systemic microbial infections. Ocular injections and corticosteroid implants with a longer durability have a greater risk of cataracts, increased intraocular pressure, and glaucoma in a significant share of patients.

[00011] These side effects can have a direct impact to patient quality of life (pain, discomfort, itching), which are exacerbated by the fact that these products are often given four to eight times a day or even more often, particularly at the beginning of their use, and often need to be tapered to lower doses because of these side effects. In clinical practice, it is not uncommon to use a corticosteroid every 1 to 2 hours for several weeks, then tapering down to labeled doses, for indications like anterior uveitis, to attempt to achieve an adequate clinical effect on the underlying inflammation inherent in this immune-mediated disease. One reason for this extreme frequency of use is to achieve the desired pharmacokinetic distribution and therapeutic levels in the anterior chamber compartment. For pan or posterior uveitis or other intraocular inflammatory diseases, corticosteroid injections or implants are more commonly used, as topical steroids typically do not reach the relevant vitreoretinal tissues in required therapeutic doses.

SUMMARY

[00012] The present application addresses the unmet need for a safe and effective topical therapy for anterior and vitreous chamber intraocular diseases. Ideal therapies can provide adequate pharmacokinetic coverage of disease targets while providing reduced side effects and improved patient preference and compliance. Thus, the present disclosure provides for an effective alternative to existing therapies, such as those involving corticosteroids.

[00013] The present application also provides for methods that include administration of optimal concentrations of roflumilast that are administered at frequencies capable of achieving drug levels sufficiently above IC50 levels in the anterior and vitreous chamber. The concentrations

of roflumilast capable of achieving drug levels sufficiently above IC50 levels in the anterior and vitreous chamber are higher than the roflumilast concentrations necessary to obtain similar levels in ocular surface tissues (e.g. the cornea and/or conjunctiva) and are administered on a more frequent basis, and yet at a lower concentration and frequency than other ophthalmic agents for the anterior and vitreous chambers such as corticosteroids.

[00014] The present disclosure includes methods of treating anterior and vitreous chamber ocular diseases by administering ophthalmic pharmaceutical compositions of roflumilast topically to the ocular surface of the eye of a patient in a concentration and frequency optimized for therapeutic coverage of PDE4A, B, and D with the goal of downregulating Th17 and Th1 immune targets in the anterior chamber compartment as well as the vitreous chamber. The inventors of the subject application have surprisingly discovered that topical administration of higher concentration, higher frequency ophthalmic pharmaceutical compositions of roflumilast applied to the ocular surface can provide more significant therapeutic activity and coverage to the tissues of the anterior and vitreous chamber of the eye than those concentrations and frequencies of topical ophthalmic pharmaceutical compositions of roflumilast used for the ocular surface, but which nonetheless still result in less frequent administration than other treatment regimens currently used, such as steroids. The present disclosure addresses the long felt and unmet need for an alternative class of agents to address anterior ophthalmic disorders using a dosing regimen involving a patient-convenient three or four times a day administration of high concentrations of roflumilast with clinically meaningful efficacy and with lower patient-based or population-based side effects. With high levels of efficacy and minimal side effects, the present disclosure can provide a short-term, mid-term, or long-term therapeutic solution for anterior ocular diseases.

