (0.2%)	3 (0.3%)	NS

Note: Adverse event mapping was based on the MedDRA Version 5.1 thesaurus.

A patient may be reported in more than one category.

The p-values were obtained from the Fisher's Exact test and were presented if they are less than 0.10.

NS = Not statistically significant at 0.10 level.

Source: Table 14.1.3-2 in the applicant's study report

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TABLE 18 (continued)
Summary of Adverse Events Occurring During the Study

	Treatment Group		Total	p-value
	Ciprofloxacin GR	Ciprofloxacin IR		
Number (%) of Patients Received Treatment	518 (100%)	509 (100%)	1027 (100%)	
Number (%) of Patients Who Reported Adverse Events by System Organ Class				
Infections and infestations (Continued)				
Vaginitis	1 (0.2%)	2 (0.4%)	3 (0.3%)	NS
Candidal infection NOS	0	2 (0.4%)	2 (0.2%)	NS
Escherichia infection NOS	2 (0.4%)	0	2 (0.2%)	NS
Herpes simplex	0	2 (0.4%)	2 (0.2%)	NS
Influenza	1 (0.2%)	1 (0.2%)	2 (0.2%)	NS
Otitis media NOS	1 (0.2%)	1 (0.2%)	2 (0.2%)	NS
Klebsiella infection NOS	1 (0.2%)	0	1 (0.1%)	NS
Lyme disease	0	1 (0.2%)	1 (0.1%)	NS
Oral candidiasis	1 (0.2%)	0	1 (0.1%)	NS
Otitis externa NOS	0	1 (0.2%)	1 (0.1%)	NS
Otitis media serous acute NOS	0	1 (0.2%)	1 (0.1%)	NS
Pharyngitis streptococcal	1 (0.2%)	0	1 (0.1%)	NS
Pharyngitis viral NOS	0	1 (0.2%)	1 (0.1%)	NS
Pharyngotonsillitis	1 (0.2%)	0	1 (0.1%)	NS
Pneumonia NOS	1 (0.2%)	0	1 (0.1%)	NS
Streptococcal infection NOS	1 (0.2%)	0	1 (0.1%)	NS
Upper respiratory tract infection viral NOS	1 (0.2%)	0	1 (0.1%)	NS
Injury, poisoning and procedural complications	4 (0.8%)	8 (1.6%)	12 (1.2%)	NS
Muscle strain	1 (0.2%)	2 (0.4%)	3 (0.3%)	NS
Thermal burn	0	2 (0.4%)	2 (0.2%)	NS
Abrasion NOS	1 (0.2%)	0	1 (0.1%)	NS
Alcohol poisoning	0	1 (0.2%)	1 (0.1%)	NS
Arthropod bite	0	1 (0.2%)	1 (0.1%)	NS
Heat exhaustion	1 (0.2%)	0	1 (0.1%)	NS
Joint sprain	0	1 (0.2%)	1 (0.1%)	NS
Periorbital haematoma	0	1 (0.2%)	1 (0.1%)	NS
Skin laceration	1 (0.2%)	0	1 (0.1%)	NS
Investigations	7 (1.4%)	8 (1.6%)	15 (1.5%)	NS
Gamma-glutamyltransferase increased	0	4 (0.8%)	4 (0.4%)	0.060

Note: Adverse event mapping was based on the MedDRA Version 5.1 thesaurus.

A patient may be reported in more than one category.

The p-values were obtained from the Fisher's Exact test and were presented if they are less than 0.10.

NS = Not statistically significant at 0.10 level.

