

Clinical outcomes with besifloxacin ophthalmic suspension 0.6% in the treatment of bacterial conjunctivitis due to potentially consequential pathogens

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Purpose: Besifloxacin is a chlorofluoroquinolone approved for use in the treatment of bacterial conjunctivitis. This study assessed the clinical efficacy of besifloxacin ophthalmic suspension 0.6% against conjunctivitis infections caused by potentially consequential pathogens.

Design: Post hoc analysis of clinical outcomes for patients with conjunctival infections due to *Pseudomonas aeruginosa*, *Serratia marcescens*, *Neisseria* spp., methicillin-resistant *Staphylococcus aureus* (MRSA), and methicillin-resistant *Staphylococcus epidermidis* (MRSE) who were treated with besifloxacin in four multicenter, double-masked, randomized clinical trials.

Methods: Minimum inhibitory concentrations (MICs) of besifloxacin against potentially consequential pathogens were pooled. Clinical outcome data for patients treated with besifloxacin with baseline infections due to these pathogens were pooled and summarized. Bacterial eradication was defined as the absence of ocular bacterial species present at or above threshold at baseline.

Results: A total of 1,317 patients had culture-confirmed bacterial conjunctivitis across the four studies, and 151 infections were due to the aforementioned pathogens (*P. aeruginosa* n=9; *S. marcescens* n=10; *Neisseria* spp. n=16; MRSA n=35; MRSE n=81). Among MRSA and MRSE infections, 48.3% demonstrated concurrent ciprofloxacin resistance (ciprofloxacin-resistant [CipR]-MRSA n=24; CipR-MRSE n=32). The MIC₉₀ (MIC for 90% of isolates) for besifloxacin was 1 µg/mL for *S. marcescens*, 0.25 µg/mL for *Neisseria* spp., 0.06 µg/mL for both ciprofloxacin-sensitive MRSA and ciprofloxacin-sensitive MRSE, and 4 µg/mL for both CipR-MRSA and CipR-MRSE. Against *P. aeruginosa*, the MIC range was 1–4 µg/mL. Bacterial eradication rates in patients treated with besifloxacin were 100% by the first follow-up visit for infections due to *P. aeruginosa*, *S. marcescens*, and *Neisseria* spp. and 87.8% by the second follow-up visit for infections due to MRSA and MRSE.

Conclusion: The use of besifloxacin ophthalmic suspension 0.6% in the treatment of conjunctival infections due to potentially consequential pathogens resulted in high rates of bacterial eradication.

Keywords: Besivance, *Pseudomonas aeruginosa*, *Serratia marcescens*, *Neisseria* spp., MRSA, MRSE

Introduction

Bacterial conjunctivitis is a common eye infection characterized by mucopurulent discharge, redness, and crusty or adherent eyelids.^{1–4} While *Haemophilus influenzae*, *Streptococcus pneumoniae*, and *Staphylococcus* spp. are the most common etiological agents, *Neisseria* spp., *Moraxella* spp., viridans streptococci groups, *Escherichia coli*, *Serratia marcescens*, *Proteus mirabilis*, and *Pseudomonas aeruginosa* have also

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been identified as causative, albeit less frequently.⁵⁻⁹ Bacterial conjunctivitis usually resolves spontaneously in the majority of patients; however, treatment with broad-spectrum topical antibiotics is recommended to speed the time to recovery, reduce rates of relapse or contagion, and lower the risk of complications.^{1,7}

Conjunctival infections caused by *P. aeruginosa*, *S. marcescens*, and *Neisseria* spp., all Gram-negative bacteria, are of concern to eye care practitioners due to their severity and potential for sequelae, if not successfully treated.^{5,10-15} *P. aeruginosa* is an opportunistic pathogen and a well-known risk factor for bacterial keratitis; as many as one-third of cases associated with contact lens wear are attributed to *P. aeruginosa*.¹⁶⁻¹⁸ *S. marcescens*, like *P. aeruginosa*, is another ubiquitous opportunistic pathogen associated with contact lens-associated keratitis as well as some cases of endophthalmitis.^{13,14,19} Conjunctival infection with *Neisseria gonorrhoeae*, generally hyperacute, can progress into keratoconjunctivitis due to the bacterium's ability to penetrate intact corneal epithelium and is associated with a risk of corneal perforation.^{5,20,21} Epidemics of gonococcal keratoconjunctivitis in adults have been reported.²² *Neisseria meningitidis* conjunctival infections are similar in presentation to gonococcal infections; while corneal sequelae tend to be milder, *N. meningitidis* infections have been linked to a significant risk for meningeal or systemic infection.^{5,12}

Of more recent and growing concern to eye care practitioners are conjunctival infections due to methicillin-resistant staphylococci.¹⁰ A recent report by the Centers for Disease Control and Prevention categorized methicillin-resistant *Staphylococcus aureus* (MRSA) among microorganisms presenting a serious threat to the US population and warned of its increased expansion beyond the health care setting into the general population.²³ Indeed, several studies have documented an increased prevalence of methicillin-resistant staphylococci, both MRSA and methicillin-resistant *Staphylococcus epidermidis* (MRSE) in ocular infections in general,^{9,24-27} as well as in conjunctival infections specifically.^{28,29} Both Adebayo et al and Cavuoto et al reported an increase of at least 30% in the prevalence of methicillin resistance among *S. aureus* isolates in their respective studies of conjunctival cultures evaluated over a 10-year period.^{28,29} Many of these methicillin-resistant strains showed concurrent resistance to other non- β -lactam antibiotics, including aminoglycosides, macrolides, tetracyclines, and/or fluoroquinolones, making the treatment of ocular infections caused by these pathogens a challenge.²⁴⁻³³ Although conjunctivitis infections with methicillin-resistant staphylococci are generally not vision-threatening,²⁴

potentially catastrophic complications have been reported with other ocular infections involving such organisms (eg, keratitis, cellulitis, endophthalmitis).³⁴⁻³⁶