[00015] In certain examples, a method for treating a patient having an anterior ophthalmic disorder is provided. The method comprises topically administering an ophthalmic pharmaceutical composition comprising 0.3% to 1.0% w/v of roflumilast or a pharmaceutically acceptable salt thereof to an ocular surface of said patient three times per day. The anterior ophthalmic disorder can be selected from the group consisting of anterior uveitis, pan-uveitis, intermediate uveitis, uveitis associated with various autoimmune or systemic diseases including juvenile idiopathic arthritis (JIA), Behçet's disease, ankylosing spondylitis, sarcoidosis, Vogt-Koyanagi-Harada disease (VKH), lupus, rheumatoid arthritis (RA), multiple sclerosis or other autoimmune conditions; Idiopathic uveitis, HLA-B27 uveitis, uveitic glaucoma, iritis, iridocyclitis, rubeosis iritis, coloboma of the iris, Fuchs heterchromic iridocyclitis, iridocorneal endothelial syndrome (ICE), scleritis, corneal endothelial disease or dysfunction including endotheliitis, Fuch's corneal or endothelial dystrophy, endothelial corneal dysfunction associated with Graves ophthalmopathy or thyroid eye disease, megalocornea, Axenfeld's syndrome, Rieger's anomaly, Peters' anomaly or Anterior segment mesenchymal dysgenesis, ocular hypertension, glaucoma (including primary congenital, open angle, angle closure, normal tension, elevated episcleral venous pressure (EVP), Sturge Weber, or secondary glaucoma), bupthalmos, Posner Schlossman Syndrome or glaucomatocyclitic crisis, cataract, post-surgical anterior ocular inflammation, post-surgical ocular inflammation affecting corneal endothelium, deep corneal epithelial defects that also involve anterior segment dysfunction such as corneal endothelial dysfunction or neurotrophic keratitis, inflammation related to DSEK/DMET keratoplasty, rebound iritis, pseudoexfoliation syndrome, pupillary abnormalities, Stevens Johnson syndrome, Sjogren's syndrome, ocular graft-versus-host disease, ocular cicatricial pemphigoid, anterior sterile or infectious endophthalmitis, toxic anterior segment syndrome (TASS), sympathetic ophthalmia, hyphema, anterior segment ischemia,

anterior chamber inflammation related to the underlying viral and other microbial causes, anterior chemical injury, and iatrogenic anterior chamber inflammation. In preferred examples, the anterior chamber ophthalmic disorder is uveitis (anterior, pan, intermediate or posterior) or uveitis associated with HLA-B27, autoimmune or systemic disease (including but not limited to JIA, Behçet's, ankylosing spondylitis, VKH lupus, RA, and psoriatic arthritis), uveitic glaucoma, anterior chamber iatrogenic inflammation, ocular pemphigoid, or intraocular inflammatory disease of the corneal endothelium, iris, sclera, or choroid. The method can improve patient convenience and/or result in a reduction of at least one side effect relative to administration of a corticosteroid.

[00015a] In an aspect of the present disclosure, there is provided use of an ophthalmic pharmaceutical composition comprising 0.3% to 1.0% w/v of roflumilast or a pharmaceutically acceptable salt thereof in the manufacture of a medicament for treating an anterior ophthalmic disorder in a patient, wherein the medicament is to be topically administered to an ocular surface of said patient three times per day.

[00016] In certain examples, a method for treating a patient having an anterior ophthalmic disorder is provided. The method comprises topically administering an ophthalmic pharmaceutical composition comprising 0.3% to 1.0% w/v of roflumilast or a pharmaceutically acceptable salt thereof to an ocular surface of said patient four times per day. The anterior ophthalmic disorder can be selected from the group consisting of anterior uveitis, pan-uveitis, intermediate uveitis, uveitis associated with various autoimmune or systemic diseases including juvenile idiopathic arthritis (JIA), Behçet's disease, ankylosing spondylitis, sarcoidosis, Vogt-Koyanagi-Harada disease (VKH), lupus, rheumatoid arthritis (RA), multiple sclerosis or other autoimmune conditions, idiopathic uveitis, HLA-B27 uveitis, uveitic glaucoma, iritis, iridocyclitis, rubeosis iritis, coloboma of the iris, Fuchs heterchromic iridocyclitis, iridocorneal endothelial syndrome (ICE), scleritis, corneal endothelial disease or dysfunction including endotheliitis, Fuch's corneal or endothelial dystrophy, endothelial

corneal dysfunction associated with Graves ophthalmopathy or thyroid eye disease, megalocornea, Axenfeld's syndrome, Rieger's anomaly, Peters' anomaly or Anterior segment mesenchymal dysgenesis, ocular hypertension, glaucoma (including primary congenital, open angle, angle closure, normal tension, elevated episcleral venous pressure (EVP),

