

Clinical Review
 Nasim Moledina, M.D.
 NDA 21-918
 Ciprofloxacin 0.2% Otic Solution

7 INTEGRATED REVIEW OF SAFETY

7.1 Methods and Findings

Extent of Exposure

Duration of exposure to study medications is summarized in Table 24. The mean duration of exposure was slightly longer than the 7 days specified in the protocol: 7.3 days for ciprofloxacin and 7.6 days for PNH. In the ciprofloxacin group, the majority (58%) of patients used study medication for 7 days as specified in the protocol, but a substantial minority (37%) used it for 8 days. In the PNH group, the majority of patients (64%) used study medication for 8 days. This may be related to the three-times-daily dosing for PNH, especially because it is likely that many patients started treatment late in the day. Very few patients used study medication for less than 7 days.

Table 24: Extent of Exposure to Study Medication: Safety Population

	Ciprofloxacin (N=319)	PNH (N=309)
Duration of treatment (days)		
Number of patients	304	302
Mean	7.3	7.6
Median	7	8
	Number (%) of patients taking study medication for this number of days	
Number of days		
1	0	3 (1.0)
2	1 (0.3)	0
3	2 (0.7)	5 (1.7)
4	2 (0.7)	2 (0.7)
5	0	1 (0.3)
6	5 (1.6)	5 (1.7)
7	176 (57.9)	83 (27.5)
8	113 (37.2)	192 (63.6)
>8	5 (1.6)	11 (3.6)

7.1.1 Deaths

There were no deaths in this study.

7.1.2 Other Serious Adverse Events

Two (0.6%) patients in the ciprofloxacin group and no patients in the PNH group experienced treatment-emergent SAEs.

Patient 135-006. Patient 135-006 was a 50-year-old Caucasian man whose medical history included hypertension since May 2003 and otitis media of the right ear with a ruptured eardrum requiring tympanoplasty in November 2003. He began to experience otitis externa of the right ear on 20 August 2004. At Visit 1 on 20 August 2004, the patient had moderate otalgia and edema, and mild otorrhea. Physical examination findings were normal except for a swollen, erythematous right ear. A culture taken at Visit 1 produced heavy growth of *Klebsiella oxytoca* and *S. aureus*. The patient was randomized to the ciprofloxacin group. On _____ the patient fell from top of his camper shell and sustained injuries to the face, head, and neck. He later reported that he did not feel dizzy at the time of the accident. Emergency personnel were called and the patient was transported to a nearby hospital. His injuries included a swollen trachea (tracheal edema), which was considered serious, as well as contusions to the back and chest, a hematoma of the left chest with a small right hemopneumothorax, a dislocated clavicle, and a hematoma in the left facial area. The patient was admitted to the intensive care unit, sedated, intubated, and placed on a ventilator. An esophagogastroduodenoscopy revealed a 3-cm tear of the hypopharynx. X-rays revealed mild atelectasis (basilar atelectatic changes) but no spinal fracture. Study medication was permanently discontinued and a 2-day course of intravenous clindamycin was started. The patient was extubated on _____. On _____, the tracheal edema, chest hematoma, hemopneumothorax, and atelectasis were considered resolved and the patient was discharged home. At last contact with the patient on _____, the contusions to the back and chest, dislocated clavicle, and facial hematoma were not resolved. The serious adverse events of fall and tracheal edema were assessed as severe; the nonserious injuries and complications associated with this event were assessed as moderate or mild. All of these events were assessed as not related to study medication.

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Patient 149-016. Patient 149-016 was a 51-year-old Caucasian woman whose medical history included drug-induced hepatitis, migraine headaches, depression, hysterectomy, allergy to tetracycline, and allergic rhinitis. She began to experience otitis externa of the left ear on 26 September 2004. Concomitant medications included acetylsalicylic acid and omega-3 triglycerides for cardioprophylaxis, conjugated estrogen for hormone replacement therapy, and sumatriptan and zolmitriptan for migraines. At Visit 1 on 30 September 2004, the patient had moderate otalgia, edema, and otorrhea in the left ear and also had signs of otitis externa in the right ear. No other physical abnormalities were noted. A culture taken at Visit 1 produced heavy growth of beta-hemolytic *Streptococcus* Group G, *P. aeruginosa*, and *S. aureus*. The patient was randomized to the ciprofloxacin

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group. On the same day, 30 September 2004, the patient was noted to have anxiety disorder and bipolar disorder and began treatment with clonazepam and risperidone. Her last dose of study medication was on 04 October 2004. On _____, the patient was admitted to the psychiatric acute unit for a severe bipolar disorder crisis. She discontinued from the study due to this event, which was considered serious because it required hospitalization. She was transferred to another hospital on _____ for psychiatric evaluation. On _____, the event was considered resolved and the patient was discharged. The patient was contacted to obtain additional information but was unwilling to discuss the event. The bipolar disorder crisis was assessed as severe and not related to study medication.

