

	(3.0%)	(4.6%)	(3.4%)	(1.3%)	(4.8%)	(2.3%)
<i>Escherichia coli</i>	5 (3.0%)	2 (3.1%)	7 (3.0%)	4 (2.6%)	2 (3.3%)	6 (2.6%)
<i>Enterobacter aerogenes</i>	2 (1.2%)	3 (4.6%)	5 (2.2%)	2 (1.3%)	1 (1.6%)	3 (1.4%)
<i>Citrobacter diversus</i>	1 (0.6%)	4 (6.2%)	5 (2.2%)	2 (1.3%)	0	2 (0.9%)
<i>Proteus mirabilis</i>	1 (0.6%)	4 (6.2%)	5 (2.2%)	0	2 (3.3%)	2 (0.9%)
<i>Serratia marcescens</i>	2 (1.2%)	3 (4.6%)	5 (2.2%)	1 (0.6%)	0	1 (0.5%)
Beta-hemolytic streptococci, Group B	0	2 (3.1%)	2 (0.9%)	2 (1.3%)	2 (3.3%)	4 (1.8%)
Beta-hemolytic streptococcus, Group G	2 (1.2%)	0	2 (0.9%)	0	0	0
<i>Pseudomonas stutzeri</i>	0	1 (1.5%)	1 (0.4%)	2 (1.3%)	0	2 (0.9%)
<i>Agrobacterium radiobacter/</i> <i>Tumefaciens</i>	1 (0.6%)	0	1 (0.4%)	1 (0.6%)	0	1 (0.5%)
<i>Enterobacter</i> species	1 (0.6%)	0	1 (0.4%)	1 (0.6%)	0	1 (0.5%)
<i>Aeromonas hydrophila</i>	1 (0.6%)	0	1 (0.4%)	0	0	0
Beta-hemolytic streptococci, Group A	0	1 (1.5%)	1 (0.4%)	0	0	0
<i>Pantoea agglomerans</i>	1 (0.6%)	0	1 (0.4%)	0	0	0
<i>Pantoea</i> species	1 (0.6%)	0	1 (0.4%)	0	0	0
<i>Proteus</i> species	0	1 (1.5%)	1 (0.4%)	0	0	0
<i>Serratia rubideae</i>	0	1 (1.5%)	1 (0.4%)	0	0	0
<i>Stenotrophomonas maltophilia</i>	0	0	0	6 (3.8%)	0	6 (2.6%)
<i>Citrobacter freundii</i>	0	0	0	2 (1.3%)	1 (1.6%)	3 (1.4%)
<i>Enterobacter sakazakii</i>	0	0	0	2 (1.3%)	0	2 (0.9%)
<i>Citrobacter</i> species	0	0	0	0	1 (1.6%)	1 (0.5%)

Note: N is the total number of patients in the ITT population.

Note: Bacterial abundance is assessed on a scale of 1+ to 4+, per standard laboratory grading (0 if the culture is sterile). To be considered a pathogen, the cultured organism must be present at a level of 2+ or higher.

Patient may have more than one pathogen.

Percentages for 'Any pathogen' are calculated using the ITT population as the denominator. All other percentages are calculated using the MTT population as the denominator.

Percentages for US and Spain are calculated using the number of patients in that country in the appropriate population as the denominator.

Source: Table 4.2, section 5.3.5.4.10, p19; Statistical Table 4.2.1.2

Sensitivity of Pathogens to Antibiotics

A central laboratory tested the sensitivity of each isolate of *S. aureus* and *P. aeruginosa* to a standard panel of antibiotics based upon Clinical and Laboratory Standards Institute (CLSI) breakpoint standards using an automated Vitek™ antibiotic microtiter panel. In addition, the central laboratory tested the sensitivity of each isolate to ciprofloxacin using a full dilution series created specifically for this study (the ciprofloxacin-custom™ series)

to determine the MIC of ciprofloxacin for each isolate. These data were then used to determine the MIC₅₀ and MIC₉₀ of ciprofloxacin for *S. aureus* and *P. aeruginosa*.