Source: Table 14.1.3-2 in the applicant's study report

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TABLE 18 (continued)
Summary of Adverse Events Occurring During the Study

	Treatment Group		Total	p-value
	Ciprofloxacin GR	Ciprofloxacin IR		
Number (%) of Patients Received Treatment	518 (100%)	509 (100%)	1027 (100%)	
Number (%) of Patients Who Reported Adverse Events by System Organ Class				
Investigations (Continued)				
Blood bilirubin increased	3 (0.6%)	0	3 (0.3%)	NS
Blood potassium increased	0	3 (0.6%)	3 (0.3%)	NS
Alanine aminotransferase increased	2 (0.4%)	0	2 (0.2%)	NS
Abdominal aortic bruit	1 (0.2%)	0	1 (0.1%)	NS
Aspartate aminotransferase increased	1 (0.2%)	0	1 (0.1%)	NS
Body temperature increased	1 (0.2%)	0	1 (0.1%)	NS
Culture urine positive	1 (0.2%)	0	1 (0.1%)	NS
Haematocrit decreased	0	1 (0.2%)	1 (0.1%)	NS
Haemoglobin decreased	0	1 (0.2%)	1 (0.1%)	NS
Platelet count decreased	1 (0.2%)	0	1 (0.1%)	NS
Red blood cell count decreased	0	1 (0.2%)	1 (0.1%)	NS
White blood cell count decreased	0	1 (0.2%)	1 (0.1%)	NS
Metabolism and nutrition disorders	1 (0.2%)	5 (1.0%)	6 (0.6%)	NS
Anorexia	1 (0.2%)	0	1 (0.1%)	NS
Appetite increased NOS	0	1 (0.2%)	1 (0.1%)	NS
Hypercalcaemia	0	1 (0.2%)	1 (0.1%)	NS
Hyperglycaemia NOS	0	1 (0.2%)	1 (0.1%)	NS
Hyperlipidaemia NOS	0	1 (0.2%)	1 (0.1%)	NS
Hypernatraemia	0	1 (0.2%)	1 (0.1%)	NS
Musculoskeletal and connective tissue disorders	21 (4.1%)	21 (4.1%)	42 (4.1%)	NS
Back pain	9 (1.7%)	8 (1.6%)	17 (1.7%)	NS
Arthralgia	2 (0.4%)	2 (0.4%)	4 (0.4%)	NS
Joint swelling	1 (0.2%)	2 (0.4%)	3 (0.3%)	NS
Chest wall pain	1 (0.2%)	1 (0.2%)	2 (0.2%)	NS
Flank pain	1 (0.2%)	1 (0.2%)	2 (0.2%)	NS
Myalgia	1 (0.2%)	1 (0.2%)	2 (0.2%)	NS
Pain in limb	2 (0.4%)	0	2 (0.2%)	NS
Back pain aggravated	1 (0.2%)	0	1 (0.1%)	NS
Bursitis	0	1 (0.2%)	1 (0.1%)	NS

Note: Adverse event mapping was based on the MedDRA Version 5.1 thesaurus.

A patient may be reported in more than one category.

The p-values were obtained from the Fisher's Exact test and were presented if they are less than 0.10.

NS = Not statistically significant at 0.10 level.

Source: Table 14.1.3-2 in the applicant's study report

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TABLE 18 (continued)
Summary of Adverse Events Occurring During the Study