Sturge Weber, or secondary glaucoma, bupthalmos, Posner Schlossman Syndrome or glaucomatocyclitic crisis, cataract, post-surgical ocular inflammation, post-surgical anterior ocular inflammation affecting corneal endothelium, deep corneal epithelial defects that also involve anterior segment dysfunction such as corneal endothelial dysfunction or neurotrophic keratitis, inflammation related to DSEK/DMET keratoplasty, rebound iritis, pseudoexfoliation syndrome, pupillary abnormalities, Stevens Johnson syndrome, Sjogren's syndrome, ocular graft-versus-host disease, ocular cicatricial pemphigoid, anterior sterile or infectious endophthalmitis, toxic anterior segment syndrome (TASS), sympathetic ophthalmia, hyphema, anterior segment ischemia, anterior chamber inflammation related to the underlying viral and other microbial causes, anterior chemical injury, and iatrogenic anterior chamber inflammation.

[00016a] In another aspect, there is provided use of an ophthalmic pharmaceutical composition comprising 0.3% to 1.0% w/v of roflumilast or a pharmaceutically acceptable salt thereof in the manufacture of a medicament for treating an anterior ophthalmic disorder in a patient, wherein the medicament is to be topically administered to an ocular surface of said patient four times per day.

[00017] In preferred examples, the anterior chamber ophthalmic disorder is uveitis (anterior, pan, intermediate or posterior) or uveitis associated with HLA-B27, autoimmune or systemic disease (including but not limited to JIA, Behçet's, ankylosing spondylitis, VKH lupus, RA, and psoriatic arthritis), uveitic glaucoma, anterior chamber iatrogenic inflammation, ocular pemphigoid, or intraocular inflammatory disease of the corneal endothelium, iris, sclera, or choroid. The method can improve patient convenience and/or result in a reduction of at least one side effect relative to administration of a corticosteroid.

[00018] In certain examples, a method for treating a patient having a vitreous ophthalmic disorder is provided. The method comprises topically administering an ophthalmic pharmaceutical composition comprising 0.3% to 1.0% w/v of roflumilast or a pharmaceutically acceptable salt thereof to an ocular surface of said patient three times per day. The vitreous ophthalmic disorder can be selected from the group consisting of posterior, pan or intermediate uveitis or uveitis associated with HLA-B27, juvenile idiopathic arthritis, Behcets disease, ankylosing spondylitis,

VKH, or other autoimmune disease, diabetic retinopathy, diabetic macular edema, retinal vein occlusion, age-related macular degeneration including dry, geographic atrophy, or exudative AMD, choroidal neovascularization, choroidal thickening associated with thyroid eye disease, Coat's disease, central serous retinopathy or chorioretinopathy, sterile or infectious endopthalmitis, inflammation associated with inherited retinal diseases, retinitis pigmentosa, Stargardt disease, Leber congenital amaurosis, Leber hereditary optic neuropathy, Usher syndrome, X-linked retinoschisis, choroidemia, zonal occult outer retinopathy, myopia, vitreomacular adhesion, retinal detachment, choroidal detachment and hemorrhage, choroidal rupture, choroidal folds, proliferative vitreoretinopathy, idiopathic ischemia, achromatopsia, retinopathy of prematurity, gyrate atrophy, central areolar choroidal dystrophy, punctate inner choroidopathy, multifocal choroiditis, choroiditis, choroidal granuloma, choroidal dystrophy, choroidal fibrosis, acute posterior multifocal placoid pigment epitheliopathy, serpiginous choroidopathy, birdshot retinochoroidopathy, multiple evanescent white dot syndrome, retinoblastoma, choroidal melanoma, retinal lymphoma, and iatrogenic posterior or vitreous chamber inflammation.

[00019] In preferred examples, the vitreous chamber ophthalmic disorder is posterior, pan or intermediate uveitis or uveitis associated with HLA-B27, juvenile idiopathic arthritis, Behcets disease, ankylosing spondylitis, VKH, or other autoimmune disease, diabetic retinopathy, diabetic macular edema, age-related macular degeneration including dry, geographic atrophy, or exudative AMD and choroidal neovascularization, choroidal thickening associated with thyroid eye disease, sterile or infectious endophthalmitis, and vitreous or posterior chamber iatrogenic inflammation. The method can improve patient convenience and/or result in a reduction of at least one side effect relative to administration of a corticosteroid.