The MIC₅₀ and MIC₉₀ of ciprofloxacin are shown in Table 11. There were no differences in MIC between isolates from patients in the ciprofloxacin group and isolates from patients in the PNH group. For *P. aeruginosa*, the MIC₅₀ of ciprofloxacin was 0.12 µg/mL and the MIC₉₀ was 0.50 µg/mL. For *S. aureus*, the MIC₅₀ was 0.25 µg/mL and the MIC₉₀ was 1 µg/mL.

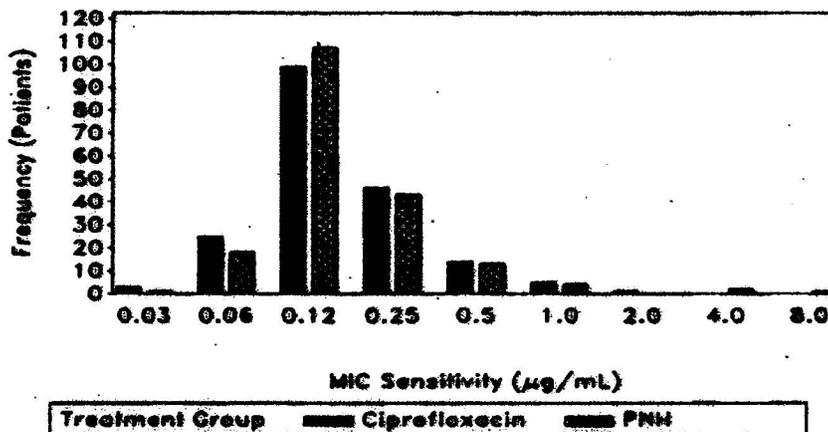
Table 11. Ciprofloxacin MIC₅₀ and MIC₉₀ (µg/mL) for *P. aeruginosa* and *S. aureus* - MITT Population

		Ciprofloxacin	PNH	Total
<i>P. aeruginosa</i>	n	193	189	382
	MIC ₅₀	0.12	0.12	0.12
	MIC ₉₀	0.50	0.50	0.50
<i>S. aureus</i>	n	33	35	68
	MIC ₅₀	0.25	0.25	0.25
	MIC ₉₀	1.0	1.0	1.0

Source: Table 5, section 5.3.5.4.11, p20;
 Statistical Tables 4.1.1.1 and 4.1.2.1

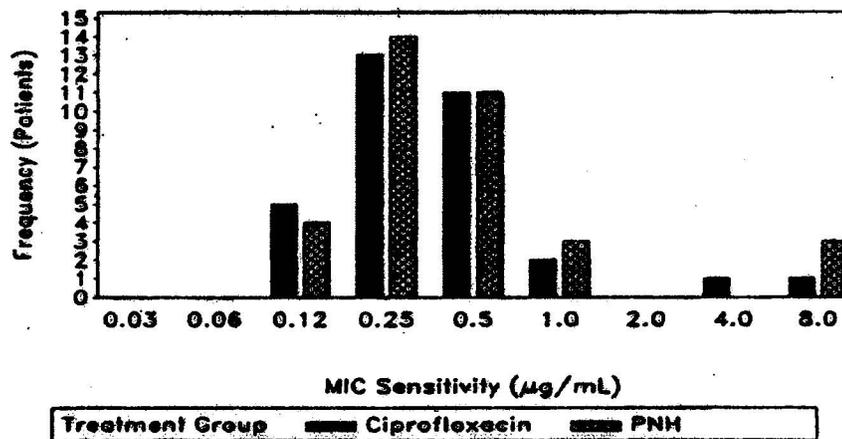
The distribution of MICs of ciprofloxacin is shown by treatment group in Figure 1 for isolates of *P. aeruginosa* and in Figure 2 for isolates of *S. aureus*. There were no substantial differences in frequency distribution of the ciprofloxacin sensitivity between isolates from patients in the different treatment groups. The MIC₅₀ and MIC₉₀ values of ciprofloxacin for *P. aeruginosa* and *S. aureus* observed in this study were similar to those previously reported in published studies involving pseudomonal and staphylococcal isolates taken from a variety of other body sites [41].

Figure 1. MICs of Ciprofloxacin for Isolates of *Pseudomonas aeruginosa*.



Source: Figure 1, section 5.3.5.4.11, p21

Figure 2. MICs of Ciprofloxacin for Isolates of *Staphylococcus aureus*.