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7.1.3 Dropouts and Other Significant Adverse Events

7.1.3.1 Overall profile of dropouts

Of patients who withdrew before completing the study, the largest proportion were lost to follow-up. Three patients in each treatment group were withdrawn because of adverse events. Consent was withdrawn by 1 patient in the ciprofloxacin group and 5 patients in the PNH group. Three patients in the ciprofloxacin group and 1 in the PNH groups were withdrawn because of treatment failure.

7.1.3.2 Adverse events associated with dropouts

Three patients in each treatment group were withdrawn because of adverse events. In the ciprofloxacin group, one patient had worsening of otitis externa, one patient developed a carbuncle on the internal canal of the affected ear, but was lost to follow-up, and one patient 3 days into therapy developed otitis media and was withdrawn from the study. In the PNH arm two patients developed otitis media, one with perforation of the tympanic membrane, and one patient developed cellulitis of the ear and was withdrawn from the study.

7.1.3.3 Other significant adverse events

Nine patients had severe TEAEs: 3 (0.9%) patients in the ciprofloxacin group and 6 (1.9%) patients in the PNH group.

In the ciprofloxacin group, Patient 135-006 had a severe injury and Patient 149-016 had a severe bipolar disorder crisis. Patient 104-004 had severe OE in the right ear (the non-evaluable ear) that led to discontinuation of study medication. All of these events were assessed as not related to study medication.

Severe TEAEs in the PNH group included nasopharyngitis in Patients 116-012 and 135-008 and a periodontal infection in Patient 105-004. Patient 113-005 had severe ear pain in the right ear (the non-evaluable ear). Patient 134-003 had perforation of the right tympanic membrane and otitis media, which led to discontinuation of study medication. All of these events were assessed as not related to study medication. Patient 120-028 had severe cellulitis of the right ear that was

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assessed as probably related to study medication and that led to discontinuation of study medication.

7.1.4 Other Search Strategies

N/A

7.1.5 Common Adverse Events

Brief Summary of Adverse Events

Adverse events reported in this study are summarized in Table 28. Adverse events were reported for 92 (29%) patients in the ciprofloxacin group and 96 (31%) in the PNH group. Most of these AEs were not treatment-related and were not considered severe. Serious adverse events were reported for 2 (0.6%) patients in the ciprofloxacin group and no patients in the PNH group. There were no deaths. Very few patients (5 [1.6%] in the ciprofloxacin group and 4 [1.3%] in the PNH group) had AEs that caused discontinuation of study medication.

Table 25: Overview of Adverse Events: Safety Population

Category	Number (%) of Patients Experiencing Event	
	Ciprofloxacin (N=319)	PNH (N=309)
Any adverse events	92 (28.8)	96 (31.1)
Treatment-related adverse events*	16 (5.0)	11 (3.6)
Severe adverse events	3 (0.9)	6 (1.9)
Serious adverse events	2 (0.6)	0
Deaths	0	0
Adverse events causing discontinuation	5 (1.6)	4 (1.3)

* Adverse events whose relationship to study medication was assessed as "definite," "probable," or "possible" or was missing.

Treatment-emergent adverse events that occurred in at least 2.0% of patients in either treatment group are shown in Table 26. In both treatment groups, the highest incidence TEAEs were Infections and Infestations, Ear and Labyrinth Disorders, Nervous System Disorders, and General Disorders and Administration Site Conditions.

The incidence of Infections and Infestations was higher in the ciprofloxacin group (16%) than in the PNH group (10%). The most common TEAE was otitis externa, which was reported in 5.6% of patients in the ciprofloxacin group and 2.9% in the PNH group. Some of the TEAEs classified as otitis externa were exacerbations or recurrences of OE in the evaluable ear, but most were new occurrences of OE in the contralateral ear. There were only 2 patients in the ciprofloxacin group that had exacerbation of otitis externa in the ears that were being treated, and both of them were

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failures. Nasopharyngitis occurred in approximately 2% of patients in each treatment group. Otitis externa fungal (otomycosis) occurred in more patients in the ciprofloxacin group (2.5%) than in the PNH group (0.3%). In addition, 1 patient in the ciprofloxacin group and no patients in the PNH group experienced otitis externa candida (otomycosis). All reported cases of otomycosis resolved, some after treatment with antifungal medication and some without treatment.