	Treatment Group		Total	p-value
	Ciprofloxacin GR	Ciprofloxacin IR		
Number (%) of Patients Received Treatment	518 (100%)	509 (100%)	1027 (100%)	
Number (%) of Patients Who Reported Adverse Events by System Organ Class				
Musculoskeletal and connective tissue disorders (Continued)				
Costochondritis	0	1 (0.2%)	1 (0.1%)	NS
Facial pain	1 (0.2%)	0	1 (0.1%)	NS
Groin pain	0	1 (0.2%)	1 (0.1%)	NS
Muscle cramp	0	1 (0.2%)	1 (0.1%)	NS
Muscle spasms	1 (0.2%)	0	1 (0.1%)	NS
Musculoskeletal stiffness	0	1 (0.2%)	1 (0.1%)	NS
Neck pain	1 (0.2%)	0	1 (0.1%)	NS
Night cramps	1 (0.2%)	0	1 (0.1%)	NS
Pain in jaw	0	1 (0.2%)	1 (0.1%)	NS
Scoliosis	1 (0.2%)	0	1 (0.1%)	NS
Spinal osteoarthritis	0	1 (0.2%)	1 (0.1%)	NS
Tendonitis	0	1 (0.2%)	1 (0.1%)	NS
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	2 (0.4%)	0	2 (0.2%)	NS
Non-Hodgkin's lymphoma NOS	1 (0.2%)	0	1 (0.1%)	NS
Papillary thyroid cancer	1 (0.2%)	0	1 (0.1%)	NS
Nervous system disorders	22 (4.2%)	29 (5.7%)	51 (5.0%)	NS
Headache	12 (2.3%)	20 (3.9%)	32 (3.1%)	NS
Dizziness	6 (1.2%)	1 (0.2%)	7 (0.7%)	NS
Migraine NOS	2 (0.4%)	1 (0.2%)	3 (0.3%)	NS
Dysgeusia	0	2 (0.4%)	2 (0.2%)	NS
Sciatica	1 (0.2%)	1 (0.2%)	2 (0.2%)	NS
Syncope	0	2 (0.4%)	2 (0.2%)	NS
Tension headaches	0	2 (0.4%)	2 (0.2%)	NS
Disturbance in attention	1 (0.2%)	0	1 (0.1%)	NS
Hypoaesthesia	0	1 (0.2%)	1 (0.1%)	NS
Paraesthesia	1 (0.2%)	0	1 (0.1%)	NS
Radiculopathy NOS	1 (0.2%)	0	1 (0.1%)	NS
Sinus headache	1 (0.2%)	0	1 (0.1%)	NS

Note: Adverse event mapping was based on the MedDRA Version 5.1 thesaurus.

A patient may be reported in more than one category.

The p-values were obtained from the Fisher's Exact test and were presented if they are less than 0.10.

NS = Not statistically significant at 0.10 level.

Source: Table 14.1.3-2 in the applicant's study report

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TABLE 18 (continued)
Summary of Adverse Events Occurring During the Study

	Treatment Group		Total	p-value
	Ciprofloxacin GR	Ciprofloxacin IR		
Number (%) of Patients Received Treatment	518 (100%)	509 (100%)	1027 (100%)	
Number (%) of Patients Who Reported Adverse Events by System Organ Class				
Pregnancy, puerperium and perinatal conditions	1 (0.2%)	0	1 (0.1%)	NS
Pregnancy NOS	1 (0.2%)	0	1 (0.1%)	NS
Psychiatric disorders	1 (0.2%)	10 (2.0%)	11 (1.1%)	0.006
Insomnia	0	3 (0.6%)	3 (0.3%)	NS
Anxiety	0	2 (0.4%)	2 (0.2%)	NS
Depression	0	2 (0.4%)	2 (0.2%)	NS
Depression aggravated	0	1 (0.2%)	1 (0.1%)	NS
Disorientation	0	1 (0.2%)	1 (0.1%)	NS
Mood swings	1 (0.2%)	0	1 (0.1%)	NS
Panic attack	0	1 (0.2%)	1 (0.1%)	NS
Renal and urinary disorders	31 (6.0%)	15 (2.9%)	46 (4.5%)	0.023
Micturition urgency	10 (1.9%)	5 (1.0%)	15 (1.5%)	NS
Urinary frequency	7 (1.4%)	5 (1.0%)	12 (1.2%)	NS
Dysuria	8 (1.5%)	1 (0.2%)	9 (0.9%)	0.038
Haematuria	4 (0.8%)	1 (0.2%)	5 (0.5%)	NS
Cystitis NOS	3 (0.6%)	1 (0.2%)	4 (0.4%)	NS
Nephrolithiasis	2 (0.4%)	1 (0.2%)	3 (0.3%)	NS
Urine odour abnormal	1 (0.2%)	2 (0.4%)	3 (0.3%)	NS
Chromaturia	2 (0.4%)	0	2 (0.2%)	NS
Bladder pain	1 (0.2%)	0	1 (0.1%)	NS
Bladder spasm	0	1 (0.2%)	1 (0.1%)	NS
Costovertebral angle tenderness	1 (0.2%)	0	1 (0.1%)	NS
Cystitis interstitial	0	1 (0.2%)	1 (0.1%)	NS
Cystocele	1 (0.2%)	0	1 (0.1%)	NS
Incontinence NOS	1 (0.2%)	0	1 (0.1%)	NS
Urethral cyst	1 (0.2%)	0	1 (0.1%)	NS
Urethral pain	1 (0.2%)	0	1 (0.1%)	NS
Urethral syndrome	0	1 (0.2%)	1 (0.1%)	NS