Source: Figure 2, section 5.3.5.4.11, p21

Isolates from patients in the ciprofloxacin group and isolates from patients in the PNH group were similar in terms of sensitivity to an array of antibiotics included in the Vitek TM microtitre panel as seen in Table 12. Most isolates of *P. aeruginosa* were sensitive to all antibiotics tested. Very few isolates were resistant to ciprofloxacin. The standard automated panel showed 2 (1%) isolates from patients in the ciprofloxacin group and three (2%) from patients in the PNH group to be resistant to ciprofloxacin. The more precise custom dilution series showed no resistant isolates from patients in the ciprofloxacin group, although one isolate had intermediate sensitivity to ciprofloxacin, and three (2%) isolates from patients in the PNH group to be resistant.

Table 12. Ciprofloxacin Resistance for Pathogens in MITT Population

		Ciprofloxacin (Custom)	PNH	Total
		N=187	N=183	N=370
<i>P. aeruginosa</i>	number	187	183	370
	Resistant	0	3 (1.6%)	3 (0.8%)
	Susceptible	186 (99.5%)	180 (98.4%)	366 (98.9%)
	Intermediate	1 (0.5%)	0	1 (0.3%)
		Ciprofloxacin (Custom)	PNH	Total
		N=33	N=35	N=68
<i>S. aureus</i>	number	33	35	68
	Resistant	2 (6.1%)	3 (8.1%)	5 (7.6%)
	Susceptible	31 (93.9%)	30 (85.9%)	61 (89.4%)
	Intermediate	0	0	0

Source: Table 6, section 5.3.5.4.11, p22; Statistical Tables 40.1.1 and 40.2.1

For *S. aureus*, resistance to methicillin/oxacillin was reported for 6% of isolates; this is Clinically relevant because ciprofloxacin is generally not active against methicillin resistant *S. aureus* [33]. The standard panel showed approximately 10% of isolates of *S.*

aureus, three (9%) isolates from patients in the ciprofloxacin group, and four (11%) isolates from patients in the PNH group to be resistant to ciprofloxacin. The more precise custom panel revealed two (6%) isolates from patients in the ciprofloxacin group and three (9%) isolates from patients in the PNH group to be resistant to ciprofloxacin. Of these five ciprofloxacin-resistant isolates, three were also methicillin-resistant strains.

Bacteriologic Response

Bacteriologic response is summarized in Table 13. In the MPP population, at both the End-of-Treatment (EOT) visit and the Test-of-Cure visit, which occurred about one week after EOT, the bacteriologic response was Eradication or Presumed Eradication for the great majority of patients in both treatment groups. At the EOT visit, 96% of patients in the ciprofloxacin group and 93% in the PNH group had Eradication or Presumed Eradication. At the Test-of-Cure visit, Eradication or Presumed Eradication was reported for 90% of patients in the ciprofloxacin group and 87% in the PNH group. In the MITT population, trends were generally similar to those in the MPP population, although several patients (4% in the ciprofloxacin group and 2% in the PNH group) had responses assessed as Indeterminate due primarily to lack of follow-up.

Table 13. Bacteriologic Response.

Visit		Microbiological per Protocol Population		Microbiological Intent to Treat Population	
		Cipro (N=174)	PNH (N=174)	Cipro (N=232)	PNH (N=217)
End of Treatment	Eradication	39 (22.4%)	46 (26.4%)	53 (22.8%)	56 (25.8%)
	Presumed Eradication	128 (73.6%)	115 (66.1%)	157 (67.7%)	136 (64.1%)
	Eradication or Presumed Eradication	167 (96%)	161 (92.5%)	210 (90.5%)	196 (89.9%)
	Persistence	1 (0.6%)	5 (2.9%)	3 (1.3%)	7 (3.2%)
	Presumed Persistence	5 (2.9%)	8 (4.6%)	8 (3.5%)	11 (5.1%)
	Superinfection	1 (0.6%)	0	1 (0.4%)	0
	Indeterminate	—	—	10 (4.3%)	4 (1.8%)
Test of Cure	Eradication	16 (9.2%)	22 (12.6%)	21 (9.1%)	27 (12.4%)
	Presumed Eradication	141 (81%)	130 (74.7%)	176 (75.9%)	156 (71.4%)
	Eradication or Presumed Eradication	157 (90.2%)	152 (87.4%)	197 (84.9%)	182 (83.9%)
	Persistence	1 (0.6%)	1 (0.6%)	1 (0.4%)	2 (0.9%)
	Presumed Persistence	16 (9.2%)	21 (12.1%)	24 (10.3%)	29 (13.4%)
	Superinfection	0	0	0	0
	Indeterminate	—	—	10 (4.3%)	4 (1.8%)