Ear and Labyrinth Disorders occurred more often in the PNH group (9%) than in the ciprofloxacin group (5%). The most common TEAEs in this group were ear pruritus and ear pain, both of which were more common in the PNH group than in the ciprofloxacin group. In the Nervous System Disorders group, headache was more common in the ciprofloxacin group (3.1%) than in the PNH group (1.9%), while dizziness was more common in the PNH group (2.3%) than in the ciprofloxacin group (0.3%). In the General Disorders and Administration Site Conditions, pyrexia was more common in the PNH group (2.3%) than in the ciprofloxacin group (0.9%).

**Table 26: Common Treatment-Emergent Adverse Events: Safety Population
 Events Occurring in at Least 2% of Patients in Either Treatment
 Group, by Systems and Preferred Term**

Any adverse event	Number (%) of Patients Experiencing Event	
	Ciprofloxacin (N=319)	PNH (N=309)
Any adverse event	92 (28.3)	96 (31.1)
Infections and Infestations	52 (16.3)	30 (9.7)
Otitis externa	18 (5.6)	9 (2.9)
Nasopharyngitis	7 (2.2)	5 (1.6)
Otitis externa fungal	8 (2.5)	1 (0.3)
Ear and Labyrinth Disorders	17 (5.3)	29 (9.4)
Ear pruritus	7 (2.2)	11 (3.6)
Ear pain	5 (1.6)	10 (3.2)
Nervous System Disorders	14 (4.4)	12 (3.9)
Headache	10 (3.1)	6 (1.9)
Dizziness	1 (0.3)	7 (2.3)
General Disorders and Administration Site Conditions	8 (2.5)	11 (3.6)
Pyrexia	3 (0.9)	7 (2.3)
Musculoskeletal and Connective Tissue Disorders*	7 (2.2)	9 (2.9)
Gastrointestinal Disorders*	3 (0.9)	11 (3.6)
Respiratory, Thoracic and Mediastinal Disorders*	3 (0.9)	9 (2.9)

Each patient was counted only once per System and per preferred term.

* No individual AE in this System was experienced by 2% or more of patients in either treatment group.

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Relationship of Adverse Events to Study Medication

TEAEs assessed as related to study medication (i.e., events assessed as definitely, probably, or possibly related to study medication or with assessment missing) are summarized in Table 27. In both treatment groups, the majority of TEAEs were not treatment-related. The TEAEs most often assessed as treatment-related were otitis externa fungal and ear pruritus. Treatment-related otitis externa fungal occurred in 7 patients in the ciprofloxacin group, and treatment-related otitis externa candida occurred in 1 patient in the ciprofloxacin group; both of these TEAEs are types of otomycosis. Treatment-related otomycosis did not occur in the PNH group. Treatment-related ear pruritus occurred in 3 patients in the ciprofloxacin group and 1 patient in the PNH group.

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**Table 27: Treatment-Related Treatment-Emergent Adverse Events:
 Safety Population Events Assessed as Definitely, Probably, or Possibly Related to Study
 Medication or with Assessment Missing**

	Number (%) of Patients Experiencing Event	
	Ciprofloxacin (N=319)	PNH (N=309)
Any treatment-related adverse event	16 (5.0)	11 (3.6)
Infections and Infestations	8 (2.5)	2 (0.6)
Otitis externa fungal	7 (2.2)	0
Otitis externa candida	1 (0.3)	0
Otitis externa	0	1 (0.3)
External ear cellulitis	0	1 (0.3)
Ear and Labyrinth Disorders	3 (0.9)	4 (1.3)
Ear pruritus	3 (0.9)	1 (0.3)
Ear pain	0	2 (0.6)
Ear discomfort	0	1 (0.3)
Nervous System Disorders	3 (0.9)	1 (0.3)
Headache	2 (0.6)	1 (0.3)
Dizziness	1 (0.3)	0
General Disorders and Administration Site Conditions	2 (0.6)	2 (0.6)
Application site pain	2 (0.6)	1 (0.3)
Application site burning	0	1 (0.3)
Respiratory, Thoracic and Mediastinal Disorders	0	2 (0.6)
Nasal congestion	0	2 (0.6)
Skin and Subcutaneous Tissue Disorders	0	1 (0.3)
Erythema	0	1 (0.3)
Gastrointestinal Disorders	0	1 (0.3)
Diarrhea	0	1 (0.3)

Each patient was counted only once per System and per preferred term.

