

visit was 89% for the ciprofloxacin group and 79% for the PNH group. The cure rate for *S. aureus* was 71% for both MPP groups at the Test-of-Cure visit.

In Spain, the clinical + microbiological cure rate by pathogen was generally the same or slightly better than that of the US patients (see Table 29 below). At the EOT visit, the MPP population had cure rates of 69% and 67%, respectively, for the ciprofloxacin and PNH groups identified with *P. aeruginosa*, while those identified with the *S. aureus* pathogen had clinical + microbiological cure rates of 80% for the ciprofloxacin group and 75% for the PNH group. The MPP population at the Test-of-Cure visit had clinical + microbiological cure rates of 83% for the ciprofloxacin group and 79% for the PNH group for those identified with *P. aeruginosa*. The cure rates for *S. aureus* were 80% and 83% for the ciprofloxacin and PNH groups, respectively.

**Table 28. Clinical + Microbiological Outcome by Pathogen, by Country (US).**

US <i>P. aeruginosa</i>		Microbiological Per-Protocol Population Number (%) of Patients		Microbiological Intent-to-Treat Population Number (%) of Patients	
		Ciprofloxacin	PNH	Ciprofloxacin	PNH
<b>Visit</b>		(N=174)	(N=174)	(N=232)	(N=217)
<b>End-of-Treatment</b>	n	110	112	142	142
	Cure	77 (70%)	64 (57.1%)	91 (64.1%)	81 (57%)
	Improvement	26 (23.6%)	35 (31.3%)	35 (24.6%)	42 (29.6%)
	Failure	7 (6.4%)	13 (11.6%)	16 (11.3%)	19 (13.4%)
<b>Test-of-Cure</b>	n	110	112	142	142
	Cure	98 (89.1%)	88 (78.6%)	115 (81%)	109 (76.8%)
	Improvement	3 (2.7%)	3 (2.7%)	6 (4.2%)	4 (2.8%)
	Failure	8 (8.2%)	21 (18.8%)	21 (14.8%)	29 (20.4%)
<b><i>S. aureus</i></b>					
<b>End-of-Treatment</b>	n	17	17	27	22
	Cure	8 (47.1%)	12 (70.6%)	12 (44.4%)	12 (54.5%)
	Improvement	6 (35.5%)	1 (5.9%)	7 (25.9%)	4 (18.2%)
	Failure	3 (17.6%)	4 (23.5%)	8 (29.6%)	6 (27.3%)
<b>Test-of-Cure</b>	n	17	17	27	22
	Cure	12 (70.6%)	12 (70.6%)	16 (59.3%)	13 (59.1%)
	Improvement	1 (5.9%)	0	1 (3.7%)	1 (4.5%)
	Failure	4 (23.5%)	5 (29.4%)	10 (37%)	8 (36.4%)

Source: Table 10.3, section 5.3.5.4.15, p37; Statistical Tables 26.2.1 and 26.2.2

**Table 29. Clinical + Microbiological Outcome by Pathogen, by Country (Spain).**

Spain <i>P. aeruginosa</i>		Microbiological Per-Protocol Population Number (%) of Patients		Microbiological Intent-to-Treat Population Number (%) of Patients	
		Ciprofloxacin	PNH	Ciprofloxacin	PNH
Visit		(N=174)	(N=174)	(N=232)	(N=217)
End-of-Treatment	n	42	42	55	51
	Cure	29 (69%)	28 (66.7%)	39 (70.9%)	35 (68.6%)
	Improvement	9 (21.4%)	7 (16.7%)	10 (18.2%)	7 (13.7%)
	Failure	4 (9.5%)	7 (16.7%)	6 (10.9%)	9 (17.6%)
Test-of-Cure	n	42	42	55	51
	Cure	35 (83.3%)	33 (78.6%)	45 (81.8%)	38 (74.5%)
	Improvement	2 (4.8%)	0	2 (3.6%)	0
	Failure	5 (11.9%)	9 (21.4%)	8 (14.5%)	13 (25.5%)
<i>S. aureus</i>					
End-of-Treatment	n	5	12	6	13
	Cure	4 (80%)	9 (75%)	5 (83.3%)	10 (76.9%)
	Improvement	1 (20%)	1 (8.3%)	1 (16.7%)	1 (7.7%)
	Failure	0	2 (16.7%)	0	2 (15.4%)
Test-of-Cure	n	5	12	6	13
	Cure	4 (80%)	12 (83.3%)	5 (83.3%)	10 (76.9%)
	Improvement	1 (20%)	0	1 (16.7%)	0
	Failure	0	2 (16.7%)	0	3 (23.1%)

Source: Table 10.4, section 5.3.5.4.15, p38; Statistical Tables 26.2.1 and 26.2.2

In general, for both countries, the MIIT population rates only differed slightly from the MPP clinical + microbiological cure rates.

**Reviewer's comments:** For MITT patients with *P. aeruginosa* regardless of country of origin, the rates of clinical failure were lower for patients treated with ciprofloxacin than patients treated with PNH. For MITT patients with *S. aureus* regardless of country of origin, the rates of clinical failure were similar for patients treated with ciprofloxacin than patients treated with PNH.

