(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
20 September 2018 (20.09.2018)

WIPO | PCT

(10) International Publication Number
WO 2018/169967 A1

(51) International Patent Classification:
A61K 31/4709 (2006.01) *A61P 31/04* (2006.01)
A61K 31/496 (2006.01) *A61P 27/02* (2006.01)
A61K 31/5383 (2006.01)

(21) International Application Number:
PCT/US2018/022197

(22) International Filing Date:
13 March 2018 (13.03.2018)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
62/471,208 14 March 2017 (14.03.2017) US
62/532,660 14 July 2017 (14.07.2017) US

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(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BN, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DJ, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IR, IS, JO, JP, KE, KG, KH, KN, KP, KR, KW, KZ, LA, LC, LK, LR, LS, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PA, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SA, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, ST, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, RU, TJ, TM), European (AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, KM, ML, MR, NE, SN, TD, TG).

Published:
— *with international search report (Art. 21(3))*

WO 2018/169967 A1

(54) Title: ACORAFLOXACIN IN TREATING OCULAR INFECTIONS

(57) Abstract: Methods for treating (including prophylactic treatment) ocular infections by administration of acorafloxacin are described. Acorafloxacin has been shown to be more potent in inhibiting ophthalmic methicillin-resistant *Staphylococcus aureus* (MRSA) and ophthalmic methicillin-resistant *Staphylococcus epidermidis* (MRSE) than at least one fluoroquinolone selected from besifloxacin, gatifloxacin, moxifloxacin, levofloxacin and ciprofloxacin.

ACORAFLOXACIN IN TREATING OCULAR INFECTIONS

CROSS-REFERENCE TO RELATED APPLICATIONS

[001] This application claims priority to US provisional applications 62/471,208 filed on March 14, 2017, and 62/532,660 filed on July 14, 2017, each of which is incorporated by reference in their entireties and serve as the basis for a benefit and/or priority claim for the present application.

TECHNICAL FIELD

[002] The subject matter described herein relates to use of the fluoroquinolone compound acorafloxacin for the treatment or control of ocular infections including, but not limited to, bacterial infections such as conjunctivitis, keratitis, vitritis, and endophthalmitis.

BACKGROUND

[003] Bacterial conjunctivitis is the second most common cause of infectious conjunctivitis in humans and affects all ages and socioeconomic classes (Alfonso, S.A. *et al.*, *Prim. Care,* 2015, 42:325-345). In the developed world, bacterial conjunctivitis is one of the primary causes of acute red eye, which in turn is responsible for 1–4% of primary care visits (Origlieri, C. *et al.*, *Expert Opin. Emerg. Drugs*, 2009, 14:523-536). The economic impact of bacterial conjunctivitis is significant, in terms of the cost of medical visits, cost of treatment, and lost work productivity (Smith, A.F. *et al.*, *BMC Ophthalmol.*, 2009, **9**:13). Although bacterial conjunctivitis is caused by a wide variety of bacterial pathogens, staphylococcus aureus and streptococcus pneumonia remain the most common pathogens.

[004] Surveillance programs have shown that antibiotic resistance, including fluoroquinolone-resistance, has increased among bacterial pathogens; however, there has been limited information among bacterial pathogens of the eye. Only recently have surveillance studies provided information on antibiotic resistance among ocular pathogens collected in the United States (Asbell, P.A. *et al., JAMA Ophthalmology,* 2015, 133(12):1445-1454).

[005] A particular concern is that many of the methicillin-resistant isolates have a high probability of concurrent resistance to fluoroquinolones, aminoglycosides and macrolides. Multi-

resistance to at least 3 additional antibiotic classes was identified among 428 methicillin-resistant *S. aureus* isolates (86.8%) and 381 methicillin-resistant coagulase-negative staphylococci (CoNS) isolates (77.3%) (Asbell, *supra*). There is an unmet need for new agents with potent antibacterial activity against ocular pathogens that includes contemporary resistant phenotypes that are resistant to existing fluoroquinolone drugs and/or other antimicrobial drugs.

BRIEF SUMMARY

[006] The following aspects and embodiments thereof described and illustrated below are meant to be exemplary and illustrative, not limiting in scope.

[007] In one aspect, a method for treating an ocular bacterial infection in a patient in recognized need of such treatment is provided. The method comprises administering to the patient in recognized need of such treatment a therapeutically effective amount of acorafloxacin.

[008] In one embodiment, administering comprises locally administering to an eye of the patient.

[009] In another embodiment, local administration to the eye comprises topical administration.

[0010] In yet another embodiment, acorafloxacin is administered as a pharmaceutical composition comprising acorafloxacin and a pharmaceutically acceptable excipient.

[0011] In still another embodiment, the pharmaceutical composition is a solution or a suspension. In another embodiment, the pharmaceutical composition is an ointment. In another embodiment, the pharmaceutical composition is a gel.

[0012] In one embodiment, given its high potency, the therapeutically effective amount of acorafloxacin is at least about 4 times less than a therapeutically effective amount of one or more of besifloxacin, gatifloxacin, moxifloxacin, levofloxacin and ciprofloxacin.

[0013] In another embodiment, the ocular infection comprises at least one bacterium selected from ophthalmic *Staphylococcus aureus* (MRSA) and ophthalmic *Staphylococcus epidermidis* (MRSE), and the administering is effective to resolve the infection at a dose of acorafloxacin that is at least about 4 times less than a dose of one or more of besifloxacin, gatifloxacin, moxifloxacin, levofloxacin and ciprofloxacin.

[0014] In yet another embodiment, the ocular infection is bacterial conjunctivitis, bacterial blepharitis, bacterial keratitis, or bacterial endophthalmitis.

[0015] The method, in another embodiment, is more effective than a corresponding method wherein acorafloxacin is replaced with at least one fluoroquinolone selected from besifloxacin, gatifloxacin, moxifloxacin, levofloxacin and ciprofloxacin.

[0016] In still another embodiment, the method is more effective than a corresponding method wherein acorafloxacin is replaced with moxifloxacin.

[0017] In another aspect, a kit comprised of (i) a pharmaceutical composition comprising acorafloxacin, and a pharmaceutically acceptable excipient; and (ii) instructions for administering the composition topically to an eye with a bacterial infection is provided.

[0018] In one embodiment, the pharmaceutical composition is a solution or a suspension administrable by drops.

[0019] In another embodiment, the pharmaceutical composition is an ointment.

[0020] In another embodiment, the pharmaceutical composition is a gel.

[0021] In yet another embodiment, the pharmaceutical composition is provided in a container suitable for multidose administration.

[0022] In still another embodiment, the composition is provided in a container suitable for unit dose administration.

[0023] In still another embodiment, the container comprises a dropper to dispense the pharmaceutical composition as single drops.

[0024] In another embodiment, the container comprises a tube that dispenses the pharmaceutical composition as an ointment.

[0025] In another embodiment, the container comprises a tube that dispenses the pharmaceutical composition as an gel.

[0026] Also contemplated is a method of inhibiting growth of at least one bacterium selected from ophthalmic *Staphylococcus aureus* (MRSA) and ophthalmic *Staphylococcus epidermidis* (MRSE), comprising: contacting acorafloxacin with the at least one bacterium.

[0027] Also disclosed is a method of treating an ocular infection in a patient that is responsive to inhibition of at least one bacterium selected from ophthalmic *Staphylococcus aureus* (MRSA) and ophthalmic *Staphylococcus epidermidis* (MRSE) comprising administering to the patient in recognized need of such treatment, (1) a therapeutically effective amount of acorafloxacin, or (2) a pharmaceutical composition comprising acorafloxacin and a pharmaceutically acceptable excipient.

[0028] Also disclosed is a method of inhibiting at least one bacterium selected from ophthalmic methicillin-resistant *Staphylococcus aureus* (MRSA) and ophthalmic methicillin-resistant *Staphylococcus epidermidis* (MRSE) comprising contacting acorafloxacin with the at least one bacterium.

[0029] Additional embodiments of the present methods will be apparent from the following description, drawings, examples, and claims. As can be appreciated from the foregoing and following description, each and every feature described herein, and each and every combination of two or more of such features, is included within the scope of the present disclosure provided that the features included in such a combination are not mutually inconsistent. In addition, any feature or combination of features may be specifically excluded from any embodiment of the present invention. Additional aspects and advantages of the present invention are set forth in the following description and claims, particularly when considered in conjunction with the accompanying examples and drawings.

[0030] Some non-limiting example embodiments are listed below.

[0031] Example Embodiment 1: A method for treating an ocular bacterial infection in a patient in recognized need of such treatment, comprising:

administering to the patient in recognized need of treatment a therapeutically effective amount of acorafloxacin, or a pharmaceutically acceptable salt thereof.

[0032] Example Embodiment 2: The method of example embodiment 1, wherein acorafloxacin, or a pharmaceutically acceptable salt thereof, is administered as a pharmaceutical composition comprising acorafloxacin, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable excipient.

[0033] Example Embodiment 3: The method of example embodiment 2, wherein the pharmaceutical composition is a solution or a suspension.

[0034] Example Embodiment 4: The method of example embodiment 2, wherein the pharmaceutical composition is an ointment or a gel.

[0035] Example Embodiment 5: The method of any one of example embodiments 3 or 4, wherein the pharmaceutical composition comprises a preservative.

[0036] Example Embodiment 6: The method of any one of example embodiments 3 or 4, wherein the pharmaceutical composition is preservative-free.

[0037] Example Embodiment 7: The method of example embodiment 2, wherein the pharmaceutical composition is an ocular implant, intracameral implant, intravitreal implant, subconjunctival implant, sub-Tenon's implant, punctum plug, canicular eluting implant, or ocular ring.

[0038] Example Embodiment 8: The method of example embodiment 2, wherein the pharmaceutical composition is a microsphere.

[0039] Example Embodiment 9: The method of any one of example embodiments 1 to 8, wherein administering comprises locally administering to an eye of the patient in recognized need of such treatment.

[0040] Example Embodiment 10: The method of example embodiment 9, wherein the local administration to the eye comprises topical administration.

[0041] Example Embodiment 11: The method of example embodiment 9, wherein the local administration to the eye comprises intravitreal administration, intracameral administration, subconjunctival administration, or sub-Tenon's administration.

[0042] Example Embodiment 12: The method of any one of example embodiments 1-11, wherein the therapeutically effective amount of acorafloxacin, or a pharmaceutically acceptable salt thereof, is at least about 4 times less than a therapeutically effective amount of one or more of besifloxacin, gatifloxacin, moxifloxacin, levofloxacin and ciprofloxacin.

[0043] Example Embodiment 13: The method of any preceding example embodiment, wherein the ocular infection comprises at least one bacterium selected from ophthalmic Staphylococcus aureus (MRSA) and ophthalmic Staphylococcus epidermidis (MRSE), and said administering is effective to resolve the infection at a dose of acorafloxacin, or a pharmaceutically acceptable salt thereof, that is at least about 4 times less than a dose of one or more of besifloxacin, gatifloxacin, moxifloxacin, levofloxacin and ciprofloxacin.

[0044] Example Embodiment 14: The method of any preceding example embodiment, wherein the ocular infection is bacterial conjunctivitis, bacterial blepharitis, bacterial keratitis, or bacterial endophthalmitis.

[0045] Example Embodiment 15: The method of any one of example embodiments 1-14, wherein the method is more effective than a corresponding method wherein acorafloxacin, or a pharmaceutically acceptable salt thereof, is replaced with at least one fluoroquinolone selected from besifloxacin, gatifloxacin, moxifloxacin, levofloxacin and ciprofloxacin.

[0046] Example Embodiment 16: The method of any one of example embodiments 1-15, wherein the method is more effective than a corresponding method wherein acorafloxacin is replaced with moxifloxacin.

[0047] Example Embodiment 17: The method of any one of any one of example embodiments 1-16, wherein the treatment is a prophylactic treatment.

[0048] Example Embodiment 18: A kit, comprising:

a composition comprising acorafloxacin, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable excipient; and

instructions for administering the composition to an eye with a bacterial infection.

[0049] Example Embodiment 19: The kit of example embodiment 18, wherein the composition is a solution or a suspension administrable by drops.

[0050] Example Embodiment 20: The kit of example embodiment 18, wherein the composition is an ointment or a gel.

[0051] Example Embodiment 21: The kit of any one of example embodiments 18-20, wherein the composition is provided in a container suitable for multidose administration.

[0052] Example Embodiment 22: The kit of example embodiment 21, wherein the container comprises a dropper to dispense the composition as single drops.

[0053] Example Embodiment 23: The kit of example embodiment 21, wherein the container comprises a tube that dispenses the composition as an ointment or a gel.

[0054] Example Embodiment 24: The kit of any one of example embodiments 18–23, wherein the composition comprises a preservative.

[0055] Example Embodiment 25: The kit of any one of example embodiments 18–23, wherein the composition is preservative-free.

[0056] Example Embodiment 26: The kit of example embodiment 18, wherein the composition is an ocular implant, intracameral implant, intravitreal implant, subconjunctival implant, sub-Tenon's implant, punctum plug, canicular eluting implant, or ocular ring.

[0057] Example Embodiment 27: The kit of example embodiment 18, wherein the composition is a microsphere.

[0058] Example Embodiment 28: A method of inhibiting growth of at least one bacterium selected from ophthalmic Staphylococcus aureus (MRSA) and ophthalmic Staphylococcus

epidermidis (MRSE), comprising: contacting acorafloxacin, or a pharmaceutically acceptable salt thereof, with the at least one bacterium.

[0059] Example Embodiment 29: A method of treating an ocular infection comprising at least one bacterium in a patient in recognized need of such treatment, the method comprising:

collecting the at least one bacterium isolate from the patient in recognized need of such treatment,

identifying MICs for each of fluoroquinolones selected from acorafloxacin, besifloxacin, gatifloxacin, moxifloxacin, levofloxacin and ciprofloxacin, or a pharmaceutically acceptable salt thereof, on the at least one bacterium isolate, and

administering to the patient in recognized need of such treatment, a therapeutically effective amount of the fluoroquinolone, or a pharmaceutically acceptable salt thereof, having the lowest MIC.

[0060] Example Embodiment 30: The method of example embodiment 29, wherein the fluoroquinolone having the lowest MIC is acorafloxacin.

[0061] Example Embodiment 31: The method of example embodiment 29 or example embodiment 30, wherein the at least one bacterium is resistant to at least one fluoroquinolone selected from besifloxacin, gatifloxacin, moxifloxacin, levofloxacin and ciprofloxacin, or a pharmaceutically acceptable salt thereof.

[0062] Example Embodiment 32: The method of any one of example embodiments 29-31, wherein the at least one bacterium is resistant to moxifloxacin.

[0063] Example Embodiment 33: The method of any one of example embodiments 29-32, wherein the treatment is a prophylactic treatment.

[0064] Example Embodiment 34: A kit comprising acorafloxacin and instructions for measuring acorafloxacin MIC on at least one bacterium selected from ophthalmic Staphylococcus aureus and ophthalmic Staphylococcus epidermidis, wherein the instructions comprise:

preparing acorafloxacin, or a pharmaceutically acceptable salt thereof, stock solution,

diluting acorafloxacin, or a pharmaceutically acceptable salt thereof, stock solution in an appropriate fold dilution series, and

contacting the dilution series with the at least one bacterium.

[0065] Example Embodiment 35: The kit of example embodiment 34, wherein the ophthalmic Staphylococcus aureus is methicillin-resistant.

[0066] Example Embodiment 36: The kit of example embodiment 34 or example embodiment 35, wherein the ophthalmic Staphylococcus epidermidis is methicillin-resistant.

[0067] Example Embodiment 37: The kit of any one of example embodiments 34-35, wherein the at least one bacterium is resistant to at least one fluoroquinolone selected from besifloxacin, gatifloxacin, moxifloxacin, levofloxacin and ciprofloxacin, or a pharmaceutically acceptable salt thereof.

[0068] Example Embodiment 38: Use of acorafloxacin, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for the treatment of an ocular bacterial infection.

[0069] Example Embodiment 39: The use of example embodiment 38 wherein the medicament is a pharmaceutical composition comprising acorafloxacin, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable excipient.

