

METHODS AND COMPOSITIONS FOR TREATING OPHTHALMIC DISEASE

FIELD OF THE DISCLOSURE

[0001] Methods and compositions for treating ophthalmic disease using a Bruton's Tyrosine Kinase (BTK) inhibitor are disclosed herein.

BACKGROUND

[0002] Dry eye disease (also referred to as keroconjunctivitis sicca or dry eye syndrome) is a multifactorial disorder characterized by either a decreased tear production or an increased tear film evaporation. Patients that suffer from dry eye disease have signs or symptoms including eye irritation, redness, ocular discharge, and decrease in tear volume. Dry eye disease is associated with lacrimal gland dysfunction. Age-related autoimmunity causes dysregulated mast cell aggregation in the lacrimal gland of the eye. Such an accumulation of mast cells is associated with chronic mast cell degranulation resulting in lacrimal gland atrophy, fibrosis, and inflammation. Mast cell-driven lacrimal unit dysfunction with desiccating stress on the ocular surface results in cytokine-mediated inflammation and ocular tissue damage. Hence, dry eye disease results in a loss of integrity of the tear film, which leads to ocular surface inflammation. Nonpharmaceutical treatments for dry eye disease include artificial tears, punctal plugs, and autologous serum drops. While the underlying mechanism of dry eye disease is unknown, recent published data support an early role of mast cells as the key initiator of the disease. Specifically, dysregulated trafficking of mast cells into the acinar junctions within the lacrimal gland result in degranulation over time, leading to a late phase inflammatory response causing lacrimal gland atrophy and fibrosis. See Elbasiony, NPJ Aging, 2023, 9:2.

[0003] Allergic conjunctivitis is a type I immunoglobulin E (IgE)-mediated hypersensitivity that results from allergens contacting the surface of the eye in a person allergic to that specific antigen. An acute response to allergens is mediated predominantly by mast cells, which are present in high concentrations in the conjunctiva. Mast cells become activated when allergens cross-link high-affinity IgE receptors (FcεRI) loaded with allergen-specific IgE. Activated mast cells release histamine and other pro-inflammatory mediators from pre-formed granules (termed degranulation), which induce itching, vasodilation, and vascular leakage, and leads to ocular redness, chemosis, and lid swelling. The late phase of the allergic reaction is characterized by continued inflammation from the recruitment of eosinophils, basophils, neutrophils, and macrophages into the conjunctival tissues.

[0004] Bruton's Tyrosine Kinase (BTK) is a Tec family non-receptor protein kinase, expressed in B cells and myeloid cells. BTK plays a crucial role in the activation of mast cells and basophils. In preclinical studies, blockade of BTK prevented IgE-mediated cell activation, degranulation, and de novo cytokine production (Hata, J. Exp. Med. 1998, 187:1235-1247; Dispenza, J. Clin. Invest. 2020, 130:4759-4770). Beyond the acute response, subsequent effects of BTK inhibition include suppression of cytokine production and inhibition of chemokine receptor signaling, which inhibits mobilization of proinflammatory cells toward sites of inflammation and reduces tissue damage and persistent inflammatory symptoms. Clinically, oral administration of covalent BTK inhibitors diminish allergen mediated tissue response in humans, as evidenced in patients with chronic spontaneous urticaria (Maurer, Journal of Allergy and Clinical Immunology 2022, 150:1498-1506), and patients with food and peanut allergy (Suresh, Journal of Allergy and Clinical Immunology 2023, 151:AB221; Dispenza, Allergy Clin. Immunol. 2018, 141:1914-1916).

SUMMARY

[0005] In one aspect, the present disclosure provides a method of treating or preventing an ophthalmic condition in a human subject in need thereof comprising topically administering to an eye of the human subject an ophthalmic composition comprising a Bruton's Tyrosine Kinase (BTK) inhibitor. In some embodiments, the BTK inhibitor is listed in Table 1. In some embodiments, the BTK inhibitor is 1-(4-(((6-amino-5-(4-phenoxyphenyl)pyrimidin-4-yl)amino)methyl)-4-fluoropiperidin-1-yl)prop-2-en-1-one or a pharmaceutically acceptable salt thereof. In some embodiments, the ophthalmic condition is dry eye disease (DED) or allergic conjunctivitis (AC). In some embodiments, the ophthalmic composition further comprises a pharmaceutical carrier. In some embodiments, the ophthalmic composition is an oil-in-water microemulsion. The ophthalmic composition described herein is also named as ophthalmic emulsion or ophthalmic microemulsion. In some embodiments, the oil-in-water microemulsion comprises:

