

Visit	Spain	Protocol Population		to Treat Population	
		Cipro (N=47)	PNH (N=50)	Cipro (N=65)	PNH (N=61)
<b><i>P. aeruginosa</i></b>					
	n	42	42	55	51
End of Treatment	Eradication	16 (38.1%)	21 (50%)	22 (40%)	25 (49%)
	Presumed Eradication	25 (59.5%)	20 (47.6%)	30 (54.5%)	24 (47.1%)
	Persistence	1 (2.4%)	0	1 (1.8%)	0
	Presumed Persistence	0	1 (2.4%)	0	2 (3.9%)
	Superinfection	0	0	0	0
	Indeterminate	--	--	2 (3.6%)	0
	n	42	42	55	51
Test of Cure	Eradication	11 (26.2%)	8 (19%)	14 (25.5%)	9 (17.6%)
	Presumed Eradication	29 (69%)	30 (71.4%)	37 (67.3%)	34 (66.7%)
	Persistence	1 (2.4%)	1 (2.4%)	1 (1.8%)	1 (2%)
	Presumed Persistence	1 (2.4%)	3 (7.1%)	1 (1.8%)	6 (11.8%)
	Superinfection	0	0	0	0
	Indeterminate	--	--	2 (3.6%)	1 (2%)
		Microbiological per Protocol Population		Microbiological Intent to Treat Population	
Visit		Cipro (N=47)	PNH (N=50)	Cipro (N=65)	PNH (N=61)
<b><i>S. aureus</i></b>					
	n	5	12	6	13
End of Treatment	Eradication	3 (60%)	4 (33.3%)	3 (50%)	5 (38.5%)
	Presumed Eradication	2 (40%)	8 (66.7%)	3 (50%)	8 (61.5%)
	Persistence	0	0	0	0
	Presumed Persistence	0	0	0	0
	Superinfection	0	0	0	0
	Indeterminate	--	--	0	0
	n	5	12	6	13
Test of Cure	Eradication	2 (40%)	2 (16.7%)	2 (33.3%)	2 (15.4%)
	Presumed Eradication	3 (60%)	9 (75%)	4 (66.7%)	9 (69.2%)
	Persistence	0	0	0	0
	Presumed Persistence	0	1 (8.3%)	0	1 (7.7%)
	Superinfection	0	0	0	0
	Indeterminate	--	--	0	1 (7.7%)

Source: Table 7.5, section 8.3.5.4.12, p28; Statistical Tables 23.3.1 and 23.3.3

**Reviewer's comments:** In the MITT population that included both countries, *S. aureus* response to ciprofloxacin was lower than the *S. aureus* response to PNH for both the EOT and the TOC visits. This observation suggests PNH may be more effective than Cipro Otic against *S. aureus* in the Spanish population. However, the above results suggest that ciprofloxacin is as effective as PNH against *P. aeruginosa*.

### Clinical Response

The primary efficacy endpoint for study CIPROT IY03 IA 02 was Clinical Cure at the Test-of-Cure visit. Results in the MPP and MITT populations are shown in Table 18. In the MPP population, 148 (85.1%) patients in the ciprofloxacin group and 136 (78.2%) in the PNH group had Clinical Cure at the Test-of-Cure visit. Compared with the PNH group, the proportion of MPP patients in the ciprofloxacin group with Sustained Clinical Cure was greater (68% vs. 56%), and the proportion with Subsequent Clinical Cure was smaller (17% vs. 22%).

In the MITT population, proportions of patients with Clinical Cure were smaller than in the MPP population, but differences between treatment groups showed the same trends. One hundred eighty-four (79.3%) patients in the ciprofloxacin group and 163 (75.1%) in the PNH group had Clinical Cure at Visit 4. Compared with the PNH group, the proportion of patients in the ciprofloxacin group with Sustained Clinical Cure was greater (63% vs. 55%), and the proportion with Subsequent Clinical Cure was smaller (16% vs. 20%). Approximately 5% of patients in the ciprofloxacin group and 2% in the PNH group had results assessed as Indeterminate.