[0070] Example Embodiment 40: The use of example embodiment 39, wherein the pharmaceutical composition is a solution or a suspension.

[0071] Example Embodiment 41: The use of example embodiment 39, wherein the pharmaceutical composition is an ointment or a gel.

[0072] Example Embodiment 42: The use of any one of example embodiments 39–41, wherein the composition comprises a preservative.

[0073] Example Embodiment 43: The use of any one of example embodiments 39–41, wherein the composition is preservative-free.

[0074] Example Embodiment 44: The use of example embodiment 39, wherein the pharmaceutical composition is an ocular implant, intracameral implant, intravitreal implant, subconjunctival implant, sub-Tenon's implant, punctum plug, canicular eluting implant, or ocular ring.

[0075] Example Embodiment 45: The use of example embodiment 39, wherein the pharmaceutical composition is a microsphere.

[0076] Example Embodiment 46: The use of any one of example embodiments 38–45, wherein the medicament, when used in the treatment of an ocular bacterial infection, is administered locally to an eye of a patient in recognized need of such treatment.

[0077] Example Embodiment 47: The use of example embodiment 46, wherein the local administration to the eye comprises topical administration.

[0078] Example Embodiment 48: The use of example embodiment 46, wherein the local administration to the eye comprises intravitreal administration, intracameral administration, subconjunctival administration, or sub-Tenon's administration.

[0079] Example Embodiment 49: The use of any one of example embodiments 38–48, wherein the acorafloxacin, or a pharmaceutically acceptable salt thereof, is present in the medicament in a therapeutically effective amount that is at least about 4 times less than a therapeutically effective amount of one or more of besifloxacin, gatifloxacin, moxifloxacin, levofloxacin and ciprofloxacin.

[0080] Example Embodiment 50: The use of any one of example embodiments 38–49, wherein the ocular infection comprises at least one bacterium selected from ophthalmic Staphylococcus aureus (MRSA) and ophthalmic Staphylococcus epidermidis (MRSE), and the medicament, when administered a patient in recognized need of treatment for the ocular bacterial infection, is effective to resolve the infection at a dose of acorafloxacin, or a pharmaceutically acceptable salt thereof, that is at least about 4 times less than a dose of one or more of besifloxacin, gatifloxacin, moxifloxacin, levofloxacin and ciprofloxacin.

[0081] Example Embodiment 51: The use of any one of example embodiments 38–50, wherein the ocular infection is bacterial conjunctivitis, bacterial blepharitis, bacterial keratitis, or bacterial endophthalmitis.

[0082] Example Embodiment 52: The use of any one of example embodiments 38–51, wherein the treatment of the ocular infection is more effective than a corresponding treatment wherein acorafloxacin, or a pharmaceutically acceptable salt thereof, is replaced with at least one fluoroquinolone selected from besifloxacin, gatifloxacin, moxifloxacin, levofloxacin and ciprofloxacin.

[0083] Example Embodiment 53: The use of any one of example embodiments 38–52, wherein the treatment of the ocular infection is more effective than a corresponding treatment wherein acorafloxacin, or a pharmaceutically acceptable salt thereof, is replaced with moxifloxacin.

[0084] Example Embodiment 54: The use of any one of example embodiments 38–53, wherein the treatment is a prophylactic treatment.

[0085] Example Embodiment 55: Use of acorafloxacin, or a pharmaceutically acceptable salt thereof, in the treatment of an ocular bacterial infection in a patient in recognized need of such treatment.

[0086] Example Embodiment 56: The use of example embodiments 55, wherein the treatment comprises administering the acorafloxacin, or a pharmaceutically acceptable salt thereof, as a pharmaceutical composition comprising the acorafloxacin, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable excipient.

[0087] Example Embodiment 57: The use of example embodiment 56, wherein the pharmaceutical composition is a solution or a suspension.

[0088] Example Embodiment 58: The use of example embodiment 56, wherein the pharmaceutical composition is an ointment or a gel.

[0089] Example Embodiment 59: The use of any one of example embodiments 56–58, wherein the composition comprises a preservative.

[0090] Example Embodiment 60: The use of any one of example embodiments 56–58, wherein the composition is preservative-free.

[0091] Example Embodiment 61: The use of example embodiment 56, wherein the pharmaceutical composition is an ocular implant, intracameral implant, intravitreal implant, subconjunctival implant, sub-Tenon's implant, punctum plug, canicular eluting implant, or ocular ring.

[0092] Example Embodiment 62: The use of example embodiment 56, wherein the pharmaceutical composition is a microsphere.

[0093] Example Embodiment 63: The use of any one of example embodiments 55–62, wherein the treatment comprises locally administering the acorafloxacin to an eye of the patient in recognized need of such treatment.

[0094] Example Embodiment 64: The use of example embodiment 63, wherein the local administration to the eye comprises topical administration,

[0095] Example Embodiment 65: The use of example embodiment 63, wherein the local administration to the eye comprises intravitreal administration, intracameral administration, subconjunctival administration, or sub-Tenon's administration.

[0096] Example Embodiment 66: The use of any one of example embodiments 55–65, wherein the treatment comprises administering the acorafloxacin to the patient in recognized

need thereof a therapeutically effective amount of acorafloxacin, or a pharmaceutically acceptable salt thereof, that is at least about 4 times less than a therapeutically effective amount of one or more of besifloxacin, gatifloxacin, moxifloxacin, levofloxacin and ciprofloxacin.

[0097] Example Embodiment 67: The use of any one of example embodiments 55–66, wherein the ocular infection comprises at least one bacterium selected from ophthalmic Staphylococcus aureus (MRSA) and ophthalmic Staphylococcus epidermidis (MRSE), and the treatment is effective to resolve the infection when a dose of acorafloxacin, or a pharmaceutically acceptable salt thereof, is administered that is at least about 4 times less than a dose of one or more of besifloxacin, gatifloxacin, moxifloxacin, levofloxacin and ciprofloxacin.

[0098] Example Embodiment 68: The use of any one of example embodiments 55–67, wherein the ocular infection is bacterial conjunctivitis, bacterial blepharitis, bacterial keratitis, or bacterial endophthalmitis.

[0099] Example Embodiment 69: The use of any one of example embodiments 55–68, wherein the treatment is more effective than a corresponding treatment wherein acorafloxacin, or a pharmaceutically acceptable salt thereof, is replaced with at least one fluoroquinolone selected from besifloxacin, gatifloxacin, moxifloxacin, levofloxacin and ciprofloxacin.

[00100] Example Embodiment 70: The use of any one of example embodiments 55–69, wherein the treatment is more effective than a corresponding treatment wherein acorafloxacin, or a pharmaceutically acceptable salt thereof, is replaced with moxifloxacin.

[00101] Example Embodiment 71: The use of any one of example embodiments 55–70, wherein the treatment is a prophylactic treatment.

[00102] Example Embodiment 72: Acorafloxacin, or a pharmaceutically acceptable salt thereof, for use in the treatment of an ocular bacterial infection in a patient in recognized need of such treatment.

[00103] Example Embodiment 73: The acorafloxacin, or pharmaceutically acceptable salt thereof, for the use of example embodiments 72, wherein the treatment comprises administering the acorafloxacin as a pharmaceutical composition comprising the acorafloxacin and a pharmaceutically acceptable excipient.

[00104] Example Embodiment 74: The acorafloxacin, or pharmaceutically acceptable salt thereof, for the use of example embodiment 73, wherein the pharmaceutical composition is a solution or a suspension.

[00105] **Example Embodiment 75:** The acorafloxacin, or pharmaceutically acceptable salt thereof, for the use of example embodiment 73, wherein the pharmaceutical composition is an ointment or a gel.

[00106] **Example Embodiment 76:** The acorafloxacin, or pharmaceutically acceptable salt thereof, for the use of any one of example embodiments 73–75, wherein the pharmaceutical composition comprises a preservative.

[00107] **Example Embodiment 77:** The acorafloxacin, or pharmaceutically acceptable salt thereof, for the use of any one of example embodiments 73–75, wherein the pharmaceutical composition is preservative-free.

[00108] **Example Embodiment 78:** The acorafloxacin, or pharmaceutically acceptable salt thereof, for use according to example embodiment 73, wherein the pharmaceutical composition is an ocular implant, intracameral implant, intravitreal implant, subconjunctival implant, sub-Tenon's implant, punctum plug, canicular eluting implant, or ocular ring.

[00109] **Example Embodiment 79:** The acorafloxacin, or pharmaceutically acceptable salt thereof, for use according to example embodiment 73, wherein the pharmaceutical composition is a microsphere.

[00110] **Example Embodiment 80:** The acorafloxacin, or pharmaceutically acceptable salt thereof, for the use of any one of example embodiments 72–79, wherein the treatment comprises locally administering the acorafloxacin to an eye of the patient in recognized need of such treatment.

[00111] **Example Embodiment 81:** The acorafloxacin, or pharmaceutically acceptable salt thereof, for the use of example embodiment 80, wherein the local administration to the eye comprises topical administration.

[00112] **Example Embodiment 82:** The acorafloxacin, or pharmaceutically acceptable salt thereof, for the use of example embodiment 80, wherein the local administration to the eye comprises intravitreal administration, intracameral administration, subconjunctival administration, or sub-Tenon's administration.

[00113] **Example Embodiment 83:** The acorafloxacin, or pharmaceutically acceptable salt thereof, for the use of any one of example embodiments 72–82, wherein the treatment comprises administering the acorafloxacin, or pharmaceutically acceptable salt thereof, to the patient in recognized need thereof a therapeutically effective amount of acorafloxacin, or

pharmaceutically acceptable salt thereof, that is at least about 4 times less than a therapeutically effective amount of one or more of besifloxacin, gatifloxacin, moxifloxacin, levofloxacin and ciprofloxacin.

[00114] Example Embodiment 84: The acorafloxacin, or pharmaceutically acceptable salt thereof, for the use of any one of example embodiments 72–83, wherein the ocular infection comprises at least one bacterium selected from ophthalmic Staphylococcus aureus (MRSA) and ophthalmic Staphylococcus epidermidis (MRSE), and the treatment is effective to resolve the infection when a dose of acorafloxacin, or pharmaceutically acceptable salt thereof, is administered that is at least about 4 times less than a dose of one or more of besifloxacin, gatifloxacin, moxifloxacin, levofloxacin and ciprofloxacin.

[00115] Example Embodiment 85: The acorafloxacin, or pharmaceutically acceptable salt thereof, for the use of any one of example embodiments 72–84, wherein the ocular infection is bacterial conjunctivitis, bacterial blepharitis, bacterial keratitis, or bacterial endophthalmitis.

[00116] Example Embodiment 86: The acorafloxacin, or pharmaceutically acceptable salt thereof, for the use of any one of example embodiments 72–85, wherein the treatment is more effective than a corresponding treatment wherein acorafloxacin is replaced with at least one fluoroquinolone selected from besifloxacin, gatifloxacin, moxifloxacin, levofloxacin and ciprofloxacin.

[00117] Example Embodiment 87: The acorafloxacin, or pharmaceutically acceptable salt thereof, for the use of any one of example embodiments 72–86, wherein the treatment is more effective than a corresponding treatment wherein acorafloxacin is replaced with moxifloxacin.

[00118] Example Embodiment 88: The acorafloxacin, or pharmaceutically acceptable salt thereof, for the use of any one of 72–87, wherein the treatment is a prophylactic treatment.

[00119] Example Embodiment 89: Use of acorafloxacin, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for the treatment of an ocular infection comprising at least one bacterium in a patient in recognized need of such treatment.

[00120] Example Embodiment 90: The use of example embodiment 89, wherein the treatment comprises:

collecting the at least one bacterium isolate from the patient in recognized need of such treatment,

identifying MICs for each of fluoroquinolones selected from acorafloxacin, besifloxacin, gatifloxacin, moxifloxacin, levofloxacin and ciprofloxacin, or a pharmaceutically acceptable salt thereof, on the at least one bacterium isolate, and

administering to the patient in recognized need of such treatment, a therapeutically effective amount of the fluoroquinolone, or a pharmaceutically acceptable salt thereof, having the lowest MIC.

[00121] Example Embodiment 91: The use of example embodiment 90, wherein the fluoroquinolone having the lowest MIC is acorafloxacin.

[00122] Example Embodiment 92: The of any one of example embodiments 89–91, wherein the at least one bacterium is resistant to at least one fluoroquinolone selected from besifloxacin, gatifloxacin, moxifloxacin, levofloxacin and ciprofloxacin, or a pharmaceutically acceptable salt thereof.

[00123] Example Embodiment 93: The use of any one of example embodiments 89–92, wherein the at least one bacterium is resistant to moxifloxacin.

[00124] Example Embodiment 94: The use of any one of example embodiments 89–93, wherein the treatment is a prophylactic treatment.

[00125] Example Embodiment 95: Use of acorafloxacin, or a pharmaceutically acceptable salt thereof, in the treatment of an ocular infection comprising at least one bacterium in a patient in recognized need of such treatment.

[00126] Example Embodiment 96: The use of example embodiment 95, wherein the treatment comprises:

collecting the at least one bacterium isolate from the patient in recognized need of such treatment,

identifying MICs for each of fluoroquinolones selected from acorafloxacin, besifloxacin, gatifloxacin, moxifloxacin, levofloxacin and ciprofloxacin, or a pharmaceutically acceptable salt thereof, on the at least one bacterium isolate, and

administering to the patient in recognized need of such treatment, a therapeutically effective amount of the fluoroquinolone, or a pharmaceutically acceptable salt thereof, having the lowest MIC.

[00127] Example Embodiment 97: The use of example embodiment 96, wherein the fluoroquinolone having the lowest MIC is acorafloxacin.

[00128] **Example Embodiment 98:** The use of any one of example embodiments 95–97, wherein the at least one bacterium is resistant to at least one fluoroquinolone selected from besifloxacin, gatifloxacin, moxifloxacin, levofloxacin and ciprofloxacin, or a pharmaceutically acceptable salt thereof.

[00129] **Example Embodiment 99:** The use of any one of example embodiments 95–98, wherein the at least one bacterium is resistant to moxifloxacin.

[00130] **Example Embodiment 100:** The use of any one of example embodiments 95–99, wherein the treatment is a prophylactic treatment.

[00131] **Example Embodiment 101:** Acorafloxacin, or a pharmaceutically acceptable salt thereof, for use in the treatment of an ocular infection comprising at least one bacterium in a patient in recognized need of such treatment.

[00132] **Example Embodiment 102:** Acorafloxacin, or a pharmaceutically acceptable salt thereof, for the use of example embodiment 101, wherein the treatment comprises:

collecting the at least one bacterium isolate from the patient in recognized need of such treatment,

identifying MICs for each of fluoroquinolones selected from acorafloxacin, besifloxacin, gatifloxacin, moxifloxacin, levofloxacin, and ciprofloxacin, or a pharmaceutically acceptable salt thereof, on the at least one bacterium isolate, and

administering to the patient in recognized need of such treatment, a therapeutically effective amount of the fluoroquinolone, or a pharmaceutically acceptable salt thereof, having the lowest MIC.

[00133] **Example Embodiment 103:** Acorafloxacin for the use of example embodiment 102, wherein the fluoroquinolone having the lowest MIC is acorafloxacin.

[00134] **Example Embodiment 104:** Acorafloxacin for the use of any one of example embodiments 101–102, wherein the at least one bacterium is resistant to at least one fluoroquinolone selected from besifloxacin, gatifloxacin, moxifloxacin, levofloxacin and ciprofloxacin, or a pharmaceutically acceptable salt thereof.

[00135] **Example Embodiment 105:** Acorafloxacin, or a pharmaceutically acceptable salt thereof, for the use of any one of example embodiments 101–104, wherein the at least one bacterium is resistant to moxifloxacin.

[00136] **Example Embodiment 106:** Acorafloxacin, or a pharmaceutically acceptable salt thereof, for the use of any one of example embodiments 101–105, wherein the treatment is a prophylactic treatment.

[00137] **Example Embodiment 107:** A method for treating an ocular bacterial infection in a patient substantially as described herein.

[00138] **Example Embodiment 108:** A method for treating an ocular bacterial infection in a patient in need thereof using acorafloxacin, or a pharmaceutically acceptable salt thereof, substantially as described herein.