Source: Table 7.1, section 3.3.5.4.12, p23; Statistical Tables 21.1.1 and 21.1.2

Similar bacterial responses could be seen when separating the eradication or presumed eradication rates by the US and Spanish populations. In the MPP population in the US, the rate was 95.3% for the ciprofloxacin group and 90.3% for the PNH group at the EOT visit; in Spain, the rates were 97.9% and 98.0% for ciprofloxacin and PNH, respectively. At the Test-of-Cure visit, the eradication or presumed eradication rates for ciprofloxacin and PNH were 89.0% and 85.5% for the US group and 93.6% and 92.0% for the Spanish

group, respectively. The rates for the MITT population analyzed by country were not significantly different (Table 14).

Table 14. Bacterial Response by Country

Visit	US	Microbiological per Protocol Population		Microbiological Intent to Treat Population	
		Cipro (N=174)	PNH (N=174)	Cipro (N=232)	PNH (N=217)
	n	127	124	167	156
End of Treatment	Eradication	19 (15%)	23 (18.5%)	25 (15%)	29 (18.6%)
	Presumed Eradication	102 (80.3%)	89 (71.8%)	124 (74.3%)	108 (69.2%)
	Eradication or Presumed Eradication	121 (95.3%)	112 (90.3%)	149 (89.2%)	137 (87.8%)
	Persistence	0	5 (4%)	1 (0.6%)	7 (4.5%)
	Presumed Persistence	5 (3.9%)	7 (5.6%)	8 (4.8%)	9 (5.8%)
	Superinfection	1 (0.8%)	0	1 (0.6%)	0
	Indeterminate	--	--	8 (4.8%)	3 (1.9%)
	n	127	124	167	156
Test of Cure	Eradication	4 (3.2%)	14 (11.3%)	5 (3%)	17 (10.9%)
	Presumed Eradication	100 (85.8%)	92 (74.2%)	133 (79.6%)	112 (71.8%)
	Eradication or Presumed Eradication	113 (89%)	106 (85.5%)	138 (82.6%)	129 (82.7%)
	Persistence	0	0	0	1 (0.6%)
	Presumed Persistence	14 (11%)	18 (14.5%)	21 (12.6%)	23 (14.7%)
	Superinfection	0	0	0	0
	Indeterminate	--	--	8 (4.8%)	3 (1.9%)
Visit	Spain	Microbiological per Protocol Population		Microbiological Intent to Treat Population	
		Cipro (N=174)	PNH (N=174)	Cipro (N=232)	PNH (N=217)
	n	47	50	65	61
End of Treatment	Eradication	20 (42.6%)	23 (46%)	28 (43.1%)	27 (44.3%)
	Presumed Eradication	26 (55.3%)	26 (52%)	33 (50.8%)	31 (50.8%)
	Eradication or Presumed Eradication	46 (97.9%)	49 (98%)	61 (93.8%)	58 (95.1%)
	Persistence	1 (2.1%)	0	2 (3.1%)	0
	Presumed Persistence	0	1 (2%)	0	2 (3.3%)
	Superinfection	0	0	0	0
	Indeterminate	--	--	2 (3.1%)	1 (1.6%)
	n	47	50	65	61
Test of Cure	Eradication	12 (25.5%)	8 (16%)	16 (24.6%)	16 (16.4%)
	Presumed Eradication	32 (68.1%)	38 (76%)	43 (66.2%)	43 (70.5%)
	Eradication or Presumed Eradication	44 (93.6%)	46 (92%)	59 (90.8%)	53 (86.9%)
	Persistence	1 (2.1%)	1 (2%)	1 (1.5%)	1 (1.6%)
	Presumed Persistence	2 (4.3%)	3 (6%)	3 (4.6%)	6 (9.8%)
	Superinfection	0	0	0	0
	Indeterminate	--	--	2 (3.1%)	1 (1.6%)