#### Microbiological Results: Core Study - Pistorius et al., 1999 [38]

In the Core Study as reported by Pistorius et al, a total of 221 bacterial isolates were obtained from patients in the ciprofloxacin group, 206 isolates from patients in the ciprofloxacin with hydrocortisone group, and 201 isolates from patients in the PNH group. The large majority of isolates were *Pseudomonas aeruginosa*. Bacteriologic success (eradication or presumed eradication at EOT) occurred in 92% of patients in the ciprofloxacin group, 95% in the ciprofloxacin with hydrocortisone group, and 87% in the PNH group as shown in Table 30. Thirty patients had bacterial superinfection ("colonization") at EOT including 13 in the ciprofloxacin group, 6 in the ciprofloxacin with hydrocortisone group, and 11 in the PNH group.

The greatest difference among treatment groups was in the proportion of patients with fungal infections after treatment as shown in Table 30. Before treatment, the number of patients with fungal infection was similar among treatment groups: seven for ciprofloxacin, eight for ciprofloxacin with hydrocortisone, and 6 for PNH. None of these fungal infections was considered clinically relevant. After treatment, substantially more patients in the ciprofloxacin and ciprofloxacin with hydrocortisone groups than in the

PNH group had fungal infections, although the large majority of these infections did not require antifungal therapy.

**Table 30. Microbial Response in Pistorius et al., 1999.**

	Ciprofloxacin	Cipro HC	PNH
Percentage of patients with bacterial eradication or presumed eradication at EOT*	92	95	87
Percentage of patients with bacterial eradication at follow-up	94	94	98
Number of reinfections at follow-up	2	1	1
Number of relapses at follow-up	1	2	1
Number of new fungal infections at EOT	33	38	1
Number of patients treated after EOT for fungal infection	1	5	0

\* If there was no exudate to culture and OE symptoms were not present at EOT, the pathogen was presumed to be eradicated.

Source: Table 11, section 5.3.5.4.15, p39

**Microbiological Results: Supportive Study CIFLOT 111100-01**

As reported in the Supportive Study, CIFLOT 111100-01, in the Intent-to-Treat (ITT) population, 82% of the patients treated with ciprofloxacin and 89% of the patients treated with Cetraxal Plus (ciprofloxacin 0.3% plus fluocinolone 0.025%) showed eradication or presumed eradication of the pathogen causing OE. In the population of valid patients, incidence of eradication or presumed eradication was 93% for ciprofloxacin and 98% for Cetraxal Plus.

**Microbiological Results: Published Studies**

Ear canal samples were collected from 2039 patients (2240 infected ears) with acute OE by 101 investigators in the United States [35]. Bacteria were identified to the species level using both phenotypic and genotypic tests. Sensitivity of each isolate to oxacillin, tobramycin, gentamicin, neomycin, ciprofloxacin, and ofloxacin was tested. A total of 2838 bacterial isolates, including 202 species of bacteria, were identified, as well as 32 yeast isolates and 17 molds. The most frequently occurring pathogenic bacterial species was *Pseudomonas aeruginosa* (38%), followed by *Staphylococcus aureus* (8%). The most common skin contaminants/commensals isolated were *Staphylococcus epidermidis* (9%) and *Microbacterium otitidis* (7%). Most bacterial isolates were sensitive to quinolones, including ciprofloxacin. Among the 1089 isolates of *P. aeruginosa* and the 221 isolates of *S. aureus*, 99% and 89%, respectively, were susceptible to ciprofloxacin. For *P. aeruginosa*, the MIC50 of ciprofloxacin was 0.13 µg/mL and the MIC90 was 0.25 µg/mL. For *S. aureus*, the MIC50 was 0.50 µg/mL and the MIC90 was 2 µg/mL.

In another study, aerobic microbes were isolated from 251 samples, 47 of which came from patients with chronic OE (the remainder came from patients with OM) [42]. The most commonly isolated microorganisms were *Pseudomonas aeruginosa*, *Staphylococcus aureus*, and other *Enterobacteriaceae*. *Pseudomonas aeruginosa* was highly susceptible to ciprofloxacin.

Swabs from the external ear canals of 180 patients with acute OE were collected from hospital and private clinics in Amman-Jordan [43]. Aerobic and anaerobic bacteria and fungi were identified according to standard microbiological methods. Bacterial isolates were tested for susceptibility to 19 antibiotics, including ciprofloxacin. Positive cultures were obtained from 167 (93%) patients. The most common bacterial pathogen was *P. aeruginosa*, isolated from 75 (42%) patients, followed by *S. aureus* from 29 (16%) patients, and *P. mirabilis* from 5 (3%) patients. Fungi, especially *Aspergillus* spp. and *Candida albicans*, were also common. A single pathogen was isolated from 75 (45%) patients, 2 pathogens from 60 (36%), and 3 pathogens from 32 (19%). *Pseudomonas aeruginosa* was relatively resistant to antibiotics, but the most effective antibiotic was ciprofloxacin, with 93% of isolates susceptible. For *S. aureus*, the most effective antibiotics were ciprofloxacin and amikacin (94% [according to the text] or 97% [calculated the Applicant] of isolates susceptible), and the least effective was tetracycline (7% susceptible). All five isolates of *P. mirabilis* were susceptible to ciprofloxacin, amikacin, ofloxacin, and imipenem.