[00139] **Example Embodiment 109:** The use of acorafloxacin, or a pharmaceutically acceptable salt thereof, substantially as described herein.

[00140] **Example Embodiment 110:** Acorafloxacin, or a pharmaceutically acceptable salt thereof, for use substantially as described herein.

BRIEF DESCRIPTION OF DRAWINGS

[00141] **FIG. 1** is a Finlandogram plot showing the cumulative percentage of ophthalmic MRSA isolates inhibited as a function of minimum inhibitory concentration (MIC; in μg/mL) (n = 80) for acorafloxacin (diamonds), besifloxacin (squares), moxifloxacin (triangles), gatifloxacin (x symbols), levofloxacin (inverted triangles) and ciprofloxacin (circles).

[00142] **FIG. 2** is a Finlandogram plot showing the cumulative percentage of ophthalmic MRSE isolates inhibited as a function of minimum inhibitory concentration (MIC; in μg/mL) (n=95) for acorafloxacin (diamonds), besifloxacin (squares), moxifloxacin (triangles), gatifloxacin (x symbols), levofloxacin (inverted triangles) and ciprofloxacin (circles).

DETAILED DESCRIPTION

I. Definitions

[00143] Various aspects now will be described more fully hereinafter. Such aspects may, however, be embodied in many different forms and should not be construed as limited to the embodiments set forth herein; rather, these embodiments are provided so that this disclosure will be thorough and complete, and will fully convey its scope to those skilled in the art.

[00144] For convenience, certain terms employed in the specification, examples and claims are collected here. Unless defined otherwise, all technical and scientific terms used in this

disclosure have the same meanings as commonly understood by one of ordinary skill in the art to which this disclosure belongs.

[00145] Unless otherwise indicated, "a" and "an," such as in a pharmaceutically acceptable salt and a pharmaceutically acceptable excipient refers to one or more.

[00146] Reference herein to acorafloxacin includes acorafloxacin free form and/or a pharmaceutically acceptable salt thereof. Such salts include, but are not limited to, acid addition salts, such as hydrochloride, hydrobromide, sulfurate, nitrate, phosphorate, acetate, propionate, glycolate, pyruvate, oxalate, malate, malonate, succinate, maleate, fumarate, tartarate, citrate, benzoate, cinnamate, mandelate, methanesulfonate, ethanesulfonate, p-toluene-sulfonate, salicylate and the like, and base addition salts, such as sodium, potassium, calcium, magnesium, lithium, aluminum, zinc, ammonium, ethylenediamine, arginine, piperazine and the like (see, e.g., *Handbook of Pharmaceutical Salts*, P. Heinrich Stahl & Camille G. Wermuth (Eds), Verlag; *Helvetica Chimica Acta*- Zürich, 2002, 329–345; and Berge et al., *Journal of Pharmaceutical Science*, 1977, 66:1–19).

[00147] The term "therapeutically effective amount" refers to an amount that is effective, when administered to a patient in recognized need, such as human or non-human patient, to alleviate the symptoms or stop the progression of an ocular bacterial infection. In one embodiment, the therapeutically effective amount is an amount effective to alleviate the symptoms or stop the progression or cause disappearance of symptoms of an ocular bacterial infection caused at least in part by ophthalmic methicillin-resistant *Staphylococcus aureus* (MRSA) and/or ophthalmic methicillin-resistant *Staphylococcus epidermidis* (MRSE).

[00148] In another embodiment, in particular when the compounds as described herein are administered for prophylactic treatment, a therapeutically effective amount is an amount that would be effective to alleviate the symptoms or stop the progression or cause disappearance of symptoms of an ocular bacterial infection if the symptoms were to arise due to an infection that developed in a prophylactically treated subject at risk for such an infection even though said subject had not had any signs or symptoms of the infection at the time of administration of the compound.

[00149] The term "treating" or "treatment" of a disease means inhibiting the disease, i.e., arresting or reducing the progression of the disease or its clinical symptoms, or relieving the disease, i.e., causing regression or disappearance of the disease or its clinical symptoms.

[00150] In some embodiments, the treatment can be prophylactic treatment. The term "prophylactic treatment" means preventing the occurrence of a disease or condition (e.g. a bacterial infection) in a subject at risk for the disease or condition, but who has otherwise not yet manifested the disease or condition (e.g. a subject undergoing, or who had recently undergone ocular surgery).

[00151] The terms "keratitis" and "bacterial keratitis" as used herein include corneal ulcer.

[00152] "MIC" refers to minimum inhibitory concentration. The MIC value is defined as the lowest concentration of antimicrobial agent that inhibits the visible growth of a given organism. MIC_{50} and MIC_{90} values were determined as the concentration of antibiotic that inhibited growth of 50% and 90% of an organism.

[00153] A bacterium is resistant to an antibiotic if the MIC on the bacterium meets the resistant definition according to Clinical & Laboratory Standards Institute (CLSI) breakpoint. For example, a bacterium is resistant to ciprofloxacin if ciprofloxacin MIC on the bacterium is greater than or equal to 4 μg/mL.

[00154] A "corresponding method" refers to a method which is similar to the method provided herein but for administration of a different active ingredient.

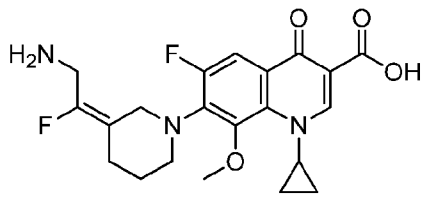
[00155] A method is "more effective than a corresponding method" if the therapeutically effective amount of the active ingredient administered in the method is less than the therapeutically effective amount of the different active ingredient administered in the corresponding method.

[00156] A "pharmaceutically acceptable excipient" means an excipient that is useful in preparing a pharmaceutical composition that is generally safe, non-toxic and neither biologically nor otherwise undesirable, and includes an excipient that is acceptable for veterinary use as well as human pharmaceutical use. "A pharmaceutically acceptable excipient" as used in the specification and claims includes both one and more than one such excipient. Exemplary pharmaceutically acceptable excipients can be pharmaceutically acceptable preservatives, surfactants, antioxidants, and stabilizers, etc.

II. **Methods of Treating Ocular Infections**

[00157] In the first aspect, a method for treating an ocular infection in a patient is provided. The method comprises administering to a patient in recognized need of treatment a therapeutically effective amount of acorafloxacin. Acorafloxacin is 7-[(3E)-3-(2-amino-l-

fluoroethylidene)-l- piperidinyl]- 1 -cyclopropyl-6-fluoro- 1 ,4-dihydro-8-methoxy-4-oxo 3-quinolinecarboxylic acid, which has a chemical structure of:



[00158] Acorafloxacin is also referred to as avarofloxacin and/or JNJ-Q2, and is a fluorinated 4-quinolone. As noted above, reference herein to 'acorafloxacin', unless otherwise indicated, includes reference to its pharmaceutically acceptable salts thereof.

[00159] In one embodiment of the treatment method, acorafloxacin is administered to the eye as a topical pharmaceutical composition comprised of acorafloxacin and a pharmaceutically acceptable excipient. Exemplary compositions, and excipients used to manufacture the compositions, are set forth below.

[00160] In studies conducted in support of the methods described herein the activity of acorafloxacin against ocular pathogens, such as methicillin resistant *S. aureus* and *S. epidermidis* (MRSA and MRSE, respectively), was determined. As will be described and shown, it was found that acorafloxacin is efficacious against ocular bacterial isolates, including ophthalmic drug resistant bacteria.

[00161] In one study, described in Example 1, the antibiotic activity of acorafloxacin against an isolate panel of ophthalmic bacteria was evaluated and compared to other fluoroquinilone compounds. The antibiotic activity of acorafloxacin was evaluated by assay for minimum inhibitory concentration (MIC) using a broth microdilution method and compared to besifloxacin, moxifloxacin, ciprofloxacin, gatifloxacin, and levofloxacin. The various test compounds were tested for antibiotic activity against 262 bacteria strains, including 80 MRSA and 95 MRSE strains, isolated from ophthalmic specimen sources collected worldwide. For comparison, antibiotic activity of the compounds was also tested against 87 MRSA isolates from skin and respiratory infections.

[00162] FIG. 1 is a Finlandogram plot showing the cumulative percentage of ophthalmic MRSA isolates inhibited as a function of minimum inhibitory concentration (in μg/mL) for acorafloxacin (diamonds), besifloxacin (squares), moxifloxacin (triangles), gatifloxacin (X symbols), levofloxacin (inverted triangles) and ciprofloxacin (circles). Acorafloxacin was more

potent against the ophthalmic MRSA isolates than the other compounds, with a 4-fold lower MIC than besifloxacin.

[00163] Table 1 is a summary of the MIC_{50} and MIC_{90} values against ophthalmic MRSA for the compounds tested. In comparison to other fluoroquinolones against MRSA, acorafloxacin was 8-fold to 32-fold more potent based on MIC_{90} values. For example, besifloxacin had a MIC_{90} of 2.0 µg/mL and acorafloxacin had an MIC_{90} of 0.25 µg/mL demonstrating that acorafloxacin was 8-fold more potent against ophthalmic MRSA bacterial isolates than besifloxacin. Gatifloxacin had a MIC_{90} of >4 µg/mL and acorafloxacin had an MIC_{90} of 0.25 µg/mL demonstrating that acorafloxacin was 32-fold more potent against ophthalmic MRSA bacterial isolates than gatifloxacin. Out of 167 MRSA strains, 61% - 93% exhibited resistance to these fluoroquinolones according to CLSI breakpoints.

Table 1: MIC Range, MIC_{50} and MIC_{90} Values of Antibiotic Agents Against Ophthalmic MRSA

Antibacterial Compound	**MIC (µg/mL)**		
	Range	**50%**	**90%**
Acorafloxacin	0.0004 - 5	0.125	0.25
Besifloxacin	0.008 - >8	0.5	2
Moxifloxacin	0.015 - >8	2	>8
Gatifloxacin	0.06 - >4	>4	>4
Ciprofloxacin	0.25 - >8	>8	>8
Levofloxacin	0.125 - >4	>4	>4

[00164] Results for the ophthalmic MRSE isolates are shown in FIG. 2. FIG. 2 is a Finlandogram plot showing the cumulative percentage of ophthalmic MRSE isolates inhibited as a function of minimum inhibitory concentration (in µg/mL) for acorafloxacin (diamonds), besifloxacin (squares), moxifloxacin (triangles), gatifloxacin (X symbols), levofloxacin (inverted triangles) and ciprofloxacin (circles). Acorafloxacin was more potent against the ophthalmic MRSE isolates than the other compounds, with an 8-fold lower MIC than besifloxacin.

[00165] Table 2 is a summary of the MIC_{50} and MIC_{90} values against ophthalmic MRSE for the compounds tested. Against MRSE isolated from ophthalmic infections, acorafloxacin demonstrated potent activity with an MIC_{90} value of 0.5 µg/mL, which is 8- to 16-fold more active *in vitro* than besifloxacin, gatifloxacin, moxifloxacin, levofloxacin, or ciprofloxacin, respectively.

Out of 95 MRSE strains, 59% - 68% exhibited resistance to these fluoroquinolones according to CLSI breakpoints.

Table 2: MIC Range, MIC_{50} and MIC_{90} Values of Antibiotic Agents Against Ophthalmic MRSE

Antibacterial Compound	MIC (µg/mL)		
	Range	50%	90%
Acorafloxacin	0.0004 – 1	0.06	0.5
besifloxacin	0.015 - >8	0.25	4
Moxifloxacin	0.015 - >4	1	>4
Gatifloxacin	0.06 - >8	>4	>4
Ciprofloxacin	0.25 - >8	>4	>8
levofloxacin	0.125 - >8	4	>8

[00166] In summary, acorafloxacin was tested in comparison to other fluoroquinilones that are currently prescribed for ophthalmic bacterial infections, such as bacterial conjunctivitis, and the MIC_{90} values of acorafloxacin were found to be 4-32 times more potent against MRSA and MRSE ophthalmic bacteria isolates. Acorafloxacin demonstrated potent *in vitro* activity against MRSA isolated from ophthalmic infections, and from skin and respiratory infections (See Example 1, below). Both MIC_{90} values were 0.25 µg/mL indicating acorafloxacin was equally active *in vitro* against MRSA from these specimen sources.

[00167] Accordingly, a method for treating a bacterial infection in the eye by locally administering acorafloxacin to the eye is provided. In one embodiment, the acorafloxacin is locally administered by topical application to an eye affected with a bacterial infection a pharmaceutical composition comprising acorafloxacin and a pharmaceutically acceptable excipient. In another embodiment, the method includes locally administering via topical application to both eyes of a patient the acorafloxacin composition, where one or both eyes are in need of treatment.

[00168] In another embodiment, the treatment is a prophylactic treatment. For example, compounds described herein (e.g. acorafloxacin) can be administered for the prophylactic treatment of infection, (e.g., at the time of, or soon after, performance of an ophthalmic surgical procedure) so as to prevent an infection from occurring (antimicrobial prophylaxis) even though the patient was not, at the time of administration of the compound or compounds, suffering from an infection, but may have been at risk of developing an infection (e.g. from bacterial contamination of the eye during the surgical procedure). The prophylaxis obtained from the

prophylactic treatments with the compounds described herein (e.g. acorafloxacin) can include, for example, primary prophylaxis (prevention of an initial infection) and eradication prophylaxis (elimination of a colonized organism to prevent the development of an infection.) See, e.g., Bratzler, D. W., et al., *American journal of health-system pharmacy* **2013**, 70 (3), 195–283.

[00169] As another example of prophylactic treatment, compounds described herein can be administered intracamerally following cataract or other types of intraocular surgery to reduce the incidence of endophthalmitis (See, e.g., Javitt, J. C., *Ophthalmology* **2016,** *123* (2), 226–231). For example, inoculation of bacteria at the time of intraocular surgery can occur with the insertion of instrumentation, e.g. during the removal of a cataract or during a glaucoma filtering procedure. Small incision cataract surgery is minimally invasive and no sutures are placed to close the corneal incision. There is the potential for bacteria to enter the eye immediately postoperatively until the corneal incision is completely sealed. Accordingly, it is contemplated that prophylactic treatment with intracameral acorafloxacin at the end of the surgical procedure can potentially reduce the incidence of bacterial endophthalmitis, a condition that can lead to pain, vision loss, and the loss of the eye. In addition, it is also contemplated that intravitreal acorafloxacin can also be used as a prophylactic strategy to prevent infection following vitrectomy procedures. In addition, it is also contemplated that subconjunctival or sub-Tenon's injections of acorafloxacin can be used at the end of intraocular surgery for prophylaxis, and lastly, it is also contemplated that topical acorafloxacin therapy can also be used alone or in conjunction with injections in the subconjunctival, intracameral or intravitreal space for prophylaxis. For example, in some embodiments, topical therapy can be done for a number of days post operatively, typically 5 to 14 days and can also be used for ocular surgeries that do not enter the anterior chamber or the vitreous, for example, pterygia surgery, excision of a conjunctival lesion, or procedures performed on the eyelid such as a chalazia incision and drainage.

[00170] Also contemplated is a method of inhibiting bacterial growth or killing a bacterium, where the bacterial growth or the bacterium to be killed is a bacterium selected from ophthalmic methicillin-resistant *Staphylococcus aureus* (MRSA) and ophthalmic methicillin-resistant *Staphylococcus epidermidis* (MRSE) comprising contacting the bacterium with acorafloxacin. In one embodiment, acorafloxacin is contacted with the bacterium in the form of a pharmaceutical composition comprising acorafloxacin and a pharmaceutically acceptable excipient.

[00171] In some embodiments, the method is more effective than a corresponding method wherein acorafloxacin is replaced with at least one fluoroquinolone selected from besifloxacin, gatifloxacin, moxifloxacin, levofloxacin and ciprofloxacin. In another embodiment, the composition administered to the patient or contacted with the bacterium is administered at a dose of acorafloxacin that is 2, 4, 6, 8, 10, 12 or 16 times less than one or more of besifloxacin, gatifloxacin, moxifloxacin, levofloxacin and ciprofloxacin.