Source: Table 7.2, section 5.3.5.4.12, p24; Statistical Tables 21.1.1 and 21.2.2

The bacterial response rates were also determined by pathogen (Table 15). Once again this data is depicted for the two predominant pathogens, *P. aeruginosa* and *S. aureus*. For *P. aeruginosa* in the MPP population, the bacterial eradication or presumed eradication response rate was over 90% for both the ciprofloxacin (97.3%) and the PNH (92.2%) groups at the End-of-Treatment visit. At the Test-of-Cure visit, the eradication or presumed eradication rate for *P. aeruginosa* decreased slightly for the ciprofloxacin patients (93.4%) while the response rate for the PNH group decreased to 87.7%. The comparison of the MITT population response rates was similar to that of the MPP population; however, the bacterial response rate for the *P. aeruginosa* group was lower for both ciprofloxacin- and PNH-treated populations at the End-of-Treatment and Test of- Cure visits.

For *S. aureus* in the MPP population, the bacterial eradication or presumed eradication response rates for ciprofloxacin and PNH were 91.3% and 96.5% at the EOT visit and 81.8% and 86.2% at the Test-of-Cure visit, respectively. The eradication or presumed eradication rate for the MITT population at EOT was noticeably different from the MPP: bacterial response to ciprofloxacin was 79.4% while the bacterial response to PNH was 91.4%. The bacterial response rate at the Test-of-Cure visit for ciprofloxacin was 69.7%, and the PNH group showed a response rate of 77.1%.

Data for the less predominant pathogens can be found in Statistical Tables 23.1.1 and 23.1.2 (this submission) for the MPP and MITT populations, respectively.

Table 15. Bacterial Response by Pathogen.

	Microbiological per	Microbiological intent
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Visit		Protocol Population		to Treat Population	
		Cipro (N=174)	PNH (N=174)	Cipro (N=232)	PNH (N=217)
<i>P. aeruginosa</i>					
	n	152	154	197	193
End of Treatment	Eradication	32 (21.1%)	40 (26%)	43 (21.8%)	50 (25.9%)
	Presumed Eradication	116 (76.3%)	102 (66.2%)	139 (70.6%)	125 (64.8%)
	Eradication or Presumed Eradication	148 (97.4%)	142 (92.2%)	182 (92.4%)	175 (90.7%)
	Persistence	1 (0.7%)	4 (2.6%)	1 (0.5%)	5 (2.6%)
	Presumed Persistence	3 (2%)	8 (5.2%)	6 (3%)	11 (5.7%)
	Superinfection	0	0	0	0
	Indeterminate	--	--	8 (4.1%)	2 (1%)
	n	152	154	197	193
Test of Cure	Eradication	14 (9.2%)	20 (13%)	18 (9.1%)	23 (11.9%)
	Presumed Eradication	128 (84.2%)	115 (74.7%)	155 (78.7%)	139 (72%)
	Eradication or Presumed Eradication	142 (93.4%)	135 (87.7%)	173 (87.8%)	162 (82.9%)
	Persistence	1 (0.7%)	1 (0.6%)	1 (0.5%)	2 (1%)
	Presumed Persistence	9 (5.9%)	18 (11.7%)	15 (7.6%)	25 (13%)
	Superinfection	0	0	0	0
	Indeterminate	--	--	8 (4.1%)	4 (2.1%)
		Microbiological per Protocol Population		Microbiological Intent to Treat Population	
Visit		Cipro (N=174)	PNH (N=174)	Cipro (N=232)	PNH (N=217)
<i>S. aureus</i>					
	n	23	29	34	35
End of Treatment	Eradication	8 (34.8%)	7 (24.1%)	9 (26.5%)	11 (31.4%)
	Presumed Eradication	13 (56.5%)	21 (72.4%)	18 (52.9%)	21 (60%)
	Eradication or Presumed Eradication	21 (91.3%)	28 (96.5%)	27 (79.4%)	32 (91.4%)
	Persistence	0	1 (3.4%)	1 (2.9%)	2 (5.7%)
	Presumed Persistence	1 (4.3%)	0	2 (5.9%)	0
	Superinfection	1 (4.3%)	0	1 (2.9%)	0
	Indeterminate	--	--	3 (8.8%)	1 (2.9%)
	n	22	29	33	35
Test of Cure	Eradication	3 (13.6%)	4 (13.8%)	3 (9.1%)	5 (14.3%)
	Presumed Eradication	15 (68.2%)	21 (72.4%)	20 (60.6%)	22 (62.9%)
	Eradication or Presumed Eradication	18 (81.8%)	25 (86.2%)	23 (69.7%)	27 (77.1%)
	Persistence	0	0	0	0
	Presumed Persistence	4 (18.2%)	4 (13.8%)	7 (21.2%)	7 (20%)
	Superinfection	0	0	0	0
	Indeterminate	--	--	3 (9.1%)	1 (2.9%)