- (i) 1-(4-(((6-amino-5-(4-phenoxyphenyl)pyrimidin-4-yl)amino)methyl)-4-fluoropiperidin-1-yl)prop-2-en-1-one or a pharmaceutically acceptable salt thereof;
- (ii) an oil selected from the group consisting of isopropyl myristate, isopropyl palmitate, and medium chain triglycerides;
- (iii) a pair of surfactants selected from the group consisting of two polysorbates, a polysorbate and propylene glycol, a polysorbate and glycerol, a polysorbate and 1,2,3- triacetoxyp propane,

polyethoxylated castor oil and 1,2,3-triacetoxyp propane, and polyethoxylated castor oil and propylene glycol; and (iv) water,

wherein the water represents about 50% to about 95% (v/v) of the oil-in-water microemulsion; and the ratio of percent (v/v) total surfactant to percent (v/v) oil is at least about 10: 1.

[0006] In some embodiments, the oil-in-water microemulsion comprises:

(i) 1-(4-(((6-amino-5-(4-phenoxyphenyl)pyrimidin-4-yl)amino)methyl)-4-fluoropiperidin-1-yl)prop-2-en-1-one or a pharmaceutically acceptable salt thereof;

(ii) an oil selected from the group consisting of isopropyl myristate, isopropyl palmitate, and medium chain triglycerides;

(iii) a pair of surfactants selected from the group consisting of two polysorbates, a polysorbate and propylene glycol, a polysorbate and glycerol, a polysorbate and 1,2,3- triacetoxyp propane, polyethoxylated castor oil and 1,2,3-triacetoxyp propane, and polyethoxylated castor oil and propylene glycol; and (iv) a buffer,

wherein the buffer represents about 50% to about 95% (v/v) of the oil-in-water microemulsion; and the ratio of percent (v/v) total surfactant to percent (v/v) oil is at least about 10: 1. In some embodiments, the buffer is phosphate-buffered saline (PBS).

[0007] In some embodiments, the pair of surfactants represent about 10% to about 50% (v/v) of the oil-in-water microemulsion.

[0008] In some embodiments, the pair of surfactants represent about 15% to about 40% (v/v) of the oil-in-water microemulsion.

[0009] In some embodiments, the pair of surfactants represent about 20% to about 40% (v/v) of the oil-in-water microemulsion.

[0010] In some embodiments, the pair of surfactants represent about 15%, about 20%, about 25%, about 30%, about 35%, about 40%, or about 45% percent (v/v) of the oil-in-water microemulsion.

[0011] In some embodiments, the oil represents about 1% to about 5% (v/v) of the oil-in-water microemulsion. In some embodiments, the oil represents about 1%, about 2%, about 3%, about 4%, or about 5% (v/v) of the oil-in-water microemulsion.

[0012] In some embodiments, the ratio of the pair of surfactants (v/v) is in a range of about 1:10 to 10:1. In some embodiments, the ratio of the pair of surfactants (v/v) is in a range of about 1:4 to 4:1. In some embodiments, the ratio of the pair of surfactants (v/v) is in a range of about 1:2 to 2:1. In some embodiments, the ratio of the pair of surfactants (v/v) is about 1:1. In some embodiments, one of the surfactants is polysorbate 20. In some embodiments, one of the surfactants is polysorbate 80.

[0013] In some embodiments, the appearance of the oil-in-water microemulsion is clear.

[0014] In some embodiments, the particle size of the oil-in-water microemulsion is between about 1 nm and 20 nm. In some embodiments, the particle size of the oil-in-water microemulsion is between about 1 nm and 10 nm. In some embodiments, the particle size of the oil-in-water microemulsion is between about 1 nm and 8 nm. In some embodiments, the particle size of the oil-in-water microemulsion is between about 1 nm and 5 nm. In some embodiments, the particle size of the oil-in-water microemulsion is between about 2 nm and 5 nm. In some embodiments, the particle size of the oil-in-water microemulsion is between about 2 nm and 3 nm. In some embodiments, the particle size of the oil-in-water microemulsion is between about 2 nm and 8 nm.