[00172] In addition, without being bound by theory, the inventors believe that the high potency of acorafloxacin (in particular relative to other fluoroquinolone antibiotics) described herein gives it the potential to interrupt biofilm production, which in turn give it the ability to treat chronic eye infections such as blepharitis in which biofilm formation may play a role. Infections can be seen as acute or chronic. For example, acute infections include, e.g. conjunctivitis or post-operative endophthalmitis, and chronic infections include, e.g. blepharitis, in which the infection can persist for years since the eyelid produces oils via the Meibomian glands and it is possible to have a scaffold for persistent growth. In addition, bacteria form biofilms. Biofilms are thought to cause chronic infections such as with gingivitis and lately that have been linked to blepharitis.

[00173] In some embodiments, the pharmaceutical composition is in the form of a solution for ophthalmic application. In one embodiment, the solution is prepared using a physiological saline solution as a major vehicle. The pH of such ophthalmic solutions should for example be maintained from 4.5 to 8.0 with an appropriate buffer system, a neutral pH being preferred but not essential. Various buffers and means for adjusting pH may be used so long as the resulting preparation is ophthalmically acceptable. Accordingly, buffers include, but are not limited to, acetate buffers, citrate buffers, phosphate buffers and borate buffers. Acids or bases may be used to adjust the pH of these formulations as needed.

[00174] The formulations may also contain conventional, pharmaceutically acceptable preservatives, stabilizers and surfactants. Exemplary preservatives that may be used in the pharmaceutical compositions include, but are not limited to, benzalkonium chloride, chlorobutanol, thimerosal, phenylmercuric acetate and phenylmercuric nitrate. Stabilizers include, but are not limited to, polyvinyl alcohol, povidone, hydroxypropyl methyl cellulose, poloxamers, carboxymethyl cellulose, and hydroxyethyl cellulose cyclodextrin. In addition, the formulations can also be devoid of preservatives. Such formulations devoid of preservatives are said to be "preservative-free."

[00175] The ophthalmic solution preparation may also include a surfactant. Surfactants are useful to assist in dissolving an excipient or an active agent, dispersing a solid or liquid in a composition, enhancing wetting, modifying drop size, etc. Useful surfactants include, but are not limited to surfactants of the following classes: alcohols; amine oxides; block polymers; carboxylated alcohol or alkylphenol ethoxylates; carboxylic acids/fatty acids; ethoxylated alcohols; ethoxylated alkylphenols; ethoxylated aryl phenols; ethoxylated fatty acids; ethoxylated; fatty esters or oils (animal & veg.); fatty esters; fatty acid methyl ester ethoxylates; glycerol esters; glycol esters; lanolin-based derivatives; lecithin and lecithin derivatives; lignin and lignin derivatives; methyl esters; monoglycerides and derivatives; polyethylene glycols; polymeric surfactants; propoxylated and ethoxylated fatty acids, alcohols, or alkyl phenols; protein-based surfactants; sarcosine derivatives; sorbitan derivatives; sucrose and glucose esters and derivatives.

[00176] Tonicity adjustors may be added as needed or convenient. They include, but are not limited to, salts, particularly sodium chloride, potassium chloride, mannitol and glycerin, or any other suitable ophthalmically acceptable tonicity adjustor.

[00177] An ophthalmically acceptable antioxidant may be included, and examples include sodium metabisulfite, sodium thiosulfate, acetylcysteine, butylated hydroxyanisole and butylated hydroxytoluene.

[00178] Other excipient components which may be included in the ophthalmic preparations are chelating agents. An exemplary chelating agent is edetate disodium, although other chelating agents are known and suitable, alone or in combination with edetate disodium.

[00179] The composition (also referred to herein as a preparation) may comprise acorafloxacin in an amount between about 0.1% and about 1% (w/v), or between about 0.1% and about 0.2% (w/v), about 0.1% and about 0.3% (w/v), about 0.1% and about 0.4% (w/v), about 0.1% and about 0.5% (w/v), about 0.1% and about 0.5% (w/v), about 0.1% and about 0.6% (w/v), about 0.1% and about 0.7% (w/v), about 0.1% and about 0.8% (w/v), or about 0.1% and about 0.9% (w/v). The composition may also comprise acorafloxacin in an amount between about 0.1% and about 0.2% (w/v), about 0.2% and about 0.3% (w/v), about 0.3% and about 0.4% (w/v), about 0.4% and about 0.5% (w/v), about 0.5% and about 0.6% (w/v), about 0.6% and about 0.7% (w/v), about 0.7% and about 0.8% (w/v), about 0.8% and about 0.9% (w/v), about 0.9% and about 1% (w/v). Additional amounts of acorafloxacin for the compositions described herein would be identifiable to a skilled person upon a reading of the present disclosure. The

composition in one embodiment comprises an amount of acorafloxacin sufficient to provide a concentration in the aqueous humor and lacrimal fluid of the eye equal to or greater than the MIC_{90} (minimum inhibitory concentration levels to inhibit 90% growth) relative to gram-negative and gram-positive organisms commonly associated with ophthalmic infections. For example, a MIC_{90} of 0.25 μg/mL would correspond to an amount of 0.000025% (w/v) and a MIC_{90} of 0.5 μg/mL would correspond to an amount of 0.00005% (w/v). Accordingly, in some embodiments the composition may comprise acorafloxacin in an amount between about 0.000025% (w/v) to about 0.00005% (w/v), about 0.000025% (w/v) to about 0.00025% (w/v), about 0.000025% (w/v) to about 0.0025%% (w/v), about 0.000025% (w/v) to about 0.025% (w/v), about 0.000025% (w/v) to about 0.05% (w/v), about 0.000025% (w/v) to about 0.75% (w/v), about 0.000025% (w/v) to about 0.1% (w/v), about 0.000025% (w/v) to about 0.25% (w/v), about 0.00005% (w/v) to about 0.00025% (w/v), about 0.00025% (w/v) to about 0.0025%% (w/v), about 0.0025%% (w/v) to about 0.025% (w/v), about 0.025% (w/v) to about 0.05% (w/v), about 0.05% (w/v) to about 0.75% (w/v), about 0.75% (w/v) to about 0.1% (w/v), and other amounts that would provide a concentration in the aqueous humor and lacrimal fluid of the eye equal to or greater than the MIC_{90} relative to gram-negative and gram-positive organisms commonly associated with ophthalmic infections. This amount is referred to as "an antimicrobial effective concentration".

[00180] In some embodiments, when the compounds described herein (e.g. acorafloxacin) are part of a composition, the compounds are the only active ingredients which have antimicrobial activity such that would be of use for the treatment (including prophylactic treatment) or control of ocular infections (e.g. conjunctivitis, keratitis, vitritis, and endophthalmitis). The term "active ingredient" as used herein refers to a component which is responsible for the antimicrobial biological effect of composition, whereas the other components of the composition (e.g. excipients, carriers, and diluents) are not responsible for the antimicrobial biological effect of composition, even if they have other functions in the composition which are necessary or desired as part of the formulation (such as lubrication, flavoring, pH control, emulsification, and other functions other than the antimicrobial biological effect of composition as described herein). In particular, in some embodiments, compositions described herein in which the compound or compounds (e.g. acorafloxacin) are the only active

ingredient or ingredient which have antimicrobial activity are compositions in which there are no other components which would be considered to have antimicrobial activity.

[00181] The ophthalmic formulation, in another embodiment, is packaged in a form suitable for metered application, such as in a container equipped with a dropper, to facilitate application to the eye. Containers suitable for drop wise application are usually made of suitable inert, non-toxic plastic material, and generally contain between about 0.5 and about 15 ml solution. One package may contain one or more unit doses. Preservative-free solutions are often formulated in non-resealable containers containing up to about ten, such as up to about five units doses, where a typical unit dose is from one to about 8 drops, such as from one to about 3 drops. The volume of one drop usually is about 20-35 μL.

[00182] In addition, in some embodiments, various ocular delivery methods for administration to the eye are also contemplated for the compositions and/or compounds described herein. For example, ocular administration methods can include, for example, intravitreal administration, intracameral administration, and subconjunctival administration, and other ocular administration methods identifiable to a skilled person. In addition, additional administration methods such as using ocular drug delivery systems (e.g. ocular implants, intracameral implants, intravitreal implants, subconjunctival implants, sub-Tenon's implants, punctum plugs, canicular eluting implants, and ocular rings) are also envisioned for delivering the compounds and/or compositions described herein (for example, for sustained release over periods of days, weeks, or other periods recommended by a physician), as are injectable sustained-release formulations resulting in a depot, such as acorafloxacin in a PLGA-based microsphere, which can also be used in any of the intraocular compartments such as the subconjunctiva, sub-Tenon's, intracameral, and intravitreal spaces (see, e.g., Kuno *Polymers* **2011**, *3*, 193–221; US patents 9,289,413 and 9,504,653; US patent application publications 2011/0182966, 2016/0022695, and 2016/0296532; and Chee, S.-P., *Journal of Ocular Pharmacology and Therapeutics* **2012,** *28* (4), 340–349 and Tejpal, Y., et al., *J Drug Deliv. Therap.* **2013,** *3*, 114–123).

[00183] Also contemplated is a kit comprised of an ocular preparation comprising acorafloxacin and instructions for administering the preparation to the eye. The ocular preparation is, in one embodiment, provided or packaged in multidose form. In this embodiment, the preparation preferably comprises acorafloxacin and a pharmaceutically acceptable excipient. Any

of the excipients discussed herein are suitable for the ocular preparation. In one embodiment, the preparation comprises a preservative that prevents microbial contamination during use (i.e., repeated use). Suitable preservatives include benzalkonium chloride, thimerosal, chlorobutanol, methyl paraben, propyl paraben, phenylethyl alcohol, edetate disodium, ascorbic acid, ONAMER® M, PURITE® or other agents known to those skilled in the art. In ophthalmic products, typically such preservatives are employed at a level of from 0.004% to 0.02%. In addition, the preparations can also be devoid of preservatives. Such preparations devoid of preservatives are said to be "preservative-free."

[00184] The instructions for administration typically provide dosing instructions. In various embodiments, the instructions may be to administer the preparation once per day, twice per day or three times per day. In embodiments where the preparation is a liquid preparation, the administration may be to place one drop, two drops, or three drops in the infected eye or in both eyes (e.g., if one eye is infected, both eyes may be treated, or if both eyes are infected) once per day, twice per day, three times per day, or more. In embodiments where the preparation is an ointment (e.g., an oily preparation with a viscosity at room temperature that is greater than saline), the instructions may be to administer the ointment to the infected eye or in both eyes once per day, twice per day, three times per day, or more. In embodiments where the preparation is a gel (e.g., a preparation with a viscosity at room temperature that is greater than saline but less than that of an ointment), the instructions may be to administer the ointment to the infected eye or in both eyes once per day, twice per day, three times per day, or more.

[00185] In some embodiments, the ocular infection contemplated for treatment by the methods and kits described herein is bacterial conjunctivitis. In this embodiment, the method of treatment is effective to inhibit growth of one or more of *S. aureus*, *Streptococcus pneumoniae* and *Haemophilius influenza*. In one embodiment, the composition is applied to the eye two or three times per day for 5, 6, 7, 8, 9, or 10 days. In another embodiment, the methods and kits described herein are contemplated for treating bacterial blepharitis, bacterial keratitis, or bacterial endophthalmitis. In some embodiments, one or more bacterium present at the site of infection is resistant to at least one fluoroquinolone selected from besifloxacin, gatifloxacin, moxifloxacin, levofloxacin and ciprofloxacin. In some embodiments, the at least one bacterium is resistant to moxifloxacin.

[00186] Further contemplated is a method of treating an ocular infection comprising at least one bacterium, comprising:

collecting the at least one bacterium isolate from the patient,

identifying MICs for each of fluoroquinolones selected from acorafloxacin, besifloxacin, gatifloxacin, moxifloxacin, levofloxacin and ciprofloxacin on the at least one bacterium isolate, and

administering to the patient in recognized need of such treatment, a therapeutically effective amount of the fluoroquinolone having the lowest MIC. Each of the fluoroquinolone as described herein includes the free form and/or a pharmaceutically acceptable salt thereof.

[00187] In some embodiments, the at least one bacterium is selected from ophthalmic *Staphylococcus aureus* (MRSA) and ophthalmic *Staphylococcus epidermidis* (MRSE), In some embodiments, the MRSA and MRSE are methicillin-resistant. In some embodiments, the fluoroquinolone having the lowest MIC is acorafloxacin. The manner of administration can be any described herein, such as administration of the fluoroquinolone in the form of a pharmaceutical composition to the eye.

III. **Examples**

[00188] The following examples are illustrative in nature and are in no way intended to be limiting.

EXAMPLE 1

Acorafloxacin Minimum Inhibitory Concentrations for Ophthalmic Methicillin-Resistant *S. aureus* and Methicillin-Resistant *S. epidermidis*

[00189] Acorafloxacin, besifloxacin, moxifloxacin, ciprofloxacin, gatifloxacin and levofloxacin, and oxacillin were obtained from commercial vendors. All compounds tested were in free base form.

[00190] Acorafloxacin and besifloxacin stock solutions were diluted from 5 mg/mL and 3 mg/mL, respectively, in water and methanol into cation-adjusted Mueller-Hinton broth (MHB) to give a two-fold serial dilutions to cover the historical MIC data ranges (Haas, W. et al., *Clinical Ophthalmology*, 2011, 5:1359-1367). Stock solution of moxifloxacin, ciprofloxacin, gatifloxacin, levofloxacin and oxacillin were prepared according to Clinical and Laboratory Standards Institute (CLSI) guidelines (CLSI M100-S26). Two-fold serial dilutions were made in

cation-adjusted Mueller-Hinton broth (obtained from Becton, Dickinson and Company) to MIC ranges that cover CLSI breakpoints of each antibiotics against *Staphylococcus spp*.

Test System (Isolates)

[00191] Ophthalmic MRSA and MRSE isolates tested in this study were purchased from International Health Management Associates, Inc. and were from ocular infection specimens collected during 2014 to 2015 in 13 countries in the regions of North America, Latin America, Europe, and Middle East. Skin and respiratory MRSA isolates tested in this study were collected from skin and respiratory infections in United States in 2011 for Furiex Clinical Trials. Those ophthalmic MRSA and MRSE isolates were usually resistant to both Oxacillin and methicillin.

Broth Microdilution Assay

[00192] MIC determinations were performed according to CLSI guidelines (CLSI M100-S26). Cultures were streaked onto Mueller-Hinton agar (obtained from Hardy Diagnostics) from frozen stocks and incubated at 37 °C overnight. Antibiotic test plates were prepared in a 2-fold dilution series containing 10μL 10X the desired final concentration in 96-well round-bottom plates. Bacterial cell suspensions were made by picking colonies directly from the agar plate and suspending in saline. The cell density was adjusted until it reached an OD_{600} of 0.08 to 0.1 (equivalent to ~2 x 10^8 CFU/mL) as measured by a spectrophotometer. Bacterial suspensions were diluted in cation-adjusted Mueller-Hinton broth so that the final culture density in the microtiter plates was equal to 5 x 10^5 CFU/mL. Bacteria (90 μL) were then added to the microtiter plates containing antibiotic and incubated for 18 hours at 37 °C. Plates were evaluated for growth and results were recorded. The MIC was recorded as the lowest concentration where there was no visible bacterial growth.

[00193] The MIC microtitration plates were read by unaided eyes using an inverted reading mirror and by a spectrophotometer plate reader measuring the absorbance at 450 nm. The results were recorded and analyzed using Microsoft® Excel 2007service pack 2 (Microsoft Corp. Redmond, Washington). A summary of the results is presented in Tables 1-2 and FIGS. 1-2 above, and detailed results are shown in Tables 1.1-1.6 below.