**Table 18. Summary of Clinical Cure at Test-of-Cure Visit.**

	Microbiological Per-Protocol Population		Microbiological Intent-to-Treat Population	
	Ciprofloxacin (N=174)	PNH (N=174)	Ciprofloxacin (N=232)	PNH (N=217)
n	174	174	232	217
Clinical Cure	148 (85.1%)	136 (78.2%)	184 (79.3%)	163 (75.1%)
Sustained	118 (67.8%)	97 (55.7%)	147 (63.4%)	119 (54.8%)
Subsequent	30 (17.2%)	39 (22.4%)	37 (15.9%)	44 (20.3%)
Clinical Failure	26 (14.9%)	38 (21.8%)	48 (20.7%)	54 (24.9%)
Indeterminate	—	—	11 (4.7%)	5 (2.3%)

\*Meets the protocol criteria for non-inferiority

Source: Table 8.1, section 5.3.5.4.13, p28; Statistical Tables 7.1.3 and 7.1.4

The Clinical Cure rates at Test-of-Cure visit by country were similar to one another and consistent with the overall population results (Tables 19 and 20).

**Table 19. Summary of Clinical Cure at Test-of-Cure Visit by Country (US).**

US	Microbiological Per-Protocol Population		Microbiological Intent-to-Treat Population	
	Ciprofloxacin (N=174)	PNH (N=174)	Ciprofloxacin (N=232)	PNH (N=217)
n	174	174	232	217
Clinical Cure	108 (61.9%)	96 (55.0%)	131 (56.4%)	116 (53.4%)
Sustained	85 (48.9%)	63 (36.0%)	101 (43.5%)	79 (36.2%)
Subsequent	24 (13.9%)	32 (18.4%)	30 (12.9%)	37 (17.1%)
Clinical Failure	18 (10.2%)	28 (15.8%)	38 (16.3%)	40 (18.4%)
Indeterminate	—	—	8 (3.4%)	3 (1.4%)

Source: Table 8.2, section 5.3.5.4.13, p30; Statistical Tables 7.6.1 and 7.6.2

**Table 20. Summary of Clinical Cure at Test-of-Cure Visit by Country (Spain).**

Spain	Microbiological Per-Protocol Population		Microbiological Intent-to-Treat Population	
	Ciprofloxacin (N=174)	PNH (N=174)	Ciprofloxacin (N=232)	PNH (N=217)
n	47	50	65	61
Clinical Cure	39 (83%)	41 (82%)	53 (81.5%)	47 (77%)
Sustained	33 (70.2%)	34 (68%)	46 (70.6%)	40 (65.6%)
Subsequent	6 (12.6%)	7 (14%)	7 (10.8%)	7 (11.5%)
Clinical Failure	8 (17%)	9 (18%)	12 (18.5%)	14 (23%)
Indeterminate	--	--	3 (4.6%)	2 (3.3%)

Source: Table 8.3, section 5.3.5.4.13, p30; Statistical Table 7.6.1 and 7.6.2

The incidence of Clinical Cure was also analyzed by pathogen. Incidence of Clinical Cure was higher in patients infected with *P. aeruginosa* than in patients infected with *S. aureus*. In patients infected with *P. aeruginosa*, incidence of Clinical Cure was higher in the ciprofloxacin group than in the PNH group. In patients infected with *S. aureus*, incidence of Clinical Cure was slightly higher in the PNH group than in the ciprofloxacin group (Table 21).

Table 21. Summary of Clinical Cure at Test-of-Cure Visit, by Pathogen.