[0015] In some embodiments, Dv90 of the particle size of the oil-in-water microemulsion is between about 4 nm and 15 nm. In some embodiments, Dv90 of the particle size of the oil-in-water microemulsion is between about 4 nm and 13 nm. In some embodiments, Dv90 of the particle size of the oil-in-water microemulsion is about 15 nm. In some embodiments, Dv90 of the particle size of the oil-in-water microemulsion is about 13 nm. In some embodiments, Dv90 of the particle size of the oil-in-water microemulsion is about 10 nm.

[0016] In some embodiments, the viscosity of the oil-in-water microemulsion is between about 0 to about 500 centipoise. In some embodiments, viscosity of the oil-in-water microemulsion is between about 0 to about 400 centipoise.

[0017] In some embodiments, osmolality of the oil-in-water microemulsion is between about 5 to about 100 mOsm/kg at 1:3 dilution. In some embodiments, osmolality of the oil-in-water microemulsion is between about 5 to about 50 mOsm/kg at 1:3 dilution. In some embodiments, osmolality of the oil-in-water microemulsion is between about 15 to about 40 mOsm/kg at 1:3 dilution. In some embodiments, osmolality of the oil-in-water microemulsion is between about 20 to about 30 mOsm/kg at 1:3 dilution.

[0018] In an embodiment, the ophthalmic composition is an oil-in-water microemulsion comprising: about 0.1% (1.0 mg/ml) of 1-(4-(((6-amino-5-(4-phenoxyphenyl)pyrimidin-4-yl)amino)methyl)-4-

fluoropiperidin-1-yl)prop-2-en-1-one or a pharmaceutically acceptable salt thereof; about 8.43% polysorbate 20 (w/w); about 16.19% polysorbate 80 (w/w); about 1.77% isopropyl myristate (w/w); and phosphate buffered saline.

[0019] In an embodiment, the ophthalmic composition is an oil-in-water microemulsion comprising: about 0.1% (1.0 mg/ml) of 1-(4-(((6-amino-5-(4-phenoxyphenyl)pyrimidin-4-yl)amino)methyl)-4-fluoropiperidin-1-yl)prop-2-en-1-one or a pharmaceutically acceptable salt thereof; about 8.43% polysorbate 20 (w/w); about 16.19% polysorbate 80 (w/w); about 1.77% isopropyl myristate (w/w); and about 73.52% phosphate buffered saline (w/w).

[0020] In an embodiment, the ophthalmic composition is an oil-in-water microemulsion comprising: about 0.1% (1.0 mg/ml) of 1-(4-(((6-amino-5-(4-phenoxyphenyl)pyrimidin-4-yl)amino)methyl)-4-fluoropiperidin-1-yl)prop-2-en-1-one or a pharmaceutically acceptable salt thereof; about 8% polysorbate 20 (v/v); about 17% polysorbate 80 (v/v); about 2% isopropyl myristate (v/v); and about 73% phosphate buffered saline (v/v).

[0021] In an embodiment, the ophthalmic composition is an oil-in-water microemulsion comprising: about 0.1% (1.0 mg/ml) of 1-(4-(((6-amino-5-(4-phenoxyphenyl)pyrimidin-4-yl)amino)methyl)-4-fluoropiperidin-1-yl)prop-2-en-1-one or a pharmaceutically acceptable salt thereof; about 36% polysorbate 20 (v/v); about 4% polysorbate 80 (v/v); about 3% isopropyl myristate (v/v); and about 57% phosphate buffered saline (v/v).

[0022] In an embodiment, the ophthalmic composition is an oil-in-water microemulsion comprising: about 0.1% (1.0 mg/ml) of 1-(4-(((6-amino-5-(4-phenoxyphenyl)pyrimidin-4-yl)amino)methyl)-4-fluoropiperidin-1-yl)prop-2-en-1-one or a pharmaceutically acceptable salt thereof; about 7% polysorbate 20 (v/v); about 28% polysorbate 80 (v/v); about 3% isopropyl myristate (v/v); and about 62% phosphate buffered saline (v/v).