Results for Ophthalmic MRSA Isolates

[00194] For 80 ophthalmic MRSA isolates, acorafloxacin MICs ranged from 0.004 to 0.5 μg/mL. The MIC_{90} of acorafloxacin was 0.25 μg/mL, which was 8 times lower than that of besifloxacin where the MIC_{90} was 2 μg/mL and the MICs ranged from 0.016 μg/mL to

≥8 μg/mL. Moxifloxacin MICs ranged from 0.03 to ≥8 μg/mL and MIC_{90} was ≥8 μg/mL. According to CLSI breakpoint (1 μg/mL are intermediate; ≥2 are resistant), 65% of the isolates were intermediate or resistant to moxifloxacin. Ciprofloxacin MICs ranged from 0.25 to ≥8 μg/mL and 70% of isolates were intermediate or resistant to ciprofloxacin according to CLSI breakpoint (2 μg/mL are intermediate; ≥4 μg/mL are resistant). Gatifloxacin MICs ranged from 0.06 to ≥4 μg/mL and 65% of the isolates were intermediate or resistant to gatifloxacin according to CLSI breakpoint (1 μg/mL are intermediate; ≥2 μg/mL are resistant). Levofloxacin MICs ranged from 0.125 to ≥4 μg/mL, and 65% of isolates were intermediate or resistant to levofloxacin according to CLSI breakpoint (4 μg/mL are intermediate; ≥8 μg/mL are resistant).

TABLE 1.1 Ophthalmic MRSA Cumulative % inhibited at MIC (μg/mL) (n=80)

	Cumulative % Inhibited at MIC (μg/mL)											
	≤0.004	**0.008**	**0.016**	**0.03**	**0.06**	**0.125**	**0.25**	**0.5**	**1**	**2**	**≥4**	**≥8**
Acorafloxacin	18.8	31.3	35.0	-	46.3	67.5	93.8	100	-	-	-	-
Besifloxacin	-	-	7.50	26.3	32.5	33.8	-	55.0	82.5	90.0	-	100
Moxifloxacin	-	-	-	6.25	25.0	28.8	32.5	35.0	36.3	53.8	100	
Ciprofloxacin	-	-	-	-	-	-	8.75	25.0	30.0	31.3	32.5	100
Gatifloxacin	-	-	-	-	11.3	28.8	30.0	32.5	33.8	38.8	100	-
Levofloxacin	-	-	-	-	-	1.25	17.5	32.5	33.8	35.0	100	-
Oxacillin	-	-	-	-	-	-	-	-	-	-	1.25	100

TABLE 1.2 *In Vitro* Activity of Acorafloxacin and Comparators Against Ophthalmic MRSA

Organism	No. of Isolates	Compound	MIC Range	MIC_{50}	MIC_{90}	S	I	R
MRSA (ophthalmic)	80	Acorafloxacin	≤0.004 - 0.5	0.125	0.25	N/A	N/A	N/A
(All Isolates)	80	Besifloxacin	0.016 - 8	0.5	2	N/A	N/A	N/A
	80	Moxifloxacin	0.03 - ≥8	2	≥8	35%	1%	64%
	80	Ciprofloxacin	0.25 - ≥8	≥8	≥8	30%	1%	69%
	80	Gatifloxacin	0.06 - ≥4	≥4	≥4	33%	1%	64%
	80	Levofloxacin	0.125 - ≥4	≥4	≥4	35%	65%	
MRSA (ophthalmic)	51	Acorafloxacin	0.06 - 0.5	0.125	0.25	N/A	N/A	N/A
(Moxifloxacin ≥2 µg/mL)	51	Besifloxacin	0.5 - 8	1	8	N/A	N/A	N/A
	51	Moxifloxacin	2 - ≥4	4	>4			100%
	51	Ciprofloxacin	8 - >8	>8	>8			100%
	51	Gatifloxacin	2 - ≥4	4	>4			100%
	51	Levofloxacin	4 - >4	>4	>4		100%	
MRSA (ophthalmic)	55	Acorafloxacin	0.016 - 0.5	0.125	0.25	N/A	N/A	N/A
(Ciprofloxacin≥4 µg/mL)	55	Besifloxacin	0.06 - 8	1	8	N/A	N/A	N/A
	55	Moxifloxacin	0.25 - >4	4	>4	6%	2%	93%
	55	Ciprofloxacin	4 - >8	>8	>8			100%
	55	Gatifloxacin	0.5 - >4	4	>4	2%	2%	96%
	55	Levofloxacin	0.5 - >4	>4	>4	5.6%	94.4%	
MRSA (ophthalmic)	53	Acorafloxacin	0.016 - 0.5	0.125	0.25	N/A	N/A	N/A
(Gatifloxacin>2 µg/mL)	53	Besifloxacin	0.5 - 8	1	8	N/A	N/A	N/A
	53	Moxifloxacin	0.5 - >4	4	>4	2%	2%	96.2%
	53	Ciprofloxacin	8 - >8	>8	>8			100%
	53	Gatifloxacin	2 - >4	4	>4			100%
	53	Levofloxacin	2 - >4	>4	>4			100%
MRSA (ophthalmic)	40	Acorafloxacin	0.125 - 0.5	0.25	0.5	N/A	N/A	N/A
(Levofloxacin>4 µg/mL Intermediate)	40	Besifloxacin	0.5 - 8	1	8	N/A	N/A	N/A
	40	Moxifloxacin	2 - >4	4	>4			100%
	40	Ciprofloxacin	>8	>8	>8			100%
	40	Gatifloxacin	4 - >4	4	>4			100%
	40	Levofloxacin	>4	>4	>4		100%	

Results for Ophthalmic MRSE Isolates

[00195] For 95 ophthalmic MRSE isolates, acorafloxacin MICs ranged from 0.004 to 1 µg/mL. The MIC_{90} of acorafloxacin was 0.5 µg/mL, which was eight times lower than that of besifloxacin where the MIC_{90} was ≥4µg/mL and the MICs ranged from 0.016 to ≥8 µg/mL. Moxifloxacin MICs ranged from 0.03 to ≥4 µg/mL and 56% of the isolates were intermediate or resistant to moxifloxacin according to CLSI breakpoint (1 µg/mL are intermediate; >2 are resistant). Ciprofloxacin MICs ranged from 0.125 to >8 µg/mL and 63% of isolates were intermediate or resistant to ciprofloxacin according to CLSI breakpoint (2 µg/mL are intermediate; >4 µg/mL are resistant). Gatifloxacin MICs ranged from 0.06 to ≥4 µg/mL and 61% of the isolates were intermediate or resistant to gatifloxacin according to CLSI breakpoint (1 µg/mL are intermediate; >2 µg/mL are resistant). Levofloxacin MICs ranged from 0.125 to ≥4 µg/mL, and 61% of isolates were intermediate or resistant to levofloxacin according to CLSI breakpoint (4 µg/mL are intermediate; >8 are resistant).

TABLE 1.3 Ophthalmic MRSE Cumulative % inhibited at MIC (µg/mL) (n=95)

	Cumulative % Inhibited at MIC (µg/mL)											
	≤0.004	**0.008**	**0.016**	**0.03**	**0.06**	**0.125**	**0.25**	**0.5**	**1**	**2**	**≥4**	**≥8**
Acorafloxacin	25.3	37.9	41.1	43.2	71.6	81.1	83.2	91.6	100	-	-	-
Besifloxacin	-	-	7.4	30.5	36.8	38.9	54.7	70.5	80.0	85.3	96.8	100
Moxifloxacin	-	-	-	10.5	33.7	37.9	40.0	44.2	60.0	74.7	100	
Ciprofloxacin	-	-	-	-	-	17.9	34.7	36.8	-	40.0	53.7	100
Gatifloxacin	-	-	-	-	6.30	31.6	37.9	38.9	42.1	71.6	100	-
Levofloxacin	-	-	-	-	-	17.9	33.7	38.9	-	-	100	-
Oxacillin	-	-	-	-	-	-	-	2.11	6.32	23.2	36.8	100

TABLE 1.4 *In Vitro* Activity of Acorafloxacin and Comparators Against Ophthalmic MRSE

Organism	No. of Isolates	Compound	MIC Range	MIC_{50}	MIC_{90}	S	I	R
MRSE (ophthalmic)	95	Acorafloxacin	≤0.004 - 1	0.06	0.5	N/A	N/A	N/A
(All Isolates)	95	Besifloxacin	0.016 - 8	0.25	4	N/A	N/A	N/A
	95	Moxifloxacin	0.03 - ≥4	1	≥4	44%	16%	40%
	95	Ciprofloxacin	0.125 - ≥8	≥4	≥8	37%	3%	60%
	95	Gatifloxacin	0.06 - ≥4	2	≥4	39%	3%	58%
	95	Levofloxacin	0.125 - ≥4	4	>4	39%	61%	
MRSE (ophthalmic)	38	Acorafloxacin	0.06 - 1	0.5	1	N/A	N/A	N/A
(Moxifloxacin ≥2 µg/mL)	38	Besifloxacin	0.5 - 8	1	4	N/A	N/A	N/A
	38	Moxifloxacin	2 ->4	4	>4			100%
	38	Ciprofloxacin	8 - >8	>8	>8			100%
	38	Gatifloxacin	2 ->4	4	>4			100%
	38	Levofloxacin	>4	>4	>4			100%
MRSE (ophthalmic)	57	Acorafloxacin	0.016 - 1	0.06	1	N/A	N/A	N/A
(Ciprofloxacin≥4 µg/mL)	57	Besifloxacin	0.25 - 8	1	4	N/A	N/A	N/A
	57	Moxifloxacin	0.5 - >4	2	>4	7%	26%	67%
	57	Ciprofloxacin	4 - >8	>8	>8			100%
	57	Gatifloxacin	1 - >4	2	>4		4%	96%
	57	Levofloxacin	4 - >4	>4	>4		100%	
MRSE (ophthalmic)	55	Acorafloxacin	0.03 - 1	0.06	1	N/A	N/A	N/A
(Gatifloxacin>2 µg/mL)	55	Besifloxacin	0.25 - 8	1	4	N/A	N/A	N/A
	55	Moxifloxacin	0.5 - >4	2	>4	4%	27%	69%
	55	Ciprofloxacin	4 - >8	>8	>8			100%
	55	Gatifloxacin	2 - >4	2	>4			100%
	55	Levofloxacin	4 - >4	>4	>4		100%	
MRSE (ophthalmic)	39	Acorafloxacin	0.06 - 1	0.125	1	N/A	N/A	N/A
(Levofloxacin>4 µg/mL Intermediate)	39	Besifloxacin	0.5 - 8	1	4	N/A	N/A	N/A
	39	Moxifloxacin	1 - >4	4	>4		3%	97%
	39	Ciprofloxacin	8 - >8	>8	>8			100%
	39	Gatifloxacin	2 - >4	4	>4			100%
	39	Levofloxacin	>4	>4	>4			100%

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Results for Skin and Respiratory MRSA Isolates

[00196] For 87 skin and respiratory MRSA isolates, the MICs of acorafloxacin ranged from 0.06 to 1 μg/mL. The MIC_{90} of acorafloxacin was 0.25 μg/mL, which was 4 times lower than that of besifloxacin where the MIC_{90} was 1 μg/mL and the MICs ranged from 0.5 μg/mL to ≥8 μg/mL. Moxifloxacin MICs ranged from 1 to >4 μg/mL and 90% of the isolates were intermediate or resistant to moxifloxacin according to CLSI breakpoint (1 μg/mL are intermediate; >2 are resistant). Ciprofloxacin MICs were ≥8 μg/mL and 100% of isolates were intermediate or resistant to ciprofloxacin according to CLSI breakpoint (2 μg/mL are intermediate; >4 are resistant). Gatifloxacin MICs ranged from 2 to ≥4 μg/mL and 100% of the isolates were resistant to gatifloxacin according to CLSI breakpoint (1 μg/mL are intermediate; >2 are resistant). Levofloxacin MICs were ≥4 μg/mL, and 100% of the isolates were intermediate or resistant to levofloxacin according to CLSI breakpoint (4 μg/mL are intermediate; >8 are resistant).

TABLE 1.5 Skin and Respiratory MRSA Cumulative % inhibited at MIC (μg/mL) (n=87)

	Cumulative % Inhibited at MIC (μg/mL)											
	≤0.004	**0.008**	**0.016**	**0.03**	**0.06**	**0.125**	**0.25**	**0.5**	**1**	**2**	**≥4**	**≥8**
Acorafloxacin	-	-	-	-	5.75	86.2	92.0	98.9	100	-	-	-
Besifloxacin	-	-	-	-	-	-	-	86.2	94.3	96.6	97.7	100
Moxifloxacin	-	-	-	-	-	-	-	-	2.3	75.9	100	-
Ciprofloxacin	-	-	-	-	-	-	-	-	-	-	-	100
Gatifloxacin	-	-	-	-	-	-	-	-	-	13.8	100	-
Levofloxacin	-	-	-	-	-	-	-	-	-	-	100	-
Oxacillin	-	-	-	-	-	-	-	-	-	-	3.4	100

TABLE 1.6 *In Vitro* Activity of Acorafloxacin and Comparators Against Skin & Respiratory MRSA

Organism	No. of Isolates	Compound	MIC Range	MIC_{50}	MIC_{90}	S	I	R
MRSA (skin & Respiratory)	87	Acorafloxacin	0.06 - 1	0.125	0.25	N/A	N/A	N/A
(All Isolates)	87	Besifloxacin	0.5 - 8	0.5	1	N/A	N/A	N/A
	87	Moxifloxacin	1 - >4	2	4	-	2%	88%
	87	Ciprofloxacin	8 - >8	>8	>8			100%
	87	Gatifloxacin	2 - >4	4	>4	-	-	100%
	87	Levofloxacin	4 - >4	>4	>4		100%	
MRSA (skin & Respiratory)	85	Acorafloxacin	0.06 - 1	0.125	0.25	N/A	N/A	N/A
(Moxifloxacin ≥2 µg/mL)	85	Besifloxacin	0.5 - 8	0.5	1	N/A	N/A	N/A
	85	Moxifloxacin	2 - >4	2	4			100%
	85	Ciprofloxacin	8 - >8	>8	>8			100%
	85	Gatifloxacin	2 - >4	4	>4			100%
	85	Levofloxacin	4 - >4	>4	>4		100%	
MRSA (skin & Respiratory)	87	Acorafloxacin	0.06 - 1	0.125	0.25	N/A	N/A	N/A
(Ciprofloxacin≥4 µg/mL)	87	Besifloxacin	0.5 - 8	0.5	1	N/A	N/A	N/A
	87	Moxifloxacin	2 > 4	2	4		2%	98%
	87	Ciprofloxacin	8 - >8	>8	>8			100%
	87	Gatifloxacin	2 - >4	>4	>4			100%
	87	Levofloxacin	4 - >4	4	>4		100%	
MRSA (skin & Respiratory)	87	Acorafloxacin	0.06 - 1	0.125	0.25	N/A	N/A	N/A
(Gatifloxacin>2 µg/mL)	87	Besifloxacin	0.5 - 8	0.5	1	N/A	N/A	N/A
	87	Moxifloxacin	1 - >4	2	4		2%	98%
	87	Ciprofloxacin	8 - >8	>8	>8			100%
	87	Gatifloxacin	2 - >4	>4	>4			100%
	87	Levofloxacin	4 - >4	4	>4		100%	
MRSA (skin & Respiratory)	84	Acorafloxacin	0.06 - 1	0.125	0.5	N/A	N/A	N/A
(Levofloxacin>4 µg/mL Intermediate)	84	Besifloxacin	0.5 - 8	0.5	1	N/A	N/A	N/A
	84	Moxifloxacin	1 - >4	2	4			100%
	84	Ciprofloxacin	8 - >8	>8	>8			100%
	84	Gatifloxacin	2 - >4	4	>4			100%
	84	Levofloxacin	4 - >4	>4	>4		100%	

EXAMPLE 2

MIC Comparison of Acorafloxacin (ACOR) and Moxifloxacin (MOX) against ocular bacterial pathogens

Overview

[00197] The Minimum Inhibitory Concentrations (MICs) of acorafloxacin (ACOR) to moxifloxacin was compared for a number of bacteria isolated from patients with conjunctivitis patients based on incidence. A select number of bacteria isolated from patients with keratitis and endophthalmitis were also tested.