Note: Adverse event mapping was based on the MedDRA Version 5.1 thesaurus.

A patient may be reported in more than one category.

The p-values were obtained from the Fisher's Exact test and were presented if they are less than 0.10.

NS = Not statistically significant at 0.10 level.

Source: Table 14.1.3-2 in the applicant's study report

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TABLE 18 (continued)
Summary of Adverse Events Occurring During the Study

	Treatment Group		Total	p-value
	Ciprofloxacin GR	Ciprofloxacin IR		
Number (%) of Patients Received Treatment	518 (100%)	509 (100%)	1027 (100%)	
Number (%) of Patients Who Reported Adverse Events by System Organ Class				
Reproductive system and breast disorders	12 (2.3%)	11 (2.2%)	23 (2.2%)	NS
Genital pruritus female	2 (0.4%)	3 (0.6%)	5 (0.5%)	NS
Ovarian cyst	0	3 (0.6%)	3 (0.3%)	NS
Vaginal discharge	2 (0.4%)	1 (0.2%)	3 (0.3%)	NS
Adnexa uteri pain	0	2 (0.4%)	2 (0.2%)	NS
Vaginal burning sensation	0	2 (0.4%)	2 (0.2%)	NS
Vaginal haemorrhage	2 (0.4%)	0	2 (0.2%)	NS
Amenorrhoea NOS	0	1 (0.2%)	1 (0.1%)	NS
Dysmenorrhoea	1 (0.2%)	0	1 (0.1%)	NS
Dyspareunia NOS	1 (0.2%)	0	1 (0.1%)	NS
Menstruation irregular	0	1 (0.2%)	1 (0.1%)	NS
Metrorrhagia	1 (0.2%)	0	1 (0.1%)	NS
Pelvic pain NOS	0	1 (0.2%)	1 (0.1%)	NS
Uterine pain	1 (0.2%)	0	1 (0.1%)	NS
Vaginal disorder NOS	1 (0.2%)	0	1 (0.1%)	NS
Vaginal irritation	1 (0.2%)	0	1 (0.1%)	NS
Vulvovaginal dryness	1 (0.2%)	0	1 (0.1%)	NS
Respiratory, thoracic and mediastinal disorders	36 (6.9%)	25 (4.9%)	61 (5.9%)	NS
Nasopharyngitis	14 (2.7%)	7 (1.4%)	21 (2.0%)	NS
Pharyngitis	6 (1.2%)	5 (1.0%)	11 (1.1%)	NS
Nasal congestion	6 (1.2%)	1 (0.2%)	7 (0.7%)	NS
Bronchitis NOS	1 (0.2%)	3 (0.6%)	4 (0.4%)	NS
Cough	1 (0.2%)	3 (0.6%)	4 (0.4%)	NS
Dyspnoea NOS	1 (0.2%)	2 (0.4%)	3 (0.3%)	NS
Sinus congestion	2 (0.4%)	1 (0.2%)	3 (0.3%)	NS
Postnasal drip	1 (0.2%)	1 (0.2%)	2 (0.2%)	NS
Rhinitis allergic NOS	1 (0.2%)	1 (0.2%)	2 (0.2%)	NS
Rhinitis seasonal	2 (0.4%)	0	2 (0.2%)	NS
Rhinorrhoea	2 (0.4%)	0	2 (0.2%)	NS
Allergic sinusitis	0	1 (0.2%)	1 (0.1%)	NS
Emphysema	0	1 (0.2%)	1 (0.1%)	NS