[00020] In certain examples, a method for treating a patient having a vitreous ophthalmic disorder is provided. The method comprises topically administering an ophthalmic pharmaceutical composition comprising 0.3% to 1.0% w/v of roflumilast or a pharmaceutically acceptable salt thereof to an ocular surface of said patient four times per day. The vitreous ophthalmic disorder can be selected from the group consisting of posterior, pan or intermediate uveitis or uveitis associated with HLA-B27, Juvenile Idiopathic Arthritis, Behcets disease, ankylosing spondylitis, VKH, or other autoimmune disease, diabetic retinopathy, diabetic macular edema, retinal vein occlusion, age-related macular degeneration including dry, geographic atrophy, or exudative AMD, choroidal neovascularization, choroidal thickening associated with thyroid eye disease, Coat's disease, central serous retinopathy or chorioretinopathy, sterile or infectious endopthalmitis, inflammation associated with inherited retinal diseases, retinitis pigmentosa, Stargardt disease, Leber congenital amaurosis, Leber hereditary optic neuropathy, Usher syndrome, or X-linked retinoschisis, choroidemia, zonal occult outer retinopathy, myopia, vitreomacular adhesion, retinal detachment, choroidal detachment and hemorrhage, choroidal rupture, choroidal folds, proliferative vitreoretinopathy, idiopathic ischemia, achromatopsia, retinopathy of prematurity, gyrate atrophy, central areolar choroidal dystrophy, punctate inner choroidopathy, multifocal choroiditis, choroiditis, choroidal granuloma, choroidal dystrophy, choroidal fibrosis, acute posterior multifocal placoid pigment epitheliopathy, serpiginous choroidopathy, birdshot retinochoroidopathy, multiple evanescent white dot syndrome, retinoblastoma, choroidal melanoma, retinal lymphoma, and iatrogenic posterior or vitreous chamber inflammation.

[00021] In preferred examples, the vitreous chamber ophthalmic disorder is posterior, pan or intermediate uveitis or uveitis associated with HLA-B27, Juvenile Idiopathic Arthritis, Behcets disease, ankylosing spondylitis, VKH, or other autoimmune disease, diabetic retinopathy, diabetic

CLAIMS

What is claimed is:

1. Use of an ophthalmic pharmaceutical composition comprising 0.3% to 1.0% w/v of roflumilast or a pharmaceutically acceptable salt thereof in the manufacture of a medicament for treating an anterior ophthalmic disorder in a patient, wherein the medicament is to be topically administered to an ocular surface of said patient three times per day.

2. The use of claim 1, wherein the anterior ophthalmic disorder is selected from the group consisting of anterior uveitis, pan-uveitis, intermediate uveitis, uveitis associated with autoimmune or systemic diseases including juvenile idiopathic arthritis (JIA), Behçet's disease, ankylosing spondylitis, sarcoidosis, Vogt-Koyanagi-Harada disease (VKH), lupus, rheumatoid arthritis (RA), multiple sclerosis, an autoimmune condition, idiopathic uveitis, HLA-B27 uveitis, uveitic glaucoma, iritis, iridocyclitis, rubeosis iritis, coloboma of the iris, Fuch's heterchromic iridocyclitis, iridocorneal endothelial syndrome (ICE), scleritis, corneal endothelial disease or dysfunction including endotheliitis, Fuch's corneal or endothelial dystrophy, endothelial corneal dysfunction associated with Graves ophthalmopathy or thyroid eye disease megalocornea, Axenfeld's syndrome, Rieger's anomaly, Peters' anomaly, Anterior segment mesenchymal dysgenesis, ocular hypertension, glaucoma, bupthalmos, Posner Schlossman Syndrome, glaucomatocyclitic crisis, cataract, anterior post-surgical ocular inflammation, post-surgical ocular inflammation affecting corneal endothelium, deep corneal epithelial defects that also involve anterior segment dysfunction such as corneal endothelial dysfunction or neurotrophic keratitis, inflammation related to DSEK/DMET keratoplasty, rebound iritis, pseudoexfoliation syndrome, pupillary abnormalities, Stevens Johnson syndrome, Sjogren's syndrome, ocular graft-versus-host

disease, ocular cicatricial pemphigoid, anterior sterile or infectious endophthalmitis, toxic anterior segment syndrome (TASS), sympathetic ophthalmia, hyphema, anterior segment ischemia, anterior chamber inflammation related to an underlying viral and other microbial cause, anterior chemical injury, and iatrogenic anterior chamber inflammation.