Experimental Design

[00198] MICs were determined for the ocular bacterial isolates using the recommended Clinical and Laboratory Standards Institute (CLSI) protocols and methodology. All antibacterials were tested with eleven 2-fold dilutions from 32 to 0.03125 µg/ml. All testing was performed in fresh Mueller-Hinton medium except for Streptococcus species (3% lysed horse red blood cells were added to the Mueller-Hinton medium) and Haemophilus species (fresh Haemophilus Test Medium (remel)).

[00199] After 24 h of incubation, all plates were examined for positive growth in comparison with the control. The lowest antibacterial dilution that demonstrated no growth was deemed the MIC for that specific isolate. The data were placed in a Minitab file for MIC50, MIC90, and range calculations.

[00200] The isolates used in the study were based on the incidence of bacteria isolated from conjunctivitis as determined from our clinical Ophthalmic Microbiology laboratory. Based on percent incidence, *Staphylococcus aureus* (SA) (n = 36); coagulase-negative Staphylococcus (CNS) (14); *Streptococcus pneumoniae* (22); other Gram-positive bacteria (8) (2 *Streptococcus viridans* group, 4 beta-hemolytic *Streptococcus* species, and 2 non-hemolytic *Streptococcus* species); *Haemophilus* species (20), and other Gram-negative bacteria (10) (2 *Serratia marcescens*, 2 *Proteus mirabilis*, 3 *Pseudomonas aeruginosa*, 1 *Enterobacter aerogenes*, 1 *Pseudomonas fluorescens*, and 1 *Klebsiella species*) were tested for MIC susceptibilities using CLSI broth dilution methodology.

[00201] In addition, 26 *Pseudomonas aeruginosa* isolated from keratitis (20 FQ-susceptible and 6 FQ-resistant); 10 methicillin-resistant *Staphylococcus aureus* (MRSA) and 10 methicillin-susceptible *Staphylococcus aureus* (MSSA) isolated from endophthalmitis; and 10 methicillin-resistant coagulase-negative *Staphylococcus* (MRCNS) and 10 methicillin-susceptible coagulase-negative *Staphylococcus* (MSCNS) isolated from endophthalmitis, were also tested.

[00202] All bacterial isolates were collected and stored at –80°C from patients at the Charles T. Campbell Ophthalmic Microbiology Laboratory. These isolates are part of a clinical bank of bacterial isolates that are de-identified and stored for antibiotic validation testing of new anti-infectives.

[00203] The bacterial isolates used are the same as those used in a previous study (Romanowski EG et al., The *in vitro* evaluation of tigecycline and the *in vivo* evaluation of RPX-978 (0.5% tigecycline) as an ocular antibiotic. *J Oc Pharm Ther*. 2016;32(2):119-126).

Data Analysis

[00204] Descriptive statistics were calculated from the MIC data. The median MIC, MIC_{50} (concentration that inhibits the growth of 50% of the tested bacterial isolates), MIC_{90} (concentration that inhibits the growth of 90% of the tested bacterial isolates), and the range of MICs were determined. The data for each bacterial group was analyzed statistically using the non-parametric Mann-Whitney Test (Minitab, State College, PA). The results are shown in table 3 below.

Table 3. MIC[1] Comparison of Acorafloxacin (ACOR) and Moxifloxacin (MOX) against bacterial isolates (FQ refers to Fluoroquinolone)

Bacteria[2]	FQ[3]	Median[4]	MIC_{50}[5]	MIC_{90}[6]	Range[7]	Mann-Whitney[8]
Staphylococcus aureus Conjunctivitis (N=36)	MOX	1.0	1.0	4.0	0.03-16	p=0.0002
	ACOR	0.12	0.12	0.25	0.007-0.5	ACOR < MOX
Streptococcus pneumoniae Conjunctivitis (N=22)	MOX	0.12	0.12	0.25	0.06-0.5	p=0.00001
	ACOR	0.007	0.007	0.03	0.007-0.06	ACOR < MOX
Coagulase negative Staph (CNS) Conjunctivitis (N=14)	MOX	4.0	4.0	32	0.06-32	p=0.003
	ACOR	0.25	0.25	1.0	0.007-1.0	ACOR < MOX
Other Gram-positives Conjunctivitis (N=8)	MOX	0.25	0.25	0.25	0.12-4.0	p=0.001
	ACOR	0.007	0.007	0.03	0.007-0.12	ACOR < MOX
Haemophilus sp. Conjuctivitis (N=20)	MOX	0.045	0.03	0.12	0.007-4.0	p=0.005
	ACOR	0.0185	0.007	0.06	0.007-0.25	ACOR < MOX
Other Gram-negatives Conjunctivitis (N=10)	MOX	0.65	0.5	4.0	0.03-8	p=0.07
	ACOR	0.12	0.12	0.5	0.03-2.0	ACOR = MOX
Pseudomonas aeruginosa Keratitis (N=26)	MOX	1	1	32	0.5-32	p=0.009
	ACOR	0.5	0.5	16	0.25-32	ACOR < MOX
Pseudomonas aeruginosa Keratitis (N=20) (minus 6 FQ resistant isolates)	MOX	1	1	2	0.5-4.0	p=0.005
	ACOR	0.5	0.5	1	0.25-2.0	ACOR < MOX
MR(CNS) Endophthalmitis (N=10)	MOX	2	2	32	0.12-32	p=0.02
	ACOR	0.25	0.25	2	0.03-8.0	ACOR < MOX
MS(CNS) Endophthalmitis (N=10)	MOX	1.5	1	32	0.06-32	p=0.17
	ACOR	0.38	0.25	16	0.007-16	ACOR = MOX
MRSA Endophthalmitis (N=10)	MOX	2	2	8	0.06-8.0	p=0.002
	ACOR	0.12	0.12	0.25	0.007-0.5	ACOR < MOX
MSSA Endophthalmitis (N=10)	MOX	2	2	4	0.03-8.0	p=0.002
	ACOR	0.12	0.12	0.25	0.007-0.25	ACOR < MOX

Table footnotes:

1 - **MICs** - The minimum inhibitory concentrations were determined by the CLSI broth dilution method in a 96 well round bottom plate. Eleven 2-fold serial dilutions were tested from16 µg/ml to 0.015 µg/ml. The MIC is

the lowest concentration that inhibits growth denoted by no turbidity or a pellet compared to the positive control (no antibiotic). Growth in the 16 μg/ml well was denoted as 32 μg/ml and the lack of growth in the 0.015 μg/ml was denoted as 0.007 μg/ml. This was necessary to determine descriptive statistics and statistical comparison. The concentration of moxifloxacin in the assay was confirmed by comparing the MICs to a range of MICs predetermined to the following ATTC isolates: *Staphylococcus aureus* 29212, *Enterococcus faecalis* 29212, *Escherichia coli* 25922, and *Pseudomonas aeruginosa* 27853. There were no MIC ranges for the ATCC isolates to confirm the concentration of acorafloxacin.

2 - Bacteria - All of the bacteria were isolated from clinical cases of conjunctivitis, keratitis, and endophthalmitis. The conjunctivitis isolates (SA, CNS, *St. pneumoniae*, *Haemophilus sp.*, other Gram-positives and other Gram-negatives) were based on the incidence of occurrence from a University of Pittsburg laboratory and chosen consecutively over a time period. The *Pseudomonas aeruginosa* isolated from keratitis were also consecutive isolates except for six that were chosen for fluoroquinolone resistance. The six FQ resistant *Pseudomonas aeruginosa* isolates were obtained from Dr. David Ritterband (New York Eye & Ear Infirmary). The MRSA and MSSA were isolated from endophthalmitis based on methicillin resistance (MR) and susceptibility (MS).

3 - FQ - Fluoroquinolone - Moxifloxacin (MOX) was compared to an experimental fluoroquinolone (acorafloxacin).

4 - Median - The MICs for each bacterial group was sorted from the lowest MIC to the highest MIC. The MIC in the middle of the set was determined to be the median.

5 - MIC_{50} - The MIC at the 50% rank was determined to be the MIC_{50}. The MIC_{50} and the median are often the same but can be different with even number of values. This is the concentration that inhibits the growth of 50% of the tested bacterial isolates.

6 - MIC_{90} - The MIC at the 90% rank was determined to be the MIC_{90}. This is the concentration that inhibits the growth of 50% of the tested bacterial isolates.

7 - Range - The range is the lowest MIC and the highest MIC.

8 - Mann-Whitney - In general, the MICs of different classes of antibiotics (anti-infectives) cannot be statistically compared. For fluoroquinolones, similar chemical structures and tissue penetrations are assumed which could provide similar values of susceptibility interpretation. MICs are discrete values and are interpreted with non-parametric statistical analysis. MOX and acorafloxacin MICs were comparedusing the Mann-Whitney non-parametric analysis of two sample groups for discrete values.

[00205] As can be seen from Table 3, the MICs for many of bacterial group for acorafloxacin were significantly lower than the MICs to moxifloxacin, including isolates that are resistant to moxifloxacin using Clinical and Laboratory Standards Institute (CLSI) breakpoints. This demonstrates the increased potency of acorafloxacin as a lower dose of acorafloxacin is required to inhibit the same concentration of bacteria than moxifloxacin.

Table 4 Comparison of selected MIC_{90} values for acorafloxacin and moxifloxacin in MRSA ocular isolates to selected literature values for various antibiotics MIC_{90} values in ocular and non-ocular isolates

	Bacteria	Acorafloxacin	Cefuroxime (ESCRS)	Vancomycin	Besifloxacin	Moxifloxacin
Gram positive	MRSA	0.25	128	1	4	8
	MRSE	0.25	> 32	2	4	4
	MSSA	0.015	2	2	0.25	0.25
	MSSE	0.015	2	2	0.06	0.12
	Streptococcus Pneumonia	0.12	0.25	0.5	0.125	0.25
Gram negative	H Influenzae	0.015	2	>32	0.06	0.03
	Enterobacter	0.12 (cloacae) 0.25 (Aerogenes)	>32	>32	2 (cloacae) 8 (Aerogenes)	0.12 (cloacae) 0.25 (Aerogenes)
	Klebsiella	0.25	16	>32	1-4	0.25
	P Aeruginosa	2	>32	>32	4	4
	Serratia marcesens	1	16	>32	1	1

[00206] Additionally, selected MIC_{90} values for acorafloxacin and moxifloxacin from this example were compared to selected literature values for other antibiotics. In particular, in table 4 above, the MIC_{90} values for acorafloxacin and moxifloxacin in the ophthalmic isolates of MRSA of this example are compared to selected literature MIC_{90} values of various antibiotics in ocular (for certain besifloxacin values) and non-ocular (for certain besifloxacin values and for cefuroxime and vancomycin values, as well as for non-MRSA acorafloxacin and moxifloxacin values) isolates of selected bacteria including some associated with ophthalmic infections (see, e.g., Morrow, B. J. et al., *Antimicrobial agents and chemotherapy* **2010,** *54* (5), 1955-1964; www page antimicrobe.org/b237tabrev.htm; US Pat. 8,415,342; and Haas, W., et al. *Antimicrobial agents and chemotherapy* **2009,** *53* (8), 3552-3560.)

[00207] As can be seen from Table 4, the MICs for many of bacterial groups for acorafloxacin were significantly lower than the MICs of moxifloxacin and besifloxacin, as well as other antibiotics.

EXAMPLE 3

Tolerability of intracameral injection of acorafloxacin in dogs

[00208] The tolerability of acorafloxacin when injected into the eye was evaluated in 3 research beagle dogs.

[00209] **Methods:** Under anesthesia, 250µg of acorafloxacin in 50µl was injected intracamerally in the right eye and vehicle injected intracamerally in the left eye. Gross ocular and Slit lamp Examinations were performed at Baseline, 5 min, 24 and 48 h.

[00210] **Results:** Slit lamp shows no particle formation post-injection, no AC cells or flare in all 3 dogs at each timepoint post-injection. Gross ocular shows trace to 1+ conjunctival hyperemia equal in both eyes, typical of what is observed with injection procedures, and less overall by 48 hours. No adverse effects observed.

[00211] **Summary:** An acorafloxacin intracameral injectable solution appears well-tolerated in this pilot study in dogs. This is surprising given the fact that the fifth generation fluoroquinolone antibiotics have often been associated with adverse effects (See Michelle Stephenson at the www page reviewofophthalmology.com/article/fluoroquinolones-the-last-generation) and none were observed in this study.

EXAMPLE 4

One-Month Ocular Toxicity Study in Rabbits

[00212] New Zealand white (NZW) rabbits (n = 7/sex/group) were given one drop of 0.5% acorafloxacin topical ophthalmic suspension (ATOS) or vehicle via topical ophthalmic administration in the left eye 8 times daily (approximately 1 hour apart) for 3 days followed by 4 times daily (approximately 2 hours apart) for 25 days (dose levels of 1.4 and 0.7 mg/day, respectively). Rabbits were sacrificed at the end of dosing (5/sex/group) or after a 14-day recovery period (2/sex/group). The following parameters and end points were evaluated: clinical signs (cage side, detailed and veterinary examinations), body weights, food consumption, ophthalmology, tonometry, gross ocular examinations for irritation (redness, swelling, and discharge), corneal sensitivity, clinical pathology parameters (hematology, and clinical chemistry), toxicokinetic parameters, organ weights, and gross and microscopic pathology.

[00213] There were no acorafloxacin-related findings in any of the parameters evaluated. In particular, there were no deaths and no acorafloxacin-related clinical signs or effects on body weights, body weight gains or food consumption. There were no treatment-related ophthalmology findings and there were no effects on intraocular pressure, gross ocular observations for irritation (redness, swelling, discharge), and corneal sensitivity. There were no acorafloxacin-related differences in hematology, or clinical biochemistry parameters; no acorafloxacin-related changes in organ weights or macroscopic or microscopic observations.

[00214] In conclusion, Administration of 0.5% ATOS by topical ophthalmic administration 8 times daily for 3 days followed by 4 times daily for 25 days (dose levels of 1.4 and 0.7 mg/day, respectively) was clinically well-tolerated in rabbits, despite the fact that the fifth generation fluoroquinolone antibiotics have often been associated with adverse effects.

[00215] Furthermore, based on the results in this example, the no observable adverse effect level (NOAEL) in rabbits was considered to be 1.4 (3 days)/0.7 (25 days) mg/day acorafloxacin 0.5%. At 1.4 mg/day on day 1 (8 times daily) for males and females, the C_{max} was 0.00628 ± 0.00143 μg/mL and 0.0161 ± 0.00386 μg/mL and $AUC_{0\text{-}24hr}$ values at day 1 were and 0.0139 ± 0.000931 μg•hr/mL and 0.0450 ± 0.0189 μg•hr/mL, respectively. At 0.7 mg/day on day 28 (4 times daily) for males and females, the C_{max} was 0.00254 ± 0.000187 μg/mL and 0.00197 ± 0.000747 μg/mL and $AUC_{0\text{-}24hr}$ was 0.00776 ± 0.000588 μg•hr/mL and 0.00529 ± 0.00136 μg•hr/mL, respectively.

EXAMPLE 5

1-Month Ocular Toxicity Study in Dogs

[00216] Beagle dogs (n = 5/sex/group) were given one drop of 0.5% acorafloxacin topical ophthalmic suspension (ATOS) or vehicle via topical ophthalmic administration in the left eye 8 times daily (approximately 1 hour apart) for 3 days followed by 4 times daily (approximately 2 hours apart) for 25 days (dose levels of 1.4 and 0.7 mg/day, respectively). Dogs were sacrificed at the end of dosing (3/sex/group) or after a 14-day recovery period (2/sex/group). The following parameters and end points were evaluated: clinical signs, body weights, food consumption, ophthalmology, tonometry, gross ocular examinations, corneal sensitivity, electroretinography, fluorescein angiography, clinical pathology parameters (hematology, coagulation, clinical chemistry, and urinalysis), toxicokinetic parameters, organ weights, and gross and microscopic pathology.

[00217] There were no acorafloxacin-related findings in any of the parameters evaluated. In particular, there were no deaths and no treatment-related clinical signs. There were no treatment-related effects on body weights, body weight gains or food consumption. There were no treatment-related ophthalmology findings and there were no effects on intraocular pressure, corneal sensitivity, electroretinography or fluorescein angiography. There were no acorafloxacin-related differences in hematology, coagulation, clinical biochemistry or urinalysis parameters. There were also no acorafloxacin-related changes in organ weights or acorafloxacin-related macroscopic or microscopic observations.