Topical fluoroquinolones are often used in the treatment of bacterial conjunctivitis due to their low toxicity, broad spectrum of activity, and bactericidal activity.^{37,38} While their efficacy against the common pathogens of bacterial conjunctivitis is well established, their clinical efficacy against infection due to the above Gram-negative pathogens or due to methicillin-resistant staphylococci is not as clear.^{37,38} Besifloxacin (Figure 1) is a relatively new fluoroquinolone, specifically a chlorofluoroquinolone, introduced in 2009.³⁹ Cambau et al showed that besifloxacin has potent and balanced dual-targeting activity against both DNA gyrase and topoisomerase IV.⁴⁰ This balanced activity, in turn, results in broad-spectrum in vitro activity, including activity against *P. aeruginosa*, *S. marcescens*, and *Neisseria* spp., as well as ciprofloxacin-resistant (CipR) and methicillin-resistant staphylococcal isolates.^{6,31,32,41,42} The ophthalmic formulation of besifloxacin, which contains 0.663% besifloxacin hydrochloride or 0.6% besifloxacin free base (Besivance[®]; Bausch + Lomb, Bridgewater, NJ, USA)³⁹ is formulated with DuraSite[®] (InSite Vision, Alameda, CA, USA), a mucoadhesive polycarbophil polymer designed to prolong a drug's residence time on the ocular surface and improve bioavailability.⁴³⁻⁴⁶ DuraSite has also been reported to inhibit staphylococcal biofilm formation in vitro.⁴⁷ The ophthalmic formulation of besifloxacin is currently approved for the treatment of bacterial conjunctivitis in the US, Canada, and several Latin American and Asian countries.

The objective of this post hoc analysis was to assess the clinical efficacy of besifloxacin ophthalmic suspension 0.6% against ocular infections caused by *P. aeruginosa*, *S. marcescens*, *Neisseria* spp., and methicillin-resistant staphylococci from four clinical studies of besifloxacin in the

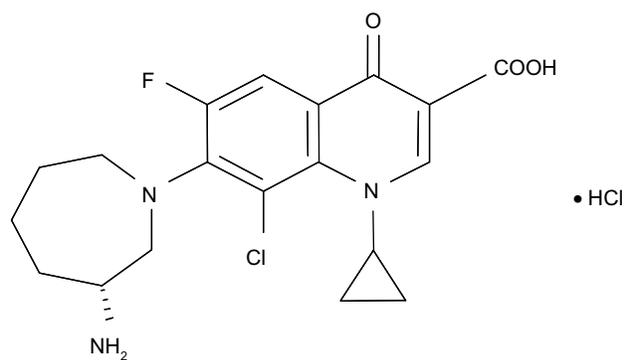


Figure 1 Molecular structure of besifloxacin hydrochloride.

treatment of bacterial conjunctivitis. Because conjunctival infections due to these bacterial pathogens are uncommon, clinical outcomes for patients with these infections were pooled across the four studies for analysis. Case summaries for individual patients with *P. aeruginosa* conjunctival infections across these studies were described previously,⁴⁸ and pooled outcomes for these patients are repeated here.

Methods

Study design

This study evaluated cases of conjunctivitis caused by *P. aeruginosa*, *S. marcescens*, *Neisseria* spp., MRSA, and MRSE from four prospective, randomized, multicenter, double-masked clinical studies of besifloxacin ophthalmic suspension 0.6%, including three vehicle-controlled studies (NCT00622908,⁴⁹ NCT00347932,⁵⁰ and NCT00972777)⁵¹ and one active-comparator study (NCT00348348).⁵² All trial protocols were conducted in accordance with Good Clinical Practice, the International Conference on Harmonization guidelines, the Declaration of Helsinki, and the Health Insurance Portability and Accountability guidelines. Individual study results have been published previously.^{53–56} The active comparator study⁵⁵ and two of the vehicle-controlled studies^{53,54} employed a 5-day thrice-daily treatment regimen, while the third vehicle-controlled study⁵⁶ employed a 3-day twice-daily treatment regimen (Table 1).

Detailed subject inclusion and exclusion criteria and study procedures were described previously.^{53–56} Briefly, eligible patients were aged ≥ 1 year with a diagnosis of bacterial conjunctivitis, as evidenced by a severity for both purulent ocular discharge and bulbar conjunctival injection of grade 1 or higher on a 4-point scale (0= absent, 1= mild,

2= moderate, and 3= severe) in at least one eye, and had a pinhole visual acuity (VA) of 20/200 or better in both eyes. The severity of bulbar conjunctival injection was determined using photographic standards (Ora Calibra™ Bacterial Conjunctivitis Bulbar Conjunctiva Redness Scale; Ora Inc., North Andover, MA, USA) employed in previous conjunctivitis research.⁸ Patients were excluded if they had used any topical ophthalmic products within 48 hours of enrollment or systemic or topical antimicrobial medication within 72 hours of enrollment or had suspected viral or allergic conjunctivitis, iritis, corneal erosion, or keratitis. Eligible patients completed three study visits. At the first visit (day 1 or baseline), patients underwent an eye examination that included pinhole VA, biomicroscopy, and ophthalmoscopy in both eyes. Samples for microbial cultures were taken from the conjunctival cul-de-sac of the affected eye(s), and patients were randomized to study treatment. Patients were instructed to administer one drop of study medication in the affected eye(s) three times daily at approximately 6-hour intervals for 5 days,^{53–55} or twice daily at approximately 8-hour intervals during waking hours for a total of 3 days.⁵⁶ Patients returned to the study site at or near the end of treatment (visit 2, day 5 $[\pm 1]$ ^{53,55} or day 4 or 5^{54,56}) and after treatment ended on days 7 through 9 (visit 3, day 8 or 9^{53–55} or day 7 $[\pm 1]$ ⁵⁶) for clinical assessment of ocular signs and symptoms, VA testing, biomicroscopy, ophthalmoscopy (visit 3 only), and culture of infected eye(s). Ocular and non-ocular adverse events (AEs) were recorded at each visit.