3. The use of claim 2, wherein the anterior ophthalmic disorder is selected from the group consisting of anterior, pan, intermediate, or posterior uveitis, uveitis associated with HLA-B27 or an autoimmune or systemic disease uveitic glaucoma, anterior chamber iatrogenic inflammation, and inflammatory disease of the iris, sclera, or choroid.

4. The use of claim 1, wherein said administration results in a reduction of at least one side effect relative to administration of a corticosteroid.

5. The use of claim 1, wherein said administration results in a reduction of dose frequency relative to the administration of a corticosteroid.

6. The use of claim 1, wherein said administration results in a significant increase in anterior tissue concentration of roflumilast at a therapeutic level.

7. The use of claim 1, wherein the ophthalmic pharmaceutical composition is a suspension.

8. Use of an ophthalmic pharmaceutical composition comprising 0.3% to 1.0% w/v of roflumilast or a pharmaceutically acceptable salt thereof in the manufacture of a medicament for treating an anterior ophthalmic disorder in a patient, wherein the medicament is to be topically administered to an ocular surface of said patient four times per day.

9. The use of claim 8, wherein the anterior ophthalmic disorder is selected from the group consisting of anterior compartment disorders including anterior uveitis, pan-uveitis, intermediate uveitis, uveitis associated with autoimmune or systemic diseases including juvenile idiopathic arthritis (JIA), Behçet's disease, ankylosing spondylitis, sarcoidosis, Vogt-Koyanagi-Harada disease (VKH), lupus, rheumatoid arthritis (RA), multiple sclerosis, an autoimmune condition, idiopathic uveitis, HLA-B27 uveitis, uveitic glaucoma, iritis, iridocyclitis, rubeosis iritis, coloboma of the iris, Fuchs heterchromic iridocyclitis, iridocorneal endothelial syndrome (ICE), scleritis, corneal endothelial disease or dysfunction including endotheliitis, Fuch's corneal or endothelial dystrophy, endothelial corneal dysfunction associated with Graves ophthalmopathy or thyroid eye disease, megalocornea, Axenfeld's syndrome, Rieger's anomaly, Peters' anomaly, anterior segment mesenchymal dysgenesis, ocular hypertension, glaucoma, bupthalmos, Posner Schlossman Syndrome, glaucomatocyclitic crisis, cataract, anterior post-surgical ocular inflammation, post-surgical ocular inflammation affecting corneal endothelium, deep corneal epithelial defects that also involve anterior segment dysfunction such as corneal endothelial dysfunction or neurotrophic keratitis, inflammation related to DSEK/DMET keratoplasty, rebound iritis, pseudoexfoliation syndrome, pupillary abnormalities, Stevens Johnson syndrome, Sjogren's syndrome, ocular graft-versus-host disease, ocular cicatricial pemphigoid, anterior sterile or infectious endophthalmitis, toxic anterior segment syndrome (TASS), sympathetic ophthalmia,

hyphema, anterior segment ischemia, anterior chamber inflammation related to the underlying viral and other microbial causes, anterior chemical injury, and iatrogenic anterior chamber inflammation.

10. The use of claim 8, wherein said administration results in a reduction of at least one side effect relative to administration of a corticosteroid.

11. The use of claim 8, wherein said administration results in a reduction of dosing frequency relative to administration of a corticosteroid.

12. The use of claim 8, wherein said administration results in a significant increase in anterior tissue concentration of roflumilast at a therapeutic level.

13. The use of claim 12, wherein the ophthalmic pharmaceutical composition is a suspension.