Note: Adverse event mapping was based on the MedDRA Version 5.1 thesaurus.

A patient may be reported in more than one category.

The p-values were obtained from the Fisher's Exact test and were presented if they are less than 0.10.

NS = Not statistically significant at 0.10 level.

Source: Table 14.1.3-2 in the applicant's study report

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TABLE 18 (continued)
Summary of Adverse Events Occurring During the Study

	Treatment Group		Total	p-value
	Ciprofloxacin GR	Ciprofloxacin IR		
Number (%) of Patients Received Treatment	518 (100%)	509 (100%)	1027 (100%)	
Number (%) of Patients Who Reported Adverse Events by System Organ Class				
Respiratory, thoracic and mediastinal disorders (Continued)				
Epistaxis	1 (0.2%)	0	1 (0.1%)	NS
Haemoptysis	0	1 (0.2%)	1 (0.1%)	NS
Laryngitis NOS	1 (0.2%)	0	1 (0.1%)	NS
Pleurisy	0	1 (0.2%)	1 (0.1%)	NS
Pleuritic pain	0	1 (0.2%)	1 (0.1%)	NS
Rhonchi	1 (0.2%)	0	1 (0.1%)	NS
Sinus pain	1 (0.2%)	0	1 (0.1%)	NS
Wheezing	1 (0.2%)	0	1 (0.1%)	NS
Skin and subcutaneous tissue disorders	13 (2.5%)	10 (2.0%)	23 (2.2%)	NS
Rash NOS	3 (0.6%)	2 (0.4%)	5 (0.5%)	NS
Contusion	3 (0.6%)	1 (0.2%)	4 (0.4%)	NS
Erythema	1 (0.2%)	2 (0.4%)	3 (0.3%)	NS
Acne NOS	1 (0.2%)	1 (0.2%)	2 (0.2%)	NS
Pruritus	2 (0.4%)	0	2 (0.2%)	NS
Urticaria NOS	2 (0.4%)	0	2 (0.2%)	NS
Dermatitis contact	0	1 (0.2%)	1 (0.1%)	NS
Eczema	1 (0.2%)	0	1 (0.1%)	NS
Parapsoriasis	0	1 (0.2%)	1 (0.1%)	NS
Rash maculo-papular	0	1 (0.2%)	1 (0.1%)	NS
Sweating increased	0	1 (0.2%)	1 (0.1%)	NS
Swelling face	1 (0.2%)	0	1 (0.1%)	NS
Surgical and medical procedures	1 (0.2%)	0	1 (0.1%)	NS
Nasal cyst removal	1 (0.2%)	0	1 (0.1%)	NS
Vascular disorders	1 (0.2%)	5 (1.0%)	6 (0.6%)	NS
Hot flushes NOS	1 (0.2%)	1 (0.2%)	2 (0.2%)	NS
Hypertension aggravated	0	2 (0.4%)	2 (0.2%)	NS
Aortic aneurysm	0	1 (0.2%)	1 (0.1%)	NS
Hypertension NOS	0	1 (0.2%)	1 (0.1%)	NS

Note: Adverse event mapping was based on the MedDRA Version 5.1 thesaurus.

A patient may be reported in more than one category.

The p-values were obtained from the Fisher's Exact test and were presented if they are less than 0.10.

NS = Not statistically significant at 0.10 level.