[00218] In summary, Administration of 0.5% ATOS by topical ophthalmic administration 8 times daily for 3 days followed by 4 times daily for 25 days (dose levels of 1.4 and 0.7 mg/day, respectively) was clinically well-tolerated in dogs, despite the fact that the fifth generation fluoroquinolone antibiotics have often been associated with adverse effects.

[00219] Furthermore, based on the results in this example, the no observable adverse effect level (NOAEL)in dogs was considered to be 1.4 (3 days)/0.7 (25 days) mg/day 0.5% ATOS. At 1.4 mg/day on Day 1 (8 times daily) for males and females, the C_{max} was 0.00249 ± 0.00132 and 0.00237 ± 0.000567 µg/mL and $AUC_{0\text{-}24hr}$ was 0.00936 ± 0.00372 and 0.00982 ± 0.00188 µg•hr/mL, respectively. At 0.7 mg/day on Day 28 (4 times daily) for males and females, the C_{max} was 0.00135 ± 0.000241 and 0.00230 ± 0.000761 µg/mL and $AUC_{0\text{-}24hr}$ was 0.00428 ± 0.000865 and 0.00694 ± 0.000172 µg•hr/mL, respectively.

EXAMPLE 6

Treatment of bacterial conjunctivitis

[00220] A 36-year old male patient presents to the ophthalmologist with sore, red eyes and a yellowish mucopurulent discharge. The patient indicated the condition began in the left eye but spread to both eyes and had not resolved in over four days. After making a differential diagnosis, the ophthalmologist determines that the condition is bacterial conjunctivitis. The patient is instructed to administer moxifloxacin to his eyes daily in accordance with the package insert of the medication. However, the patient's condition does not improve even after four days of administering the moxifloxacin and the ophthalmologist suspects a resistant strain of bacteria, likely a gram positive, is infecting the eye. The patient is then instructed to discontinue the moxifloxacin administration and instead administer acorafloxacin eye drops to his eyes daily according to the package insert of the medication. After about three days of administering the eye drops daily, the signs and symptoms have rapidly subsided and the bacterial conjunctivitis is determined to have been resolved upon a follow up visit to the ophthalmologist.

EXAMPLE 7

Treatment of bacterial keratitis

[00221] A 28-year old female contact lens wearer presents complaining of ocular pain, eye redness, and decreased vison. The patient reports that she has been spending large amounts of time working on a project at her work and as a result has been keeping her contact lenses in her eyes for prolonged periods of time and has not been able to be diligent in properly cleaning and replacing the lenses. The physician finds corneal infiltrate upon slit lamp examinations and diagnoses the patient as suffering from bacterial keratitis. The patient is instructed to administer moxifloxacin to her eyes daily in accordance with the package insert of the medication and refrain from wearing contact lenses for the time being. However, despite the administration of the moxifloxacin eye drops, the infection still persists after about 4 days and the ophthalmologist suspects a resistant strain of bacteria, likely a gram negative since the patient is wearing contact lenses. The patient is then instructed to discontinue the moxifloxacin administration and instead administer acorafloxacin eye drops to her eyes daily according to the package insert of the medication. After about 4 days of administering the acorafloxacin eye drops, the patient's

symptoms have significantly subsided, and by a follow-up visit 10 days later, the infection appears to have resolved almost completely.

EXAMPLE 8

Prophylactic use

[00222] A 68-year old female with prior diagnosis of cataracts complains that her vison has steadily declined over the last year to the point of interfering with her daily activities thus impacting her quality of life. Her ophthalmologist recommends that she consider cataract surgery in which her clouded lens is removed and replaced with an artificial lens, which she agrees to undergo. The case is referred to a surgeon, who is concerned that the patient might develop an infection leading to endophthalmitis as a result of the surgery since cataract surgery (and other ophthalmic surgical procedures) can in some cases put a patient at risk for ophthalmic infections such as endophthalmitis due to inadvertent bacterial contamination of the eye during the surgery. Thus, at the conclusion of the cataract surgery, the surgeon injects a solution comprising acorafloxacin into the anterior chamber of the surgically treated eye (i.e. intracameral injection) as a prophylactic measure against endophthalmitis. Upon several follow up visits, patient displays no signs or symptoms of endophthalmitis (or other ocular infections), and goes on to have a positive outcome from the surgery in the form of significantly restored vision in the treated eye.

[00223] Throughout this specification reference is made to publications such as US and foreign patent applications, journal articles, book chapters, and others. All such publications are expressly incorporated by reference in their entirety, including supplemental/supporting information sections published with the corresponding references, for all purposes unless otherwise indicated.

[00224] While a number of exemplary aspects and embodiments have been discussed above, those of skill in the art will recognize certain modifications, permutations, additions and sub-combinations thereof. It is therefore intended that the following appended claims and claims hereafter introduced are interpreted to include all such modifications, permutations, additions and sub-combinations as are within their true spirit and scope.

WHAT IS CLAIMED IS:

1. A method for treating an ocular bacterial infection in a patient in recognized need of such treatment, comprising:

administering to the patient in recognized need of treatment a therapeutically effective amount of acorafloxacin, or a pharmaceutically acceptable salt thereof.

2. The method of claim 1, wherein acorafloxacin, or a pharmaceutically acceptable salt thereof, is administered as a pharmaceutical composition comprising acorafloxacin, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable excipient.

3. The method of claim 2, wherein the pharmaceutical composition is a solution or a suspension.

4. The method of claim 2, wherein the pharmaceutical composition is an ointment or a gel.

5. The method of any one of claims 3 or 4, wherein the pharmaceutical composition comprises a preservative.

6. The method of any one of claims 3 or 4, wherein the pharmaceutical composition is preservative-free.

7. The method of claim 2, wherein the pharmaceutical composition is an ocular implant, intracameral implant, intravitreal implant, subconjunctival implant, sub-Tenon's implant, punctum plug, canicular eluting implant, or ocular ring.

8. The method of claim 2, wherein the pharmaceutical composition is a microsphere.

9. The method of any one of claims 1 to 8, wherein administering comprises locally administering to an eye of the patient in recognized need of such treatment.

10. The method of claim 9, wherein the local administration to the eye comprises topical administration.

11. The method of claim 9, wherein the local administration to the eye comprises intravitreal administration, intracameral administration, subconjunctival administration, or sub-Tenon's administration.

12. The method of any one of claims 1-11, wherein the therapeutically effective amount of acorafloxacin, or a pharmaceutically acceptable salt thereof, is at least about 4 times less than a therapeutically effective amount of one or more of besifloxacin, gatifloxacin, moxifloxacin, levofloxacin and ciprofloxacin.

13. The method of any preceding claim, wherein the ocular infection comprises at least one bacterium selected from ophthalmic *Staphylococcus aureus* (MRSA) and ophthalmic *Staphylococcus epidermidis* (MRSE), and said administering is effective to resolve the infection at a dose of acorafloxacin, or a pharmaceutically acceptable salt thereof, that is at least about 4 times less than a dose of one or more of besifloxacin, gatifloxacin, moxifloxacin, levofloxacin and ciprofloxacin.

14. The method of any preceding claim, wherein the ocular infection is bacterial conjunctivitis, bacterial blepharitis, bacterial keratitis, or bacterial endophthalmitis.

15. The method of any one of claims 1-14, wherein the method is more effective than a corresponding method wherein acorafloxacin, or a pharmaceutically acceptable salt thereof, is replaced with at least one fluoroquinolone selected from besifloxacin, gatifloxacin, moxifloxacin, levofloxacin and ciprofloxacin.

16. The method of any one of claims 1-15, wherein the method is more effective than a corresponding method wherein acorafloxacin is replaced with moxifloxacin.

17. The method of any one of any one of claims 1-16, wherein the treatment is a prophylactic treatment.

18. A kit, comprising:

a composition comprising acorafloxacin, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable excipient; and

instructions for administering the composition to an eye with a bacterial infection.

19. The kit of claim 18, wherein the composition is a solution or a suspension administrable by drops.

20. The kit of claim 18, wherein the composition is an ointment or a gel.

21. The kit of any one of claims 18-20, wherein the composition is provided in a container suitable for multidose administration.

22. The kit of claim 21, wherein the container comprises a dropper to dispense the composition as single drops.

23. The kit of claim 21, wherein the container comprises a tube that dispenses the composition as an ointment or a gel.

24. The kit of any one of claims 18–23, wherein the composition comprises a preservative.

25. The kit of any one of claims 18–23, wherein the composition is preservative-free.

26. The kit of claim 18, wherein the composition is an ocular implant, intracameral implant, intravitreal implant, subconjunctival implant, sub-Tenon's implant, punctum plug, canicular eluting implant, or ocular ring.

27. The kit of claim 18, wherein the composition is a microsphere.

28. A method of inhibiting growth of at least one bacterium selected from ophthalmic *Staphylococcus aureus* (MRSA) and ophthalmic *Staphylococcus epidermidis* (MRSE), comprising: contacting acorafloxacin, or a pharmaceutically acceptable salt thereof, with the at least one bacterium.

29. A method of treating an ocular infection comprising at least one bacterium in a patient in recognized need of such treatment, the method comprising:

collecting the at least one bacterium isolate from the patient in recognized need of such treatment,

identifying MICs for each of fluoroquinolones selected from acorafloxacin, besifloxacin, gatifloxacin, moxifloxacin, levofloxacin and ciprofloxacin, or a pharmaceutically acceptable salt thereof, on the at least one bacterium isolate, and

administering to the patient in recognized need of such treatment, a therapeutically effective amount of the fluoroquinolone, or a pharmaceutically acceptable salt thereof, having the lowest MIC.

30. The method of claim 29, wherein the fluoroquinolone having the lowest MIC is acorafloxacin.

31. The method of claim 29 or claim 30, wherein the at least one bacterium is resistant to at least one fluoroquinolone selected from besifloxacin, gatifloxacin, moxifloxacin, levofloxacin and ciprofloxacin, or a pharmaceutically acceptable salt thereof.

32. The method of any one of claims 29-31, wherein the at least one bacterium is resistant to moxifloxacin.

33. The method of any one of claims 29-32, wherein the treatment is a prophylactic treatment.

34. A kit comprising acorafloxacin and instructions for measuring acorafloxacin MIC on at least one bacterium selected from ophthalmic *Staphylococcus aureus* and ophthalmic *Staphylococcus epidermidis*, wherein the instructions comprise:
preparing acorafloxacin, or a pharmaceutically acceptable salt thereof, stock solution,
diluting acorafloxacin, or a pharmaceutically acceptable salt thereof, stock solution in an appropriate fold dilution series, and
contacting the dilution series with the at least one bacterium.

35. The kit of claim 34, wherein the ophthalmic *Staphylococcus aureus* is methicillin-resistant.

36. The kit of claim 34 or claim 35, wherein the ophthalmic *Staphylococcus epidermidis* is methicillin-resistant.

37. The kit of any one of claims 34-35, wherein the at least one bacterium is resistant to at least one fluoroquinolone selected from besifloxacin, gatifloxacin, moxifloxacin, levofloxacin and ciprofloxacin, or a pharmaceutically acceptable salt thereof.

38. Use of acorafloxacin, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for the treatment of an ocular bacterial infection.

39. The use of claim 38 wherein the medicament is a pharmaceutical composition comprising acorafloxacin, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable excipient.

40. The use of claim 39, wherein the pharmaceutical composition is a solution or a suspension.

41. The use of claim 39, wherein the pharmaceutical composition is an ointment or a gel.

42. The use of any one of claims 39–41, wherein the composition comprises a preservative.

43. The use of any one of claims 39–41, wherein the composition is preservative-free.

44. The use of claim 39, wherein the pharmaceutical composition is an ocular implant, intracameral implant, intravitreal implant, subconjunctival implant, sub-Tenon's implant, punctum plug, canicular eluting implant, or ocular ring.

45. The use of claim 39, wherein the pharmaceutical composition is a microsphere.

46. The use of any one of claims 38–45, wherein the medicament, when used in the treatment of an ocular bacterial infection, is administered locally to an eye of a patient in recognized need of such treatment.

47. The use of claim 46, wherein the local administration to the eye comprises topical administration.

48. The use of claim 46, wherein the local administration to the eye comprises intravitreal administration, intracameral administration, subconjunctival administration, or sub-Tenon's administration.

49. The use of any one of claims 38–48, wherein the acorafloxacin, or a pharmaceutically acceptable salt thereof, is present in the medicament in a therapeutically effective amount that is at least about 4 times less than a therapeutically effective amount of one or more of besifloxacin, gatifloxacin, moxifloxacin, levofloxacin and ciprofloxacin.

50. The use of any one of claims 38–49, wherein the ocular infection comprises at least one bacterium selected from ophthalmic *Staphylococcus aureus* (MRSA) and ophthalmic *Staphylococcus epidermidis* (MRSE), and the medicament, when administered a patient in recognized need of treatment for the ocular bacterial infection, is effective to resolve the infection at a dose of acorafloxacin, or a pharmaceutically acceptable salt thereof, that is at least about 4 times less than a dose of one or more of besifloxacin, gatifloxacin, moxifloxacin, levofloxacin and ciprofloxacin.

51. The use of any one of claims 38–50, wherein the ocular infection is bacterial conjunctivitis, bacterial blepharitis, bacterial keratitis, or bacterial endophthalmitis.

52. The use of any one of claims 38–51, wherein the treatment of the ocular infection is more effective than a corresponding treatment wherein acorafloxacin, or a pharmaceutically acceptable salt thereof, is replaced with at least one fluoroquinolone selected from besifloxacin, gatifloxacin, moxifloxacin, levofloxacin and ciprofloxacin.

53. The use of any one of claims 38–52, wherein the treatment of the ocular infection is more effective than a corresponding treatment wherein acorafloxacin, or a pharmaceutically acceptable salt thereof, is replaced with moxifloxacin.

54. The use of any one of claims 38–53, wherein the treatment is a prophylactic treatment.

55. Use of acorafloxacin, or a pharmaceutically acceptable salt thereof, in the treatment of an ocular bacterial infection in a patient in recognized need of such treatment.

56. The use of claims 55, wherein the treatment comprises administering the acorafloxacin, or a pharmaceutically acceptable salt thereof, as a pharmaceutical composition comprising the acorafloxacin, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable excipient.

57. The use of claim 56, wherein the pharmaceutical composition is a solution or a suspension.

58. The use of claim 56, wherein the pharmaceutical composition is an ointment or a gel.

59. The use of any one of claims 56–58, wherein the composition comprises a preservative.

60. The use of any one of claims 56–58, wherein the composition is preservative-free.

61. The use of claim 56, wherein the pharmaceutical composition is an ocular implant, intracameral implant, intravitreal implant, subconjunctival implant, sub-Tenon's implant, punctum plug, canicular eluting implant, or ocular ring.

62. The use of claim 56, wherein the pharmaceutical composition is a microsphere.

63. The use of any one of claims 55–62, wherein the treatment comprises locally administering the acorafloxacin to an eye of the patient in recognized need of such treatment.

64. The use of claim 63, wherein the local administration to the eye comprises topical administration.

65. The use of claim 63, wherein the local administration to the eye comprises intravitreal administration, intracameral administration, subconjunctival administration, or sub-Tenon's administration.

66. The use of any one of claims 55–65, wherein the treatment comprises administering the acorafloxacin to the patient in recognized need thereof a therapeutically effective amount of acorafloxacin, or a pharmaceutically acceptable salt thereof, that is at least about 4 times less than a therapeutically effective amount of one or more of besifloxacin, gatifloxacin, moxifloxacin, levofloxacin and ciprofloxacin.

67. The use of any one of claims 55–66, wherein the ocular infection comprises at least one bacterium selected from ophthalmic *Staphylococcus aureus* (MRSA) and ophthalmic *Staphylococcus epidermidis* (MRSE), and the treatment is effective to resolve the infection when a dose of acorafloxacin, or a pharmaceutically acceptable salt thereof, is administered that is at

least about 4 times less than a dose of one or more of besifloxacin, gatifloxacin, moxifloxacin, levofloxacin and ciprofloxacin.