Spain	Microbiological Per-Protocol Population		Microbiological Intent-to-Treat Population	
	Ciprofloxacin (N=174)	PNH (N=174)	Ciprofloxacin (N=232)	PNH (N=217)
<i>P. aeruginosa</i>				
n	152	154	197	193
Clinical Cure	133 (87.5%)	121 (78.6%)	160 (81.2%)	147 (76.2%)
Sustained	104 (68.4%)	85 (55.2%)	125 (63.5%)	108 (54.9%)
Subsequent	29 (19.1%)	36 (23.4%)	35 (17.8%)	41 (21.2%)
Clinical Failure	19 (12.5%)	33 (21.4%)	37 (18.8%)	46 (23.8%)
Indeterminate	--	--	9 (4.6%)	4 (2.1%)
<i>S. aureus</i>				
n	22	29	33	35
Clinical Cure	16 (72.7%)	22 (75.9%)	21 (63.6%)	23 (66.7%)
Sustained	11 (50%)	20 (69%)	15 (45.5%)	20 (57.1%)
Subsequent	5 (22.7%)	2 (6.9%)	6 (18.2%)	3 (8.6%)
Clinical Failure	6 (27.3%)	7 (24.1%)	12 (36.4%)	12 (34.3%)
Indeterminate	--	--	3 (9.1%)	1 (2.9%)

Source: Table 8.4, section 5.3.5.4.13, p31; Statistical Tables 8.1.1 and 8.1.2

Incidence of Clinical Cure at Visit 4 by country and pathogen is summarized for the MPP and MITT populations in Tables 22 and 23.

The trends described for the overall patient microbiological population at the Test-of-Cure visit were also observed in patients in the US. For patients in Spain, differences between treatment groups and between pathogens were less pronounced. The number of patients infected with *S. aureus* in Spain was too small to allow any trends to be observed.

Table 22. Summary of Clinical Cure at Test-of-Cure Visit by Pathogen (US).

US	Microbiological Per-Protocol Population		Microbiological Intent-to-Treat Population	
	Ciprofloxacin (N=174)	PNH (N=174)	Ciprofloxacin (N=232)	PNH (N=217)
<i>P. aeruginosa</i>				
n	110	112	142	142
Clinical Cure	98 (89.1%)	88 (78.6%)	115 (81%)	108 (76.6%)
Sustained	75 (68.2%)	58 (51.8%)	87 (61.3%)	74 (52.1%)
Subsequent	23 (20.9%)	30 (26.8%)	28 (19.7%)	35 (24.6%)
Clinical Failure	12 (10.9%)	24 (21.4%)	27 (19%)	33 (23.2%)
Indeterminate	--	--	6 (4.2%)	3 (2.1%)
<i>S. aureus</i>				
n	17	17	27	22
Clinical Cure	12 (70.6%)	12 (70.6%)	16 (59.3%)	13 (59.1%)
Sustained	7 (41.2%)	11 (64.7%)	10 (37%)	11 (50%)
Subsequent	5 (29.4%)	1 (5.9%)	6 (22.2%)	2 (9.1%)
Clinical Failure	5 (29.4%)	5 (29.4%)	11 (40.7%)	9 (40.9%)
Indeterminate	--	--	3 (11.1%)	0

Source: Table 8.5, section 5.3.5.4.13, p31; Statistical Tables 8.2.1 and 8.2.2

Table 23. Summary of Clinical Cure at Test-of-Cure Visit by Pathogen (Spain).

Spain	Microbiological Per-Protocol Population		Microbiological Intent-to-Treat Population	
	Ciprofloxacin (N=174)	PNH (N=174)	Ciprofloxacin (N=232)	PNH (N=217)
<i>P. aeruginosa</i>				
n	42	42	55	51
Clinical Cure	35 (83.3%)	33 (78.6%)	45 (81.8%)	38 (74.5%)
Sustained	29 (69%)	27 (64.3%)	36 (69.1%)	32 (62.7%)
Subsequent	6 (14.3%)	6 (14.3%)	7 (12.7%)	6 (11.8%)
Clinical Failure	7 (16.7%)	9 (21.4%)	10 (18.2%)	13 (25.5%)
Indeterminate	--	--	3 (5.5%)	1 (2%)
<i>S. aureus</i>				
n	5	12	8	13
Clinical Cure	4 (80%)	10 (83.3%)	5 (62.5%)	10 (76.9%)
Sustained	4 (80%)	9 (75%)	5 (62.5%)	9 (69.2%)
Subsequent	0	1 (8.3%)	0	1 (7.7%)
Clinical Failure	1 (20%)	2 (16.7%)	1 (12.5%)	3 (23.1%)
Indeterminate	--	--	0	1 (7.7%)