Ear canal samples were taken from 1125 patients, including 131 children, with OE [44, 45]. *Pseudomonas aeruginosa* was isolated in 62% of all cases (72% of children) and *Staphylococcus aureus* in 16% (14% in children). After eight days of treatment with topical ciprofloxacin 0.3%, cultures were negative in 96% of cases in both adults and children, and the remaining 4% yielded mostly fungi.

Cultures from ears of 120 adults with acute OE produced *Pseudomonas aeruginosa* from 72% of patients, *Staphylococcus aureus* from 18%, and *Proteus mirabilis* from 5% [46]. After 14 days of treatment with ciprofloxacin solution, *P. aeruginosa* was eradicated in 22 of 22 cases, *S. aureus* in seven of eight, and *P. mirabilis* in 1 of 1.

Ciprofloxacin 0.2% or oxytetracycline/polymyxin B/HC was applied topically in 30 patients with OE [47]. Cultures were taken at Day 0, Day 3, and Day 8. At Day 0, samples from 43% of patients (6 [38%] of the 16 patients in the ciprofloxacin group and 7 [50%] of the 14 patients in the oxytetracycline/polymyxin B/HC group) produced *Pseudomonas aeruginosa*, which was the only bacterium identified to species level. A variety of other bacteria, including mixed cultures, were isolated from the remaining patients. All the isolates of *P. aeruginosa* and all other Gram-negative bacteria were sensitive to ciprofloxacin and polymyxin. The microbial eradication rate was 94% for ciprofloxacin and 50% for oxytetracycline/polymyxin B/HC.

In 67 children with OE, *Pseudomonas aeruginosa* was isolated from 93% of cases [48]. All of the isolates were sensitive to ciprofloxacin.

Ear canal swabs were taken from 32 adults and children with OE (this study also included patients with OM) [49]. *Pseudomonas aeruginosa* and *Staphylococcus aureus* were found in 11 (34%) cases each. Antibiotic sensitivity was tested in a total of 110 bacterial

pathogens from patients with OE and OM. The large majority (94%) of isolates were sensitive to ciprofloxacin.

Thirty-three bacterial isolates were collected from an unspecified number of patients with OE [50]. All of the patients were professional divers who spent extensive periods in damp, hyperbaric conditions. The 33 bacterial isolates were Gram-negative rods. *Enterobacteriaceae* comprised 45% of isolates. *Proteus mirabilis* was the most common isolate (21%), followed by *Pseudomonas aeruginosa* (15%). All 33 isolates were susceptible to ciprofloxacin. The MIC of ciprofloxacin was 0.06 µg/mL or lower for all isolates of the *Enterobacteriaceae*, 0.12 µg/mL or lower for all isolates of *Pseudomonas* spp., and 0.5 µg/mL or lower for all isolates of *Acinetobacter* spp.

#### **Microbiological Results: Comparison and Analyses of Results Across Studies**

In most of the studies in which pathogens causing OE were isolated and identified, the most common pathogen was *P. aeruginosa*, followed by *S. aureus*. This pattern was observed consistently in studies conducted in the US, Europe, and the Middle East; the exception was the study in professional divers, who work in unusual environmental conditions that interfere with the skin's natural defenses against infections [50]. In that study, Gram-negative enteric bacteria were the predominant pathogens which are also identified pathogens in patients acquiring OE under more common conditions.

Antibiotic susceptibility testing revealed that most isolates of pathogens associated with OE were susceptible to ciprofloxacin. In some studies in which sensitivities to several antibiotics were compared, ciprofloxacin was found to be one of the more effective antibiotics. Because of the prevalence of *P. aeruginosa* as a pathogen associated with OE infection, the greatest amount of information was available for this species. Very few isolates of *P. aeruginosa* were resistant to ciprofloxacin. This has been a consistent finding across geographical regions and spanning more than a decade of clinical trials in this common otic indication.

Clinical observation, with culturing and identification of pathogens when feasible, showed that the great majority of pathogens were eradicated (or presumed eradicated) after treatment with otic ciprofloxacin solution. In some studies in which otic ciprofloxacin solution was compared with non-quinolone antibiotics, microbiological results were more favorable with ciprofloxacin than with the comparator. In both Core Studies, the proportions of patients with bacterial eradication or presumed eradication at EOT were slightly larger for ciprofloxacin than for FNH. In Supportive Study CIFLOT IW00-01, the proportions of patients treated with ciprofloxacin 0.3% who had eradication or presumed eradication were 82% in the ITT population and 93% in the valid population, respectively, similar to the proportions observed with Ciprofloxacin Otic Solution 0.2% in the Pivotal Study.

The results of these clinical microbiology studies lend support that treatment with Ciprofloxacin Otic Solution 0.2% is highly effective in eradicating pathogens commonly associated with OE.

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