Source: Table 7.3, section 5.3.5.4.12, p26; Statistical Tables 23.1.1 and 23.1.2

When analyzing the same pathogen-specific bacterial response data by country, the eradication and presumed eradication rates were similar in the US and in Spain for *P.*

aeruginosa and appear to higher in Spain for *S. aureus* but the number of specimens available for comparison were small (Tables 16 and 17). Data for the less predominant pathogens by country can be found in Statistical Tables 23.3.1 and 23.3.2 for the MPP and MITT populations, respectively.

Table 16. Bacterial Response by Pathogen by Country (US).

Visit	US	Microbiological per Protocol Population		Microbiological Intent to Treat Population	
		Cipro (N=127)	PNH (N=124)	Cipro (N=167)	PNH (N=156)
<i>P. aeruginosa</i>					
	n	110	112	142	142
End of Treatment	Eradication	16 (14.5%)	19 (17%)	21 (14.8%)	25 (17.6%)
	Presumed Eradication	91 (82.7%)	82 (73.2%)	100 (70.8%)	101 (71.1%)
	Persistence	0	4 (3.6%)	0	5 (3.5%)
	Presumed Persistence	3 (2.7%)	7 (6.3%)	6 (4.2%)	9 (6.3%)
	Superinfection	0	0	0	0
	Indeterminate	--	--	6 (4.2%)	2 (1.4%)
	n	110	112	142	142
Test of Cure	Eradication	3 (2.7%)	12 (10.7%)	4 (2.8%)	14 (9.9%)
	Presumed Eradication	90 (80%)	85 (75.9%)	118 (83.1%)	105 (73.9%)
	Persistence	0	0	0	1 (0.7%)
	Presumed Persistence	8 (7.3%)	15 (13.4%)	14 (9.9%)	19 (13.4%)
	Superinfection	0	0	0	0
	Indeterminate	--	--	6 (4.2%)	3 (2.1%)
<i>S. aureus</i>					
	n	18	17	28	22
End of Treatment	Eradication	5 (27.8%)	3 (17.6%)	6 (21.4%)	6 (27.3%)
	Presumed Eradication	11 (61.6%)	13 (76.5%)	15 (53.6%)	13 (59.1%)
	Persistence	0	0	1 (3.6%)	2 (9.1%)
	Presumed Persistence	1 (5.6%)	0	2 (7.1%)	0
	Superinfection	1 (5.6%)	0	1 (3.6%)	0
	Indeterminate	--	--	3 (10.7%)	1 (4.5%)
	n	17	17	27	22
Test of Cure	Eradication	1 (5.9%)	2 (11.8%)	1 (3.7%)	3 (13.6%)
	Presumed Eradication	12 (70.6%)	12 (70.6%)	18 (66.3%)	13 (59.1%)
	Persistence	0	0	0	0
	Presumed Persistence	4 (23.5%)	3 (17.6%)	7 (25.9%)	6 (27.3%)
	Superinfection	0	0	0	0
	Indeterminate	--	--	3 (11.1%)	0

Source: Table 7.4, section 5.3.5.4.12, p27; Statistical Tables 23.3.1 and 23.3.2

Table 17. Bacterial Response by Pathogen, by Country (Spain).

		Microbiological per	Microbiological Intent
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