Source: Table 14.1.3-2 in the applicant's study report

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10.2.19.3 Treatment-Related Adverse Events

During the course of the 5-week study, the most frequent treatment-related AEs in the C-GR group were fungal infection NOS in 9 of 518 patients (1.7%); dizziness in 4 of 518 patients (0.8%); and abdominal pain NOS, nausea, fungal vaginosis NOS, and headache each in 3 of 518 patients (0.6%). In the C-IR group, the most frequent treatment-related AEs were nausea in 9 of 509 patients (1.8%); fungal vaginosis NOS in 8 of 509 patients (1.6%); diarrhea NOS and headache each in 6 of 509 patients (1.2%); fungal infection NOS in 5 of 509 patients (1.0%); and dyspepsia in 3 of 509 patients (0.6%).

Severe, treatment-related AEs included abdominal pain NOS and urticaria NOS (one patient each) in C-GR-treated patients, and included dyspepsia, fatigue, and fungal vaginosis NOS (one patient each) in C-IR-treated patients.

10.2.19.4 Severity of Adverse Events

During the course of the 5-week study, the majority of AEs experienced by patients in the C-GR and C-IR groups were mild or moderate in severity.

The following severe AEs were reported in the C-GR group: urinary tract infection NOS and urticaria NOS each in two of 518 patients (0.4%); and anemia NOS, abdominal pain NOS, *Escherichia* infection NOS, pyelonephritis NOS, aggravated back pain, back pain, papillary thyroid cancer, radiculopathy NOS, sciatica, dizziness, cystitis NOS, uterine pain, nasopharyngitis, contusion, and eczema each in 1 of 518 patients (0.2%).

The following severe AEs were each experienced by one of 509 patients (0.2%) patients in the C-IR group during the 5-week study: leukopenia NOS, dyspepsia, hemorrhoids, chest pain, fatigue, urinary tract infection NOS, back pain, fungal vaginosis NOS, viral gastroenteritis NOS, viral pharyngitis NOS, pyelonephritis NOS, alcohol poisoning, headache, tension headache, and ovarian cyst.

10.2.19.5 Applicant's Analysis of Gastrointestinal Adverse Events

There was a trend toward a lower incidence of GI AEs in the C-GR group compared to the C-IR group (C-GR: 2.9%; C-IR: 5.1%; $p=0.08$). The frequencies of diarrhea during study treatment (and through 3 days following the end of treatment) and during the entire 5-week study were significantly lower in the C-GR group than in the C-IR group. During study treatment, one of 518 C-GR-treated patients (0.2%) and seven of 509 (1.4%) C-IR-treated patients experienced diarrhea ($p=0.037$). Two of 518 C-GR-treated patients (0.4%) and 9 of 509 C-IR-treated patients (1.8%) experienced diarrhea during the 5-week study ($p=0.036$).

The frequency of nausea (i.e., nausea or nausea aggravated) was also significantly lower in the C-GR group (in 3 of 518 patients, 0.6%) than in the C-IR group (in 11 of 509 patients, 2.2%) during study treatment ($p=0.033$). Seven of 518 C-GR-treated patients (1.4%) and 12 of 509 (2.4%) C-IR-treated patients had nausea during the 5-week study.

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The majority of nausea (in 2 of 3 C-GR-treated patients and in 9 of 10 C-IR-treated patients) and diarrhea AEs (in 1 of 1 C-GR-treated patients and in 6 of 7 C-IR-treated patients) during study treatment were reported to be treatment related.

Clinical Reviewer's Comment: Although the incidence of diarrhea and nausea were numerically lower in the C-GR group, the incidence of all gastrointestinal adverse events was not significantly different in the C-R group (6.2%) compared to the C-IR group (8.3%), nor was the incidence of adverse events overall (58.9% and 57.6%, respectively). The rate of discontinuations due to adverse events was also higher in the C-GR group (1.3%) compared to the C-IR group (0.6%). Finally, the incidence of renal and urinary disorders (C-GR 6.0%; C-IR 2.9%) and dysuria (C-GR 1.5%; C-IR 0.2%) were higher in the C-GR group than in the C-IR group ($p=0.023$ and $p=0.038$, respectively). The higher incidence of urinary adverse events may signify lower efficacy in the C-GR group.