In all four studies, the same central laboratory (Covance Central Laboratory Services, Indianapolis, IN, USA) identified and enumerated bacterial pathogens and/or viral pathogens in cultures from affected eye(s). For bacterial

Table 1 Multicenter, randomized, double-masked, controlled studies of besifloxacin ophthalmic suspension 0.6% in the treatment of bacterial conjunctivitis

	Karpecki et al ⁵⁴	Tepedino et al ⁵³	McDonald et al ⁵⁵	DeLeon et al ⁵⁶
Comparator	Vehicle	Vehicle	Moxifloxacin ophthalmic solution, 0.5%	Vehicle
Number of patients	269	957	1,161	474
Dosing regimen	Thrice daily, 5 days	Thrice daily, 5 days	Thrice daily, 5 days	Twice daily, 3 days
Patients with clinical resolution	Visit 2: 33.3% vs 17.2% (<i>P</i> =0.069)	Visit 2: ^a 45.2% vs 33.0% (<i>P</i> =0.0084)	Visit 2: ^a 58.3% vs 59.4% (<i>P</i> =0.6520)	Visit 2: ^a 65.9% vs 44.0% (<i>P</i> <0.001)
	Visit 3: ^a 73.3% vs 43.1% (<i>P</i> <0.001)	Visit 3: 84.4% vs 69.1% (<i>P</i> =0.0011)	Visit 3: 84.5% vs 84.0% (<i>P</i> =0.5014)	Visit 3: 76.3% vs 66.7% (<i>P</i> =0.209)
Patients with bacterial eradication	Visit 2: 90.0% vs 46.6% (<i>P</i> <0.001)	Visit 2: ^a 91.5% vs 59.7% (<i>P</i> <0.0001)	Visit 2: ^a 93.3% vs 91.1% (<i>P</i> =0.1238)	Visit 2: ^a 85.2% vs 54.6% (<i>P</i> <0.001)
	Visit 3: ^a 88.3% vs 60.3% (<i>P</i> <0.001)	Visit 3: 88.4% vs 71.7% (<i>P</i> <0.0001)	Visit 3: 87.3% vs 84.7% (<i>P</i> =0.0608)	Visit 3: 85.2% vs 64.5% (<i>P</i> <0.001)

Notes: ^aPrimary outcome visit. Visit 2 occurred at or near the end of treatment on day 5 $[\pm 1]$ ^{53,55} or day 4 or 5,^{54,56} while visit 3 occurred following cessation of treatment on day 8 or 9^{53–55} or day 7 $[\pm 1]$.⁵⁶

pathogens, serial dilutions of test samples were plated onto bacteriological media, and the resulting colony-forming units (CFUs) were enumerated and speciated by standard biochemical and/or molecular identification methods. Patients were considered culture-positive if the count for a particular species (in CFUs/mL) equaled or exceeded threshold values on the Cagle list, as modified by Leibowitz.^{57,58} For the bacteria studied in this post hoc analysis, the threshold criterion was 1 CFU/mL for infections attributed to *P. aeruginosa*, *S. marcescens*, and *Neisseria* spp.; 10 CFUs/mL for infections attributed to *S. aureus*; and 100 CFUs/mL for infections attributed to *S. epidermidis*. In vitro susceptibilities to besifloxacin and comparator antibacterial agents, also conducted by the same central laboratory, were determined for all isolates that met the threshold criteria. Antibacterial susceptibility testing was conducted by broth microdilution following the recommended procedures of the Clinical and Laboratory Standards Institute (CLSI).^{59–63} Comparator antibacterial agents evaluated included moxifloxacin, ciprofloxacin, gatifloxacin, levofloxacin, and azithromycin. *S. aureus* and *S. epidermidis* isolates were further designated as methicillin-sensitive or -resistant and as ciprofloxacin-sensitive (CipS) or CipR, based on CLSI breakpoint criteria for oxacillin and ciprofloxacin.⁶³

Outcomes

The primary efficacy endpoints in all studies included eradication of the baseline bacterial infection and resolution of the clinical signs of conjunctivitis in patients with culture-confirmed bacterial conjunctivitis. Bacterial eradication was defined as the absence of ocular bacterial species that were present at or above the Cagle threshold at baseline (visit 1).^{57,58} Clinical resolution was defined as the absence (grade 0) of both ocular discharge and bulbar conjunctival injection. In each study, a single eye (study eye) from each randomized patient was represented in the analysis of the primary efficacy endpoints. In this post hoc analysis, either eye could contribute data provided an infecting bacterial species was at or above threshold and the eye had at least grade 1 conjunctival discharge and bulbar conjunctival injection at baseline. If a patient had a bilateral infection with the same relevant pathogen, only the eye with the most severe clinical signs was included.