Severity of Adverse Events

The majority of TEAEs were mild, and the distribution of mild and moderate TEAEs was similar between treatment groups.

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As shown in Table 25, only 9 patients had severe TEAEs: 3 (0.9%) patients in the ciprofloxacin group and 6 (1.9%) patients in the PNH group.

In the ciprofloxacin group, Patient 135-006 had a severe injury and Patient 149-016 had a severe bipolar disorder crisis. Patient 104-004 had severe OE in the right ear (the non-evaluable ear) that led to discontinuation of study medication. All of these events were assessed as not related to study medication.

Severe TEAEs in the PNH group included nasopharyngitis in Patients 116-012 and 135-008 and a periodontal infection in Patient 105-004. Patient 113-005 had severe ear pain in the right ear (the non-evaluable ear). Patient 134-003 had perforation of the right tympanic membrane and otitis media, which led to discontinuation of study medication. All of these events were assessed as not related to study medication. Patient 120-028 had severe cellulitis of the right ear that was assessed as probably related to study medication and that led to discontinuation of study medication.

Adverse Events by Age Group

Adverse events were also tabulated by age group. This analysis was performed for patients 12 years old or younger (had not reached their thirteenth birthday) and patients over 12 years old (had reached their thirteenth birthday). Adverse events that occurred in at least 2% of patients in either treatment group are shown by age group in Table 28. Fewer TEAEs were reported in the younger group than in the older group. In both age groups, the overall incidence of TEAEs was similar between treatment groups.

Incidence of most TEAEs was low in both age groups and both treatment groups. In both age groups, the incidence of TEAEs in the Infections and Infestations System, particularly otitis externa was higher in the ciprofloxacin group than in the PNH group. Most of the AEs reported as otitis externa were new occurrences of OE in the non-evaluable ear. Incidence of these events was similar between age groups.

Ear and Labyrinth Disorders (especially ear pruritus), Nervous System Disorders (including headache and dizziness), Musculoskeletal and Connective Tissue Disorders, and Gastrointestinal Disorders were more common in the older group than in the younger group. General Disorders and Administration Site Conditions and Injury, Poisoning and Procedural Complications were more common in the younger group than in the older group. Dizziness and facial pain occurred most often in older patients in the PNH group, and pyrexia occurred most often in younger patients in the PNH group.

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**Table 28: Common Treatment-Emergent Adverse Events by Age Group:
 Safety Population Events Occurring in at Least 2% of Patients in Either Treatment
 Group in Either Age Group, by Systems and Preferred Term**

	Number (%) of Patients Experiencing Event			
	≤12 years		>12 years	
	Ciprofloxacin (N=145)	PNH (N=131)	Ciprofloxacin (N=174)	PNH (N=178)
Any adverse events	39 (26.9)	33 (25.2)	53 (30.5)	63 (35.4)
Infections and Infestations	26 (17.9)	13 (9.9)	26 (14.9)	17 (9.6)
Otitis externa	7 (4.8)	3 (2.3)	11 (6.3)	6 (3.4)
Otitis media	2 (1.4)	3 (2.3)	3 (1.7)	1 (0.6)
Nasopharyngitis	2 (1.4)	0	5 (2.9)	5 (2.8)
Otitis externa fungal	2 (1.4)	0	6 (3.4)	1 (0.6)
Ear and Labyrinth Disorders	5 (3.4)	8 (6.1)	12 (6.9)	21 (11.8)
Ear pruritus	0	1 (0.8)	7 (4.0)	10 (5.6)
Ear pain	4 (2.8)	2 (1.5)	1 (0.6)	8 (4.5)
Nervous System Disorders	2 (1.4)	3 (2.3)	12 (6.9)	9 (5.1)
Headache	2 (1.4)	2 (1.5)	8 (4.6)	4 (2.2)
Dizziness	0	1 (0.8)	1 (0.6)	6 (3.4)
General Disorders and Administration Site Conditions	4 (2.8)	9 (6.9)	4 (2.3)	2 (1.1)
Pyrexia	1 (0.7)	6 (4.6)	2 (1.1)	1 (0.6)
Musculoskeletal and Connective Tissue Disorders	1 (0.7)	1 (0.8)	6 (3.4)	8 (4.5)
Facial pain	0	0	1 (0.6)	5 (2.8)
Injury, Poisoning and Procedural Complications*	4 (2.8)	2 (1.5)	1 (0.6)	0
Respiratory, Thoracic and Mediastinal Disorders*	2 (1.4)	4 (3.1)	1 (0.6)	5 (2.8)
Gastrointestinal Disorders*	1 (0.7)	4 (3.1)	2 (1.1)	7 (3.9)
Eye Disorders*	3 (2.1)	1 (0.8)	1 (0.6)	1 (0.6)
Skin and Subcutaneous Tissue Disorders*	0	2 (1.5)	1 (0.6)	4 (2.2)

Each patient was counted only once per System and per preferred term.