Source: Table 8.6, section 5.3.5.4.13, p32; Statistical Tables 8.2.1 and 8.2.2

**Reviewer's comments:** When clinical cure rates were assessed by pathogen, higher rates of clinical cure were observed in patients in the ciprofloxacin arm than in the PNH arm. Spanish patients demonstrated a higher rate of clinical cure of *S. aureus*, but not *P. aeruginosa*, than American patients. The reason for this is unclear but may possibly be due to the low number of patients in the Spanish arm.

#### Clinical Response by Ciprofloxacin MIC

Clinical response was also evaluated by ciprofloxacin MIC in patients with either of the two predominant pathogens, *P. aeruginosa* or *S. aureus*, for both the MPP and MITT populations and by treatment with either ciprofloxacin or PNH. As noted in Tables 24 and 25 there was no discernible pattern of clinical response rates with increasing

ciprofloxacin MIC in patients treated with ciprofloxacin otic solution for either *P. aeruginosa* or *S. aureus* in either the MPP or MITT populations. However, there did appear to a possible trend toward decreasing clinical response with increasing ciprofloxacin MIC for patients with *P. aeruginosa* treated with PNH. No such trend was noted for patients with *S. aureus* treated with PNH.

**Table 24. Clinical Efficacy at Test-of-Cure Visit in MPP Population.**

Pathogen	MIC (µg/ml)	Ciprofloxacin (N=174) Cure	Failure	PNH (N=174) Cure	Failure
<i>P. aeruginosa</i>	0.03	1 (100%)	0	1 (100%)	0
	0.06	17 (85.5%)	3 (15%)	8 (88.7%)	4 (33.3%)
	0.12	64 (85.3%)	11 (14.7%)	72 (83.7%)	14 (16.3%)
	0.25	35 (97.2%)	1 (2.8%)	25 (75.8%)	8 (24.2%)
	0.5	10 (83.3%)	2 (16.7%)	7 (84.3%)	5 (41.7%)
	1	1 (33.3%)	2 (66.7%)	2 (50%)	2 (50%)
	2	1 (100%)	0	0	0
	4	0	0	2 (100%)	0
<i>S. aureus</i>	0.12	3 (80%)	2 (40%)	2 (50%)	2 (50%)
	0.25	6 (85.7%)	1 (14.3%)	7 (77.8%)	2 (22.2%)
	0.5	5 (71.4%)	1 (28.6%)	7 (77.8%)	2 (22.2%)
	1	2 (100%)	0	2 (66.7%)	1 (33.3%)
	4	0	1 (100%)	0	0
	8	0	0	3 (100%)	0

Source: Table 9.1, section 5.3.5.4.14, p33; Statistical Table 43.1.1

**Table 25. Clinical Efficacy at Test-of-Cure Visit in MITT Population.**

Pathogen	MIC (µg/ml)	Ciprofloxacin (N=174) Cure	Failure	PNH (N=174) Cure	Failure
<i>P. aeruginosa</i>	0.03	3 (100%)	0	1 (100%)	0
	0.06	22 (88%)	3 (12%)	13 (72.2%)	5 (27.8%)
	0.12	78 (78.8%)	21 (21.1%)	87 (81.3%)	20 (18.7%)
	0.25	38 (82.6%)	8 (17.4%)	30 (85.8%)	13 (30.2%)
	0.5	11 (78.6%)	3 (21.4%)	8 (81.5%)	5 (38.5%)
	1	3 (80%)	2 (40%)	2 (50%)	2 (50%)
	2	1 (100%)	0	0	0
	4	0	0	2 (100%)	0
<i>S. aureus</i>	0.12	3 (80%)	2 (40%)	2 (50%)	2 (50%)
	0.25	9 (89.2%)	4 (30.8%)	8 (61.5%)	5 (38.5%)
	0.5	6 (54.5%)	5 (45.5%)	7 (63.6%)	4 (36.4%)
	1	2 (100%)	0	2 (66.7%)	1 (33.3%)
	4	0	1 (100%)	0	0
	8	1 (100%)	0	3 (100%)	0