Patients with conjunctival infections attributed to infection with *P. aeruginosa*, *S. marcescens*, *Neisseria* spp., MRSA, or MRSE were identified across the four clinical studies. Baseline minimum inhibitory concentrations (MICs) for besifloxacin and comparator antibacterial agents against the causative bacterial isolates from these patients were pooled

and integrated, and MIC₉₀ values (MIC for 90% of isolates) were generated for those pathogens with 10 or more isolates. Bacterial eradication and clinical resolution data for patients infected with the aforementioned pathogens at baseline and randomized to treatment with besifloxacin were also pooled, and integrated rates in the pooled sample were summarized by follow-up visit for those patients with non-missing data. Where noted, rates for clinical resolution and bacterial eradication were analyzed using Pearson's χ^2 test.

Results

Of the 2,859 patients that were randomized and treated in the four studies, 1,317 patients had culture-confirmed bacterial conjunctivitis. Among these, there were 35 conjunctivitis infections attributed to the Gram-negative pathogens of interest: nine *P. aeruginosa* infections, ten *S. marcescens* infections, and 16 *Neisseria* spp. infections (*N. meningitidis* n=3; *N. gonorrhoeae* n=2; *Neisseria sicca* n=1; *Neisseria subflava* n=8; *Neisseria mucosa* n=2). There were 256 infections with *S. aureus* and 178 infections with *S. epidermidis*. Figure 2 presents the proportion of staphylococcal infections due to strains resistant to methicillin and/or ciprofloxacin. A total of 116 (8.8%) infections were due to methicillin-resistant staphylococci: 35 (2.7%) MRSA infections and 81 (6.2%) MRSE infections. Concurrent ciprofloxacin resistance was observed in 68.6% (24/35) of MRSA infections and 39.5% (32/81) of MRSE infections.

Figure 3 presents the MIC₉₀ for besifloxacin and comparator fluoroquinolones against *P. aeruginosa*, *S. marcescens*, and *Neisseria* spp. isolates pooled from all four studies. All fluoroquinolones demonstrated in vitro activity against these Gram-negative pathogens. Ciprofloxacin had the lowest MICs against *P. aeruginosa* and *S. marcescens*. However, besifloxacin had the same MIC₉₀ as ciprofloxacin against *Neisseria* spp. Figure 4 presents the MIC₉₀ for besifloxacin and comparator fluoroquinolones against MRSA and MRSE isolates from all four studies. The MIC₉₀ of besifloxacin against MRSA isolates was 0.06 $\mu\text{g/mL}$ for CipS-MRSA and CipS-MRSE, and 4 $\mu\text{g/mL}$ for both CipR-MRSA and CipR-MRSE. Against CipR-MRSA and CipR-MRSE, the MIC₉₀ for besifloxacin was eight- to 128-fold lower and eight- to 64-fold lower, respectively, than comparator fluoroquinolones. Azithromycin, which was also included as a comparator in susceptibility testing, had poor activity against these staphylococcal isolates, with an MIC₉₀ of either $>8 \mu\text{g/mL}$ or $\geq 256 \mu\text{g/mL}$ (dependent on the highest drug dilution tested) for CipS-MRSA, CipS-MRSE, CipR-MRSA and CipR-MRSE.

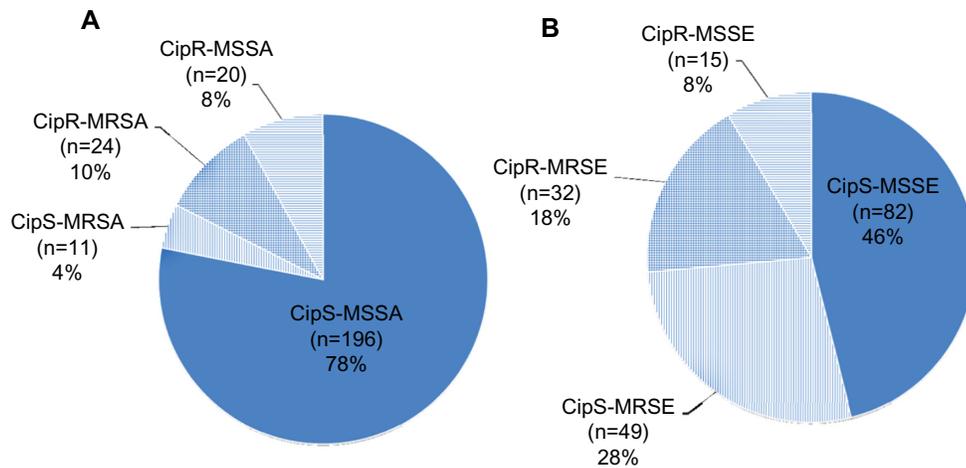


Figure 2 Drug resistance among staphylococcal isolates in four bacterial conjunctivitis trials.

Notes: (A) *Staphylococcus aureus* (n=256); (B) *Staphylococcus epidermidis* (n=178).

Abbreviations: CipS, ciprofloxacin-sensitive; CipR, ciprofloxacin-resistant; MRSA, methicillin-resistant *Staphylococcus aureus*; MRSE, methicillin-resistant *Staphylococcus epidermidis*; MSSA, methicillin-sensitive *Staphylococcus aureus*; MSSE, methicillin-sensitive *Staphylococcus epidermidis*.