68. The use of any one of claims 55–67, wherein the ocular infection is bacterial conjunctivitis, bacterial blepharitis, bacterial keratitis, or bacterial endophthalmitis.

69. The use of any one of claims 55–68, wherein the treatment is more effective than a corresponding treatment wherein acorafloxacin, or a pharmaceutically acceptable salt thereof, is replaced with at least one fluoroquinolone selected from besifloxacin, gatifloxacin, moxifloxacin, levofloxacin and ciprofloxacin.

70. The use of any one of claims 55–69, wherein the treatment is more effective than a corresponding treatment wherein acorafloxacin, or a pharmaceutically acceptable salt thereof, is replaced with moxifloxacin.

71. The use of any one of claims 55–70, wherein the treatment is a prophylactic treatment.

72. Acorafloxacin, or a pharmaceutically acceptable salt thereof, for use in the treatment of an ocular bacterial infection in a patient in recognized need of such treatment.

73. The acorafloxacin, or pharmaceutically acceptable salt thereof, for the use of claims 72, wherein the treatment comprises administering the acorafloxacin as a pharmaceutical composition comprising the acorafloxacin and a pharmaceutically acceptable excipient.

74. The acorafloxacin, or pharmaceutically acceptable salt thereof, for the use of claim 73, wherein the pharmaceutical composition is a solution or a suspension.

75. The acorafloxacin, or pharmaceutically acceptable salt thereof, for the use of claim 73, wherein the pharmaceutical composition is an ointment or a gel.

76. The acorafloxacin, or pharmaceutically acceptable salt thereof, for the use of any one of claims 73–75, wherein the pharmaceutical composition comprises a preservative.

77. The acorafloxacin, or pharmaceutically acceptable salt thereof, for the use of any one of claims 73–75, wherein the pharmaceutical composition is preservative-free.

78. The acorafloxacin, or pharmaceutically acceptable salt thereof, for use according to claim 73, wherein the pharmaceutical composition is an ocular implant, intracameral implant, intravitreal implant, subconjunctival implant, sub-Tenon's implant, punctum plug, canicular eluting implant, or ocular ring.

79. The acorafloxacin, or pharmaceutically acceptable salt thereof, for use according to claim 73, wherein the pharmaceutical composition is a microsphere.

80. The acorafloxacin, or pharmaceutically acceptable salt thereof, for the use of any one of claims 72–79, wherein the treatment comprises locally administering the acorafloxacin to an eye of the patient in recognized need of such treatment.

81. The acorafloxacin, or pharmaceutically acceptable salt thereof, for the use of claim 80, wherein the local administration to the eye comprises topical administration.

82. The acorafloxacin, or pharmaceutically acceptable salt thereof, for the use of claim 80, wherein the local administration to the eye comprises intravitreal administration, intracameral administration, subconjunctival administration, or sub-Tenon's administration.

83. The acorafloxacin, or pharmaceutically acceptable salt thereof, for the use of any one of claims 72–82, wherein the treatment comprises administering the acorafloxacin, or pharmaceutically acceptable salt thereof, to the patient in recognized need thereof a therapeutically effective amount of acorafloxacin, or pharmaceutically acceptable salt thereof, that is at least about 4 times less than a therapeutically effective amount of one or more of besifloxacin, gatifloxacin, moxifloxacin, levofloxacin and ciprofloxacin.

84. The acorafloxacin, or pharmaceutically acceptable salt thereof, for the use of any one of claims 72–83, wherein the ocular infection comprises at least one bacterium selected from ophthalmic *Staphylococcus aureus* (MRSA) and ophthalmic *Staphylococcus epidermidis* (MRSE), and the treatment is effective to resolve the infection when a dose of acorafloxacin, or pharmaceutically acceptable salt thereof, is administered that is at least about 4 times less than a dose of one or more of besifloxacin, gatifloxacin, moxifloxacin, levofloxacin and ciprofloxacin.

85. The acorafloxacin, or pharmaceutically acceptable salt thereof, for the use of any one of claims 72–84, wherein the ocular infection is bacterial conjunctivitis, bacterial blepharitis, bacterial keratitis, or bacterial endophthalmitis.

86. The acorafloxacin, or pharmaceutically acceptable salt thereof, for the use of any one of claims 72–85, wherein the treatment is more effective than a corresponding treatment wherein acorafloxacin is replaced with at least one fluoroquinolone selected from besifloxacin, gatifloxacin, moxifloxacin, levofloxacin and ciprofloxacin.

87. The acorafloxacin, or pharmaceutically acceptable salt thereof, for the use of any one of claims 72–86, wherein the treatment is more effective than a corresponding treatment wherein acorafloxacin is replaced with moxifloxacin.

88. The acorafloxacin, or pharmaceutically acceptable salt thereof, for the use of any one of 72–87, wherein the treatment is a prophylactic treatment.

89. Use of acorafloxacin, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for the treatment of an ocular infection comprising at least one bacterium in a patient in recognized need of such treatment.

90. The use of claim 89, wherein the treatment comprises:

collecting the at least one bacterium isolate from the patient in recognized need of such treatment,

identifying MICs for each of fluoroquinolones selected from acorafloxacin, besifloxacin, gatifloxacin, moxifloxacin, levofloxacin and ciprofloxacin, or a pharmaceutically acceptable salt thereof, on the at least one bacterium isolate, and

administering to the patient in recognized need of such treatment, a therapeutically effective amount of the fluoroquinolone, or a pharmaceutically acceptable salt thereof, having the lowest MIC.

91. The use of claim 90, wherein the fluoroquinolone having the lowest MIC is acorafloxacin.

92. The of any one of claims 89–91, wherein the at least one bacterium is resistant to at least one fluoroquinolone selected from besifloxacin, gatifloxacin, moxifloxacin, levofloxacin and ciprofloxacin, or a pharmaceutically acceptable salt thereof.

93. The use of any one of claims 89–92, wherein the at least one bacterium is resistant to moxifloxacin.

94. The use of any one of claims 89–93, wherein the treatment is a prophylactic treatment.

95. Use of acorafloxacin, or a pharmaceutically acceptable salt thereof, in the treatment of an ocular infection comprising at least one bacterium in a patient in recognized need of such treatment.

96. The use of claim 95, wherein the treatment comprises:

collecting the at least one bacterium isolate from the patient in recognized need of such treatment,

identifying MICs for each of fluoroquinolones selected from acorafloxacin, besifloxacin, gatifloxacin, moxifloxacin, levofloxacin and ciprofloxacin, or a pharmaceutically acceptable salt thereof, on the at least one bacterium isolate, and

administering to the patient in recognized need of such treatment, a therapeutically effective amount of the fluoroquinolone, or a pharmaceutically acceptable salt thereof, having the lowest MIC.

97. The use of claim 96, wherein the fluoroquinolone having the lowest MIC is acorafloxacin.

98. The use of any one of claims 95–97, wherein the at least one bacterium is resistant to at least one fluoroquinolone selected from besifloxacin, gatifloxacin, moxifloxacin, levofloxacin and ciprofloxacin, or a pharmaceutically acceptable salt thereof.

99. The use of any one of claims 95–98, wherein the at least one bacterium is resistant to moxifloxacin.

100. The use of any one of claims 95–99, wherein the treatment is a prophylactic treatment.

101. Acorafloxacin, or a pharmaceutically acceptable salt thereof, for use in the treatment of an ocular infection comprising at least one bacterium in a patient in recognized need of such treatment.

102. Acorafloxacin, or a pharmaceutically acceptable salt thereof, for the use of claim 101, wherein the treatment comprises:

collecting the at least one bacterium isolate from the patient in recognized need of such treatment,

identifying MICs for each of fluoroquinolones selected from acorafloxacin, besifloxacin, gatifloxacin, moxifloxacin, levofloxacin, and ciprofloxacin, or a pharmaceutically acceptable salt thereof, on the at least one bacterium isolate, and

administering to the patient in recognized need of such treatment, a therapeutically effective amount of the fluoroquinolone, or a pharmaceutically acceptable salt thereof, having the lowest MIC.

103. Acorafloxacin for the use of claim 102, wherein the fluoroquinolone having the lowest MIC is acorafloxacin.

104. Acorafloxacin for the use of any one of claims 101–102, wherein the at least one bacterium is resistant to at least one fluoroquinolone selected from besifloxacin, gatifloxacin, moxifloxacin, levofloxacin and ciprofloxacin, or a pharmaceutically acceptable salt thereof.

105. Acorafloxacin, or a pharmaceutically acceptable salt thereof, for the use of any one of claims 101–104, wherein the at least one bacterium is resistant to moxifloxacin.

106. Acorafloxacin, or a pharmaceutically acceptable salt thereof, for the use of any one of claims 101–105, wherein the treatment is a prophylactic treatment.

107. A method for treating an ocular bacterial infection in a patient substantially as described herein.

108. A method for treating an ocular bacterial infection in a patient in need thereof using acorafloxacin, or a pharmaceutically acceptable salt thereof, substantially as described herein.

109. The use of acorafloxacin, or a pharmaceutically acceptable salt thereof, substantially as described herein.

110. Acorafloxacin, or a pharmaceutically acceptable salt thereof, for use substantially as described herein.

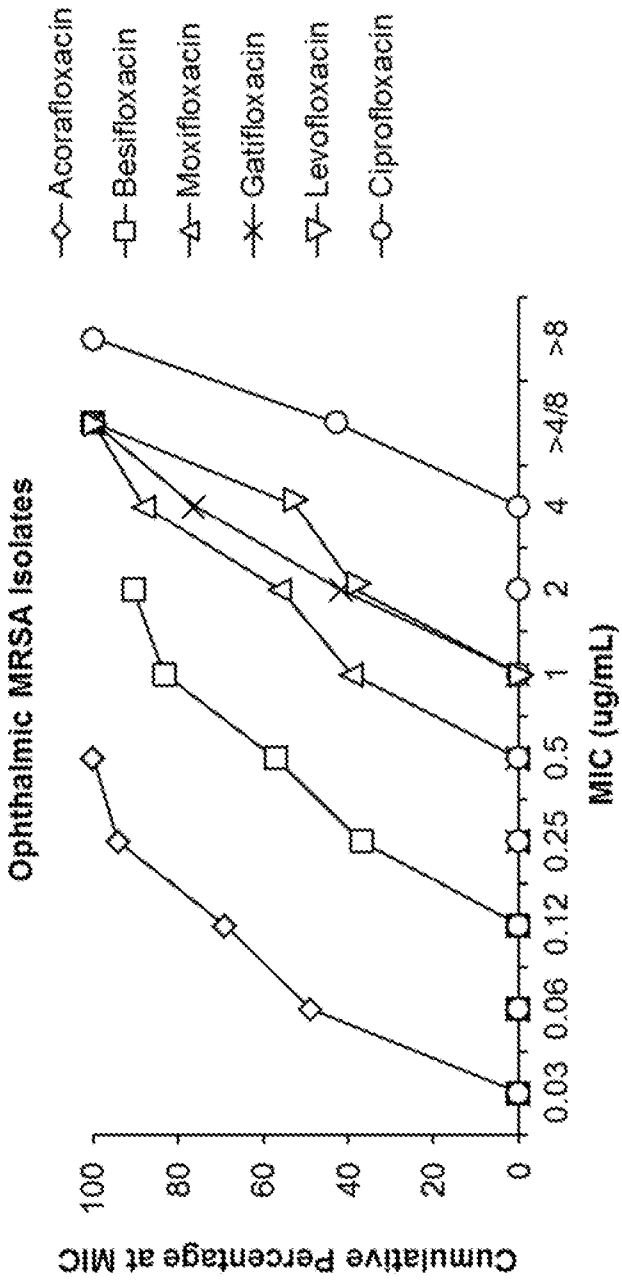

Acorafloxacin
Besifloxacin
Moxifloxacin
Gatifloxacin
Levofloxacin
Ciprofloxacin
Ophthalmic MRSA Isolates
Cumulative Percentage at MIC
100
80
60
40
20
0
0.03
0.06
0.12
0.25
0.5
1
2
4
>4/8
>8
MIC (ug/mL)

FIG. 1

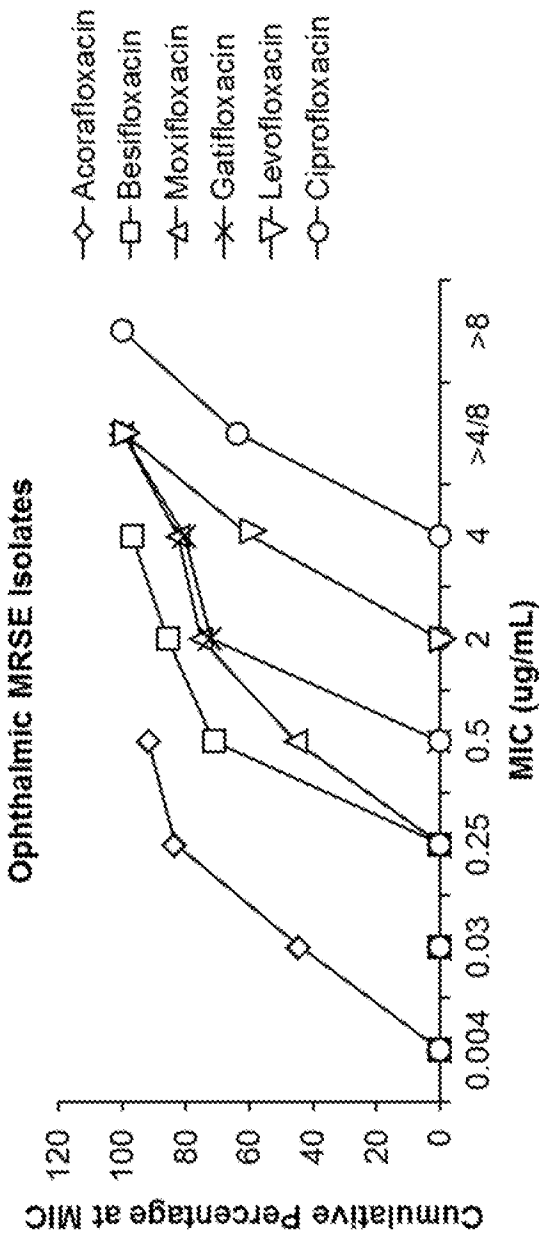

Ophthalmic MRSE Isolates
Acorafloxacin
Besifloxacin
Moxifloxacin
Gatifloxacin
Levofloxacin
Ciprofloxacin
Cumulative Percentage at MIC
120
100
80
60
40
20
0
0.004
0.03
0.25
0.5
2
4
>4/8
>8
MIC (ug/mL)

FIG. 2

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2018/022197

A. CLASSIFICATION OF SUBJECT MATTER
INV. A61K31/4709 A61K31/496 A61K31/5383 A61P31/04 A61P27/02
ADD.

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
EPO-Internal, BIOSIS, EMBASE, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	EP 2 143 422 A1 (S I F I SOCIETA IND FARMACEUTI [IT]) 13 January 2010 (2010-01-13) paragraphs [0058] - [0060]	1-110
X	BELA KOCSIS ET AL: "Chemical structure and pharmacokinetics of novel quinolone agents represented by avarofloxacin, delafloxacin, finafloxacin, zabofloxacin and nemonoxacin", ANNALS OF CLINICAL MICROBIOLOGY AND ANTIMICROBIALS, vol. 15, no. 1, 23 May 2016 (2016-05-23), XP055485246, DOI: 10.1186/s12941-016-0150-4	18-28, 34-37
Y	abstract page 3, column 1, paragraph 2-3 table 2	1-110

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[X] Further documents are listed in the continuation of Box C.

[X] See patent family annex.

* Special categories of cited documents :

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"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
20 June 2018	27/06/2018

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INTERNATIONAL SEARCH REPORT

International application No
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C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 2016/120979 A1 (HAFEZI FARHAD [CH] ET AL) 5 May 2016 (2016-05-05) abstract -----	1
X,P	WO 2017/151664 A1 (BELMONT UNIV [US]) 8 September 2017 (2017-09-08) paragraphs [0003], [0012], [0013], [0043], [0050], [0051] claims 1-16 -----	1-110

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INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/US2018/022197

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