Source: Table 9.2, section 5.3.5.4.14, p33; Statistical Table 43.1-2

**Reviewer's comments:** Only one pattern was observed that showed increasing MICs and decreasing clinical efficacy. There was a possible trend toward decreasing clinical response with increasing ciprofloxacin MIC for patients with *P. aeruginosa* treated with PNH, but no such trend was noted for patients with *S. aureus* treated with PNH. Four *S. aureus* isolates in the MITT population had MICs  $\geq 4$  µg/ml but these patients were clinical successes. Three *P. aeruginosa* isolates in the MITT population had MICs  $\geq 4$  µg/ml but were clinical successes. One *P. aeruginosa* isolate in the MITT population had a MIC = 2 µg/ml (ciprofloxacin intermediate) but

was a clinical success. Taken together, these observations suggest that MIC is not a predictor of clinical success, at least in the ciprofloxacin treatment arm.

**Clinical + Microbiological Results for CIPROT III/03 IA 02**

Clinical + Microbiological outcome is summarized in Table 25 for the MPP and MITT populations. Clinical + Microbiological Cure and Clinical + Microbiological Improvement at the End-of-Treatment [EOT] visit and at the Test-of-Cure (TOC) visit were secondary efficacy endpoints in the CIPROT study.

In the MPP population at the EOT visit, 70% of patients in the ciprofloxacin group and 60% in the PNH group had Clinical + Microbiological Cure. Clinical + Microbiological Improvement was observed in 21% of patients in the ciprofloxacin group and 26% in the PNH group. At the Test-of-Cure visit, the proportions of patients with Clinical + Microbiological Cure had increased to 85% in the ciprofloxacin group and 78% in the PNH group. The proportions of patients with Clinical + Microbiological Improvement had decreased to 3% in the ciprofloxacin group and 2% in the PNH group.

In the MITT population, results were generally similar to those in the MPP population, but differences between treatments were less pronounced. At the EOT visit, 66% of patients in the ciprofloxacin group and 59% in the PNH group had Clinical + Microbiological Cure; and 21% and 24%, respectively, had Clinical + Microbiological Improvement. At the Test-of-Cure visit, the proportions of patients with Clinical + Microbiological Cure had increased to 79% in the ciprofloxacin group and 75% in the PNH group; and the proportions with Clinical + Microbiological Improvement had decreased to 3% in the ciprofloxacin group and 2% in the PNH group.

**Table 26. Overall Clinical + Microbiological Outcome**

		Microbiological Per-Protocol Population Number (%) of Patients		Microbiological Intent-to-Treat Population Number (%) of Patients	
		Ciprofloxacin (N=174)	PNH (N=174)	Ciprofloxacin (N=232)	PNH (N=217)
Visit	n	174	174	232	217
	Cure	121 (69.5%)	104 (59.8%)	153 (65.9%)	129 (59.4%)
	Improvement	37 (21.3%)	45 (25.9%)	48 (20.7%)	53 (24.4%)
	Failure	16 (9.2%)	25 (14.4%)	31 (13.4%)	35 (16.1%)
Test-of-Cure	n	174	174	232	217
	Cure	148 (85.1%)	136 (78.2%)	184 (79.3%)	163 (75.1%)
	Improvement	5 (2.9%)	3 (1.7%)	8 (3.4%)	5 (2.3%)
	Failure	21 (12.1%)	35 (20.1%)	40 (17.2%)	48 (22.6%)