Integrated clinical outcomes

Fourteen patients with conjunctivitis infections due to Gram-negative pathogens of concern were randomized to treatment with besifloxacin ophthalmic suspension 0.6%. Two of the 14 patients were infected with both *P. aeruginosa* and *S. marcescens* (ie, both pathogens were present above the Cagle threshold at baseline)^{57,58} for a total of 16 conjunctival infections

attributed to Gram-negative pathogens of consequence (*P. aeruginosa* n=5; *S. marcescens* n=4; *Neisseria* spp. n=7 [*N. gonorrhoeae* n=2, *N. meningitidis* n=2, *N. subflava* n=2 and *N. sicca* n=1]). The 14 patients ranged in age from 1 to 81 years, and eight (57.1%) patients were female. Half of the patients were infected with additional bacterial pathogens that were not the focus of this analysis. None of the patients

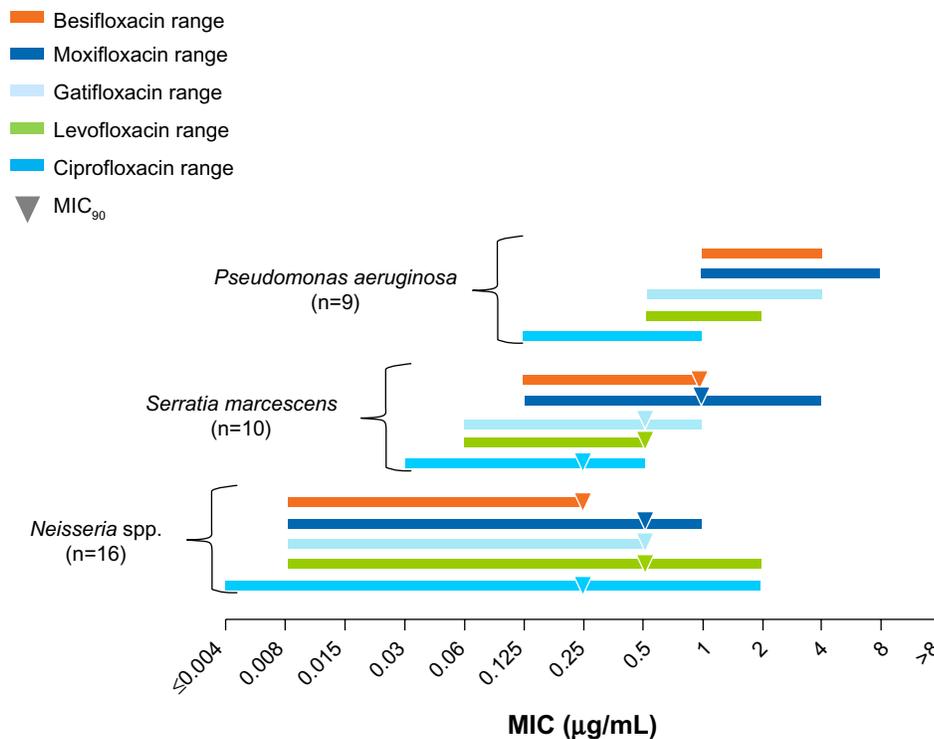


Figure 3 In vitro activity of besifloxacin and comparator fluoroquinolones against potentially consequential pathogens.

Notes: Due to the limited number of *Pseudomonas aeruginosa* isolates, a MIC₉₀ could not be calculated. The 16 *Neisseria* spp. isolates include *Neisseria meningitidis* (n=3), *Neisseria gonorrhoeae* (n=2), *Neisseria sicca* (n=1), *Neisseria subflava* (n=8), and *Neisseria mucosa* (n=2).

Abbreviations: MIC, minimum inhibitory concentration; MIC₉₀, MIC for 90% of isolates.

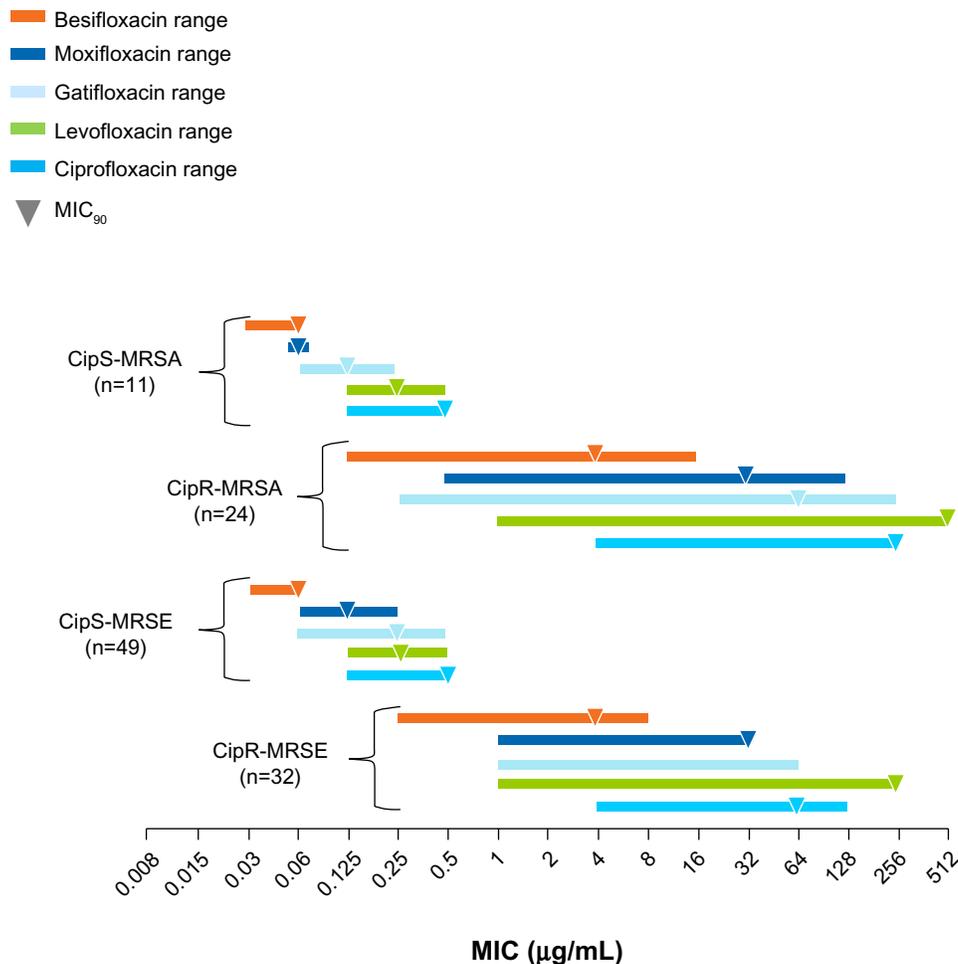


Figure 4 In vitro activity of besifloxacin and comparator fluoroquinolones against methicillin-resistant staphylococci.