Therefore, the Reviewer does not feel that the "gastric retentive" formulation of the C-GR tablet is responsible for less clinically relevant gastrointestinal adverse events.

10.2.19.6 Changes in Laboratory Parameters

There were no significant differences between the C-GR and C-IR groups in the mean changes from baseline to final study visit in test results for hematology parameters, blood chemistry parameters, and urinalysis parameters.

10.2.19.7 Changes in Vital Signs

There were no significant differences between the C-GR and C-IR groups in the mean changes from baseline to final study visit in results of vital signs measurements

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10.3 Enrollment by Study Center, Study 81-0015

Table 14.1.1-1 (Page 1 of 3)

Enrollment Summary

Investigator Site Number	Treatment Group		Total (n = 1040)
	Ciprofloxacin GR (n = 526)	Ciprofloxacin IR (n = 514)	
1	3	3	6
2	8	10	18
3	0	1	1
4	7	6	13
5	4	4	8
6	7	7	14
7	12	12	24
8	12	11	23
9	4	4	8
10	14	14	28
11	9	8	17
12	7	7	14
13	8	9	17
15	3	2	5
16	8	9	17
17	7	7	14
18	10	9	19
19	9	8	17
20	2	2	4
21	5	5	10
22	14	14	28
23	8	8	16
24	25	25	50
25	8	9	17
26	5	4	9
27	24	22	46
28	14	13	27
29	15	16	31
30	8	9	17
Total	526 (50.6%)	514 (49.4%)	1040 (100.0%)

Note: The denominator for the calculation of the percentages in the "total" row for each treatment group of all study sites is the total number of patients enrolled in this study.
 Patients 2401, 6009, and 6012 received a randomization number through interactive voice response system in error and were excluded from randomized population.

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Table 14.1.1-1 (Page 2 of 3)

Enrollment Summary

Investigator Site Number	Treatment Group		Total (n = 1040)
	Ciprofloxacin CR (n = 526)	Ciprofloxacin IR (n = 514)	
31	7	6	13
32	19	20	39
33	5	5	10
34	1	0	1
35	0	1	1
36	10	9	19
37	8	8	16
38	7	6	13
39	24	23	47
41	12	12	24
42	8	8	16
43	17	18	35
44	7	7	14
45	6	5	11
46	15	14	29
47	5	5	10
48	15	14	29
49	8	8	16
50	4	3	7
51	4	4	8
52	4	5	9
54	5	6	11
55	6	7	13
57	4	3	7
58	3	3	6
60	7	7	14
61	4	4	8
62	0	1	1
63	7	6	13
Total	526 (50.6%)	514 (49.4%)	1040 (100.0%)

Note: The denominator for the calculation of the percentages in the "total" row for each treatment group of all study sites is the total number of patients enrolled in this study. Patients 2401, 6009, and 6012 received a randomization number through interactive voice response system in error and were excluded from randomized population.

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Enrollment Summary

Investigator Site Number	Treatment Group		Total (n = 1040)
	Ciprofloxacin GR (n = 526)	Ciprofloxacin IR (n = 514)	
64	3	2	5
65	11	11	22
66	10	9	19
67	2	0	2
68	10	10	20
69	3	2	5
70	2	2	4
71	3	2	5
Total	526 (50.6%)	514 (49.4%)	1040 (100.0%)

Note: The denominator for the calculation of the percentages in the "total" row for each treatment group of all study sites is the total number of patients enrolled in this study.
Patients 2401, 6009, and 6012 received a randomization number through interactive voice response system in error and were excluded from randomized population.

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/s/

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