Source: Table 10.1, section 5.3.5.4.15, p34; Statistical Tables 24.1.1 and 24.1.2

Analyzing the data by country, the percentage of patients with clinical + microbiological cure was similar to that of the combined populations. In the US, the MPP population with clinical + microbiological cure was 69% for ciprofloxacin and 56% for PNH patients at the EOT visit. In Spain, the MPP population with clinical + microbiological cure was 70% for both the ciprofloxacin and PNH patients. At the test-of-cure visit in the

US, the MPP population patients shown to have clinical + microbiological cure was 86% in the ciprofloxacin group and 77% in the PNH group. In Spain, the clinical + microbiological cure for the ciprofloxacin and PNH MPP populations at the Test-of-Cure visit was 83% and 82%, respectively.

The MITT population when evaluated by country specific data, experienced slightly lower clinical and microbiological response rates than in the MPP population but were similar to that seen in the overall MITT population. In Spain, the cure rate was 72% for the ciprofloxacin group and 71% for the PNH group at the EOT visit. At the Test-of-Cure visit, the MITT population of the US ciprofloxacin group had a clinical + microbiological cure rate of 78% while the PNH group had a cure rate of 74%. The MITT population at the Test-of-Cure visit in Spain had clinical + microbiological cure rates of 82% for the ciprofloxacin group and 77% for the PNH group (Table 27).

**Table 27. Clinical + Microbiological Outcome by Country.**

US		Microbiological Per-Protocol Population Number (%) of Patients		Microbiological Intent-to-Treat Population Number (%) of Patients	
		Ciprofloxacin (N=174)	PNH (N=174)	Ciprofloxacin (N=232)	PNH (N=217)
Visit	n	127	124	167	156
End-of-Treatment	Cure	88 (69.3%)	69 (55.6%)	106 (63.5%)	86 (55.1%)
	Improvement	28 (22%)	37 (29.8%)	38 (22.6%)	45 (28.6%)
	Failure	11 (8.7%)	18 (14.5%)	23 (13.8%)	25 (16%)
Test-of-Cure	n	127	124	167	156
	Cure	109 (85.5%)	95 (76.6%)	131 (78.4%)	116 (74.4%)
	Improvement	3 (2.4%)	3 (2.4%)	6 (3.6%)	5 (3.2%)
Failure		15 (11.8%)	26 (21%)	30 (18%)	35 (22.4%)
	<b>Spain</b>				
	n	47	50	65	61
End-of-Treatment	Cure	33 (70.2%)	38 (76%)	47 (72.3%)	43 (70.5%)
	Improvement	9 (19.1%)	8 (16%)	10 (15.4%)	8 (13.1%)
	Failure	5 (10.6%)	7 (14%)	8 (12.3%)	10 (16.4%)
Test-of-Cure	n	47	50	65	61
	Cure	39 (83%)	41 (82%)	53 (81.5%)	47 (77%)
	Improvement	2 (4.3%)	0	2 (3.1%)	0
Failure		6 (12.8%)	9 (18%)	10 (15.4%)	14 (23%)

Source: Table 10.2, section 5.3.5.4.15, p36; Statistical Tables 24.2.1 and 24.2.2

When analyzed by country and pathogen, the clinical + microbiological cure rates for *P. aeruginosa* and *S. aureus* were as expected given the prior bacteriologic and clinical response rates (Tables 28 and 29). In Table 28, the US MPP population at the EOT visit had a clinical + microbiological cure for *P. aeruginosa* of 70% for the ciprofloxacin group and 57% for the PNH group. For *S. aureus*, the clinical + microbiological cure rate at the EOT visit was 47% for the ciprofloxacin group, although the improvement rate was 36%, and 71% for the PNH group with an improvement rate of 6%. The clinical + microbiological cure rate for *P. aeruginosa* in the US MPP population at the Test-of-Cure