Abbreviations: CipS, ciprofloxacin-sensitive; CipR, ciprofloxacin-resistant; MIC, minimum inhibitory concentration; MIC₉₀, MIC for 90% of isolates; MRSA, methicillin-resistant *Staphylococcus aureus*; MRSE, methicillin-resistant *Staphylococcus epidermidis*.

had positive viral cultures. The MIC range of besifloxacin against isolates from this subset of patients was 1–4 µg/mL for *P. aeruginosa*, 0.125–0.5 µg/mL for *S. marcescens*, and 0.008–0.25 µg/mL for *Neisseria* spp. Figure 5 presents bacterial eradication and clinical resolution rates at the first follow-up visit (visit 2) and the second follow-up visit (visit 3) for these patients by infecting Gram-negative pathogen. Treatment with besifloxacin ophthalmic suspension led to bacterial eradication of the infecting pathogen by the first follow-up visit in 100% (16/16) of these patients. The proportion of patients with clinical resolution (absence of both ocular discharge and bulbar conjunctival injection) was 40% (2/5) for *P. aeruginosa* infections, 25% (1/4) for *S. marcescens* infections, and 57% (4/7) for *Neisseria* spp. infections at the first follow-up visit and increased to 80% (4/5), 75% (3/4), and 100% (7/7), respectively, at the second follow-up visit.

Forty-eight patients with infections due to methicillin-resistant staphylococci were randomized to treatment

with besifloxacin ophthalmic suspension 0.6%. One of the 48 patients was infected with both MRSA and MRSE for a total of 12 MRSA infections and 37 MRSE infections, including ten CipR-MRSA infections and 16 CipR-MRSE infections. The 48 patients ranged in age from 1 to 87 years with a mean age of 40.8 (standard deviation 26.2) years, and 26 (54.2%) were female. One patient with MRSA was coinfecting with herpes simplex virus, and one patient with MRSE was coinfecting with adenovirus. As was reported for the Gram-negative cases, multibacterial infections were also common in this group. The MIC₉₀ of besifloxacin against these isolates was 2 µg/mL for CipR-MRSA, 0.06 µg/mL for CipS-MRSE, and 4 µg/mL for CipR-MRSE. The MIC values of besifloxacin against the two CipS-MRSA strains were 0.03 and 0.06 µg/mL.

Bacterial eradication rates in patients treated with besifloxacin for infections due to either MRSA or MRSE were 81.2% (40/49) by the first follow-up visit (visit 2) and 87.8%

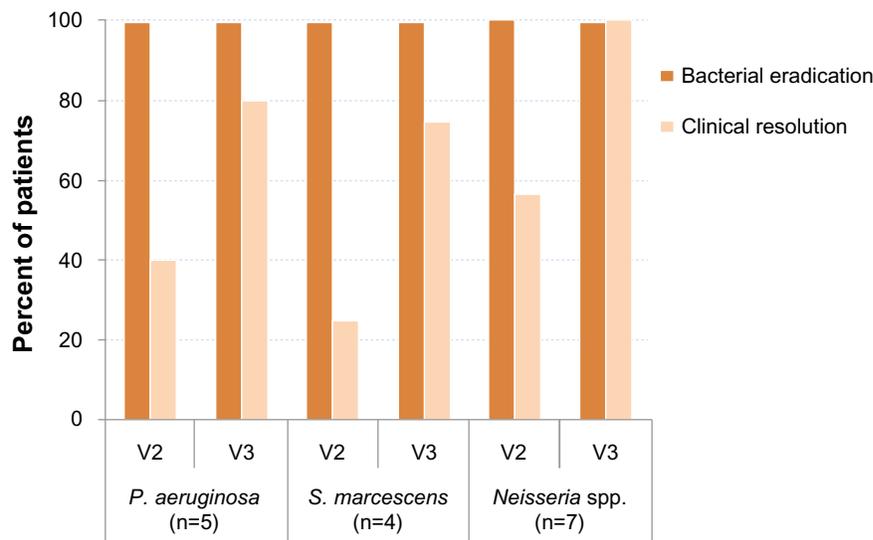


Figure 5 Bacterial eradication and clinical resolution at visit (V)2 and V3 for patients with Gram-negative pathogens of potential consequence at baseline treated with besifloxacin ophthalmic suspension 0.6%.

Abbreviations: *P. aeruginosa*, *Pseudomonas aeruginosa*; *S. marcescens*, *Serratia marcescens*.