* No individual AE in this SOC was experienced by 2% or more of patients in either treatment group in either age group.

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Adverse Events Leading to Discontinuation

Treatment-emergent AEs leading to discontinuation of study treatment are summarized in Table 29 and listed by patient in Table 30. Some patients who discontinued study treatment withdrew from the study, while some remained in the study until the final study visit.

Treatment-emergent adverse events leading to discontinuation occurred in 5 (1.6%) patients in the ciprofloxacin group and 4 (1.3%) patients in the PNH group. Most of the TEAEs leading to discontinuation in the ciprofloxacin group, and all such TEAEs in the PNH group, were AEs involving the ear (although, because of AE coding requirements, not all of these AEs were in the SOC Ear and Labyrinth Disorders). In all but 1 of these cases, as shown in Table 30, the ear involved was the evaluable ear. Also, in the ciprofloxacin group, 1 patient discontinued after experiencing a serious fall with multiple injuries and 1 patient discontinued because of a serious bipolar disorder crisis. In the ciprofloxacin group, all of the TEAEs leading to discontinuation were assessed as not related to study medication. In the PNH group, TEAEs leading to discontinuation were assessed as possibly or probably related to study medication for 2 of the 4 patients. These events included external ear cellulitis in 1 patient and an apparent reaction to study medication, characterized by erythema and pain, in 1 patient. Treatment-emergent adverse events in the PNH group that were assessed as not related to study medication were worsening of OE in 1 patient and tympanic membrane perforation and otitis media in 1 patient.

Table 29: Summary of Treatment-Emergent AEs Leading to Premature Discontinuation of Study Treatment: Safety Population

	Number (%) of Patients Experiencing Event	
	Ciprofloxacin (N=319)	PNH (N=309)
Any TEAE leading to discontinuation	5 (1.6)	4 (1.3)
Infections and Infestations	3 (0.9)	3 (1.0)
Otitis externa	1 (0.3)	1 (0.3)
Otitis media	1 (0.3)	1 (0.3)
Carbuncle	1 (0.3)	0
External ear cellulitis	0	1 (0.3)
Ear and Labyrinth Disorders	0	2 (0.6)
Ear pain	0	1 (0.3)
Tympanic membrane perforation	0	1 (0.3)
Injury, Poisoning, and Procedural Complications	1 (0.3)	0
Respiratory, Thoracic, and Mediastinal Disorders	1 (0.3)	0
Tracheal edema	1 (0.3)	0
Skin and Subcutaneous Tissue Disorders	0	1 (0.3)
Erythema	0	1 (0.3)

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**Table 30: List of Treatment-Emergent AEs Leading to Premature
 Discontinuation of Study Treatment: Safety Population**

Treatment Group: Ciprofloxacin					
104-004	Otitis externa	Right* otitis externa	No	Severe	Not related
135-006	Fall	(Swollen trachea injured in accident) fall requiring hospitalization	Yes	Severe	Not related
	Tracheal edema	Swollen trachea (injured in accidental fall requiring hospitalization)	Yes	Severe	Not related
	Fall	(Contusion to back and chest from accidental fall)	No	Moderate	Not related
	Contusion	Contusion to back and chest (from accidental fall)	No	Moderate	Not related
140-004	Carbuncle	Carbuncle right† ear internal canal	No	Moderate	Not related
141-001	Otitis media	Otitis media right† ear	No	Moderate	Not related
149-016	Bipolar disorder	Severe bipolar disorder crisis	Yes	Severe	Not related
Treatment Group: FNH					
120-028	External ear cellulitis	Cellulitis right† ear	No	Severe	Probably
128-012	Otitis externa	Worsening of right† otitis externa	No	Moderate	Not related
134-003	Tympanic membrane perforation	Right† tympanic membrane perforation	No	Severe	Not related
	Otitis media	Right† otitis media	No	Severe	Not related
134-009	Ear pain	Allergic reaction (site specific to R† ear—pain)	No	Moderate	Probably
	Erythema	Allergic reaction to study drug (site specific to R† ear—redness)	No	Moderate	Probably
	Ear pain	Increased right† ear otalgia	No	Moderate	Possibly

* The contralateral (non-evaluable) ear.

† The evaluable ear.