(43/49) by the second follow-up visit (visit 3). Clinical resolution rates were 49.0% (24/49) by the first follow-up visit and increased to 73.5% (36/49) by the second follow-up visit. Bacterial eradication rates were significantly higher than those obtained for these infections in patients treated with vehicle (57.1% [20/35] by the first and 50.0% [17/34] by the second follow-up visit; $P \leq 0.014$). Clinical resolution rates did not differ statistically from those obtained for these infections in patients treated with vehicle (51.4% [18/35] by the first and 67.6% [23/34] by the second follow-up visit; $P \geq 0.56$). Figure 6 presents bacterial eradication and clinical resolution rates at the first and second follow-up visits for

these patients by ciprofloxacin sensitivity of the infecting MRSA or MRSE strain. The bacterial eradication rate at first follow-up visit was 100% (2/2) for CipS-MRSA infections, 70% (7/10) for CipR-MRSA infections, 71% (15/21) for CipS-MRSE infections, and 100% (16/16) for CipR-MRSE infections, and the rates increased to 80% (8/10) for CipR-MRSA infections and 81% (17/21) for CipS-MRSE infections by the second follow-up visit. The clinical resolution rate at the first follow-up visit was 50% (1/2) for CipS-MRSA infections, 20% (2/10) for CipR-MRSA infections, 71% (15/21) for CipS-MRSE infections, and 37.5% (6/16) for CipR-MRSE infections, and 50% (1/2), 50% (5/10), 85.7%

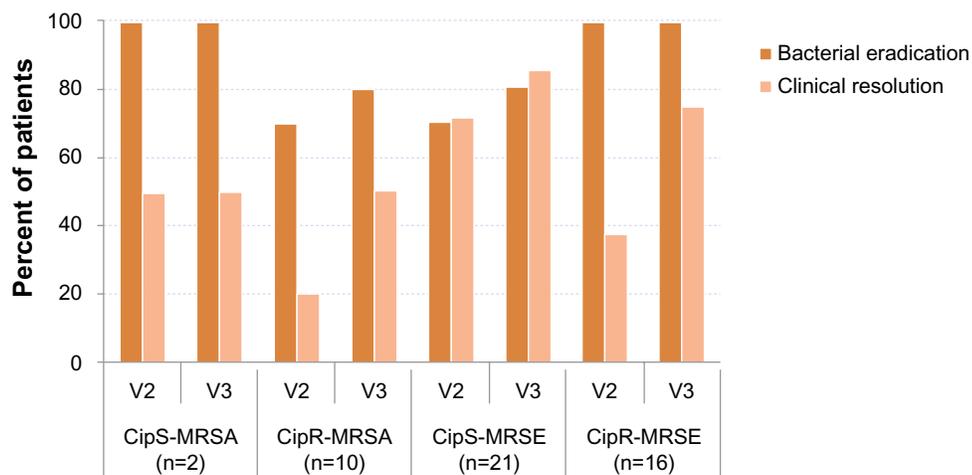


Figure 6 Bacterial eradication and clinical resolution at visit (V)2 and V3 for patients with methicillin-resistant staphylococcal infections at baseline treated with besifloxacin ophthalmic suspension 0.6%.

Abbreviations: CipS, ciprofloxacin-sensitive; CipR, ciprofloxacin-resistant; MRSA, methicillin-resistant *Staphylococcus aureus*; MRSE, methicillin-resistant *Staphylococcus epidermidis*.

(18/21), and 75% (12/16), for the respective infections, at the second follow-up visit.

Discussion

Previous multicenter, randomized, double-masked, controlled clinical studies have established the safety and efficacy of besifloxacin ophthalmic suspension 0.6% for the treatment of bacterial conjunctivitis, whether administered thrice daily for 5 days^{53–55} or twice daily for 3 days.⁵⁶ In each of these studies, clinical efficacy was demonstrated for patients with culture-confirmed bacterial conjunctivitis when pooling infections by all causative pathogens (Table 1) and also in the following subsets: infections due to Gram-positive pathogens; infections due to Gram-negative infections; and infections due to *H. influenzae*, *S. pneumoniae*, *S. aureus*, or *S. epidermidis*, the most prevalent bacterial pathogens in these studies. Based on data from thrice-daily studies, besifloxacin ophthalmic suspension 0.6% was initially approved in 2009 for treatment of bacterial conjunctivitis due to these species as well as some less frequent causative species encountered in these studies, including CDC coryneform group G, *Corynebacterium pseudodiphtheriticum*, *Corynebacterium striatum*, *Moraxella lacunata*, *Staphylococcus hominis*, *Staphylococcus lugdunensis*, *Streptococcus mitis* group, *Streptococcus oralis*, and *Streptococcus salivarius*.⁶⁴

Besifloxacin has been reported to have a broad-spectrum activity with an MIC₉₀ against *P. aeruginosa*, *S. marcescens*, *Neisseria* spp., and methicillin-resistant staphylococci that is significantly lower than the mean concentration of besifloxacin in tears following a single topical instillation in human volunteers (from 610 µg/g at 10 minutes to >10 µg/g at 12 hours following administration).⁶⁵ These data suggest that besifloxacin could be clinically effective against these potentially consequential pathogens, although there were too few infections with these pathogens in any individual clinical study to confirm this. Furthermore, the efficacy of besifloxacin has been reported in cases of *P. aeruginosa* keratitis⁶⁶ and giant fornix syndrome.⁶⁷ Besifloxacin was also effective in decreasing the bacterial counts in rabbit models of keratitis due to *P. aeruginosa*⁶⁸ and MRSA.^{69,70}

The objective of this post hoc analysis was to assess the clinical efficacy of besifloxacin ophthalmic suspension 0.6% when used in the treatment of patients with conjunctivitis caused by the aforementioned group of potentially consequential bacterial pathogens across four clinical studies.^{53–56} Case summaries for individual patients with *P. aeruginosa* conjunctival infections have been published previously,⁴⁸ and pooled outcomes for these patients repeated here. As expected,

the number of infections due to *P. aeruginosa*, *S. marcescens*, and *Neisseria* spp. was low even in the pooled data set. Nevertheless, there was a sufficient number of infections to demonstrate that besifloxacin had good in vitro activity against isolates of these Gram-negative pathogens comparable to that of ciprofloxacin against *Neisseria* spp. Analysis of integrated clinical outcome data for infections with these pathogens in patients treated with besifloxacin ophthalmic suspension demonstrated eradication of the infecting bacterial pathogen in all patients as early as the first follow-up visit. Indeed, the integrated bacterial eradication and clinical resolution data for *P. aeruginosa* formed the basis of a revision in 2012 of the US Food and Drug Administration-approved labeling for besifloxacin ophthalmic suspension 0.6% to include *P. aeruginosa* to its list of indicated bacterial pathogens (three additional pathogens – *Aerococcus viridans*, *Moraxella catarrhalis*, and *Staphylococcus warneri* – were also included at that time).³⁹ Because the approval to include a particular bacterial species in the label of an antibiotic is dependent on data being available for a minimum of five patients/infections successfully treated with that antibiotic, the addition of *S. marcescens* or any individual *Neisseria* spp. to the label for besifloxacin ophthalmic suspension 0.6% was not a consideration.

Consistent with reports on the increased prevalence of methicillin resistance among staphylococci in ocular infections,^{24–29} a larger data set, albeit still small, was available for analysis of clinical outcomes in conjunctivitis patients infected with methicillin-resistant staphylococci. Of *S. aureus* and *S. epidermidis* infections across the four clinical studies, 14% and 46%, respectively, were methicillin-resistant strains (Figure 2). In addition, a high proportion of methicillin-resistant strains were also resistant to ciprofloxacin (69% of MRSA strains and 40% of MRSE strains). In comparison, ciprofloxacin resistance was observed in a much smaller proportion of methicillin-sensitive *S. aureus* and *S. epidermidis* strains (9% and 15%, respectively). In agreement with previous studies,^{6,31,32,41} besifloxacin demonstrated potent in vitro activity against methicillin-resistant staphylococcal isolates, with MIC₉₀ values against CipR-MRSA and CipR-MRSE at least eight- to 128-fold lower than that of other fluoroquinolones and comparable to that reported for vancomycin in recent surveillance studies (1–2 µg/mL).^{31,41} Miller et al evaluated the comparative efficacy of besifloxacin against MRSA and coagulase-negative staphylococci from a wide variety of ocular infections (eg, conjunctivitis, blepharitis, keratitis, endophthalmitis, and other ocular surface disorders) and likewise showed lower MIC₉₀ values with besifloxacin compared to other fluoroquinolones and other antibacterials,

in particular against those staphylococcal isolates that were both CipR and methicillin resistant.⁴² Similar to results obtained with the Gram-negative pathogens of concern, bacterial eradication rates in patients with MRSA and MRSE infections treated with besifloxacin ophthalmic suspension were high – 81.2% by the first follow-up visit, increasing to 87.8% by the second follow-up visit – and significantly higher than those obtained in patients with these infections treated with vehicle ($P \leq 0.014$). Eradication rates were also high in the subset of infections with CipR-MRSA or CipR-MRSE – 88.5% at first follow-up visit, increasing to 92.3% by the second follow-up visit – suggesting that the combination of low MIC₉₀ and sustained ocular surface drug concentrations provides excellent coverage for these multidrug-resistant infections.

For both infections caused by the Gram-negative pathogens of concern, as well as infections caused by methicillin-resistant staphylococci, rates for clinical resolution (defined as the complete absence of both ocular discharge and conjunctival injection) were not as robust as rates for bacterial eradication. Indeed, there was no significant difference in clinical resolution rates in patients with MRSA and MRSE infections treated with besifloxacin compared to those treated with vehicle. These results were not unexpected based on the small sample size, with previous studies reporting a delay in clinical resolution relative to bacterial eradication,^{7,71,72} and strict criteria used in defining clinical resolution – namely, the complete absence (grade 0) of both ocular discharge and bulbar conjunctival injection. Notably, further evaluation of clinical signs in those patients for whom complete clinical resolution was not reported demonstrated that the severity of these clinical signs was reduced in all cases.^{73,74}

Although not a focus of this post hoc analysis, treatment with besifloxacin ophthalmic suspension 0.6% did not present any safety concerns in patients with infections due to pathogens of potential consequence. There were only two ocular AE reports considered to be at least possibly drug related: post-instillation blurred vision in one patient and mild corneal staining that was resolved at the follow-up visit in another patient. There were no clinically meaningful biomicroscopy findings or fundus pathologies observed, and final VA was the same or improved relative to baseline in nearly all patients. These findings are consistent with the overall safety findings from the individual studies.

Conclusion

Results of this post hoc analysis showed that treatment of patients with conjunctival infections due to *P. aeruginosa*,

S. marcescens, *Neisseria* spp., or methicillin-resistant staphylococci with besifloxacin ophthalmic suspension 0.6% led to high rates of bacterial eradication of these pathogens of concern to eye care practitioners. Furthermore, besifloxacin was well tolerated, with no clinically meaningful AEs or ophthalmology/biomicroscopy findings. A limitation of this post hoc analysis was the small sample size for patients with conjunctival infections due to any one of these pathogens even when pooled across four clinical studies. A statistical evaluation of outcomes among besifloxacin-treated patients compared with vehicle-treated patients was only practical for the largest of the pooled data sets – that of infections caused by methicillin-resistant staphylococci – and showed significantly higher rates for bacterial eradication with besifloxacin treatment compared to vehicle treatment. Nevertheless, the available clinical data, in conjunction with in vitro MIC data, are supportive of the efficacy of besifloxacin ophthalmic suspension 0.6% against these infections of concern.

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Disclosure

TLC, TWM, and HHD are employees of Bausch + Lomb, while LSG was an employee of Bausch + Lomb at the time of the study conduct. The authors report no other conflicts of interest in this work. All authors take responsibility for the integrity of the data and accuracy of the data analysis.

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