[0023] In an embodiment, the ophthalmic composition is an oil-in-water microemulsion comprising: about 0.1% (1.0 mg/ml) of 1-(4-(((6-amino-5-(4-phenoxyphenyl)pyrimidin-4-yl)amino)methyl)-4-fluoropiperidin-1-yl)prop-2-en-1-one or a pharmaceutically acceptable salt thereof; about 6% polysorbate 20 (v/v); about 24% polysorbate 80 (v/v); about 3% isopropyl myristate (v/v); and about 67% phosphate buffered saline (v/v).

[0024] In an embodiment, the ophthalmic composition is an oil-in-water microemulsion comprising: about 0.1% (1.0 mg/ml) of 1-(4-(((6-amino-5-(4-phenoxyphenyl)pyrimidin-4-yl)amino)methyl)-4-

fluoropiperidin-1-yl)prop-2-en-1-one or a pharmaceutically acceptable salt thereof; about 2% polysorbate 20 (v/v); about 18% polysorbate 80 (v/v); about 2% isopropyl myristate (v/v); and about 78% phosphate buffered saline (v/v).

[0025] In one aspect, the present disclosure relates to method of reducing ocular mast cell degranulation and/or ocular mast cell cytokine production in a human subject in need thereof comprising topically administering to an eye of the human subject an amount of a Bruton's Tyrosine Kinase (BTK) inhibitor compound effective to reduce the ocular mast cell degranulation and/or ocular mast cell cytokine production in the human subject, wherein the BTK inhibitor compound is 1-(4-(((6-amino-5-(4-phenoxyphenyl)pyrimidin-4-yl)amino)methyl)-4-fluoropiperidin-1-yl)prop-2-en-1-one or a pharmaceutically acceptable salt thereof.

[0026] In one aspect, the present disclosure relates to a method of inhibiting ocular mast cell activation in a lacrimal functional unit of a human subject in need thereof comprising topically administering to an eye of the human subject an amount of a Bruton's Tyrosine Kinase (BTK) inhibitor compound effective to inhibit ocular mast cell activation in the lacrimal functional unit of the human subject, wherein the BTK inhibitor compound is 1-(4-(((6-amino-5-(4-phenoxyphenyl)pyrimidin-4-yl)amino)methyl)-4-fluoropiperidin-1-yl)prop-2-en-1-one or a pharmaceutically acceptable salt thereof.

[0027] In an embodiment, the lacrimal functional unit of a human subject is a lacrimal gland.

[0028] In an embodiment, the inhibition of ocular mast cell activation occurs in the surface and glandular epithelia of the cornea.

[0029] In an embodiment, the inhibition of ocular mast cell activation occurs in the conjunctiva.

[0030] In an embodiment, the inhibition of ocular mast cell activation occurs in the lacrimal gland or accessory lacrimal glands.

[0031] In an embodiment, the reduction occurs in the meibomian gland.

[0032] In another aspect, the present disclosure relates to a method of treating meibomian gland dysfunction (MGD) in a human subject in need thereof comprising topically administering to an eye of the human subject an amount of a Bruton's Tyrosine Kinase (BTK) inhibitor compound effective to reduce the meibomian gland dysfunction in the human subject, wherein the BTK inhibitor compound is 1-(4-(((6-amino-5-(4-phenoxyphenyl)pyrimidin-4-yl)amino)methyl)-4-fluoropiperidin-1-yl)prop-2-en-1-one or a pharmaceutically acceptable salt thereof.

[0033] In another aspect, the present disclosure relates to a method of inhibiting mast cell activation in a human subject in need thereof comprising topically administering to an eye of the human subject an amount of a Bruton's Tyrosine Kinase (BTK) inhibitor compound effective to reduce a meibomian gland dysfunction in the human subject, wherein the BTK inhibitor compound is 1-(4-(((6-amino-5-(4-phenoxyphenyl)pyrimidin-4-yl)amino)methyl)-4-fluoropiperidin-1-yl)prop-2-en-1-one or a pharmaceutically acceptable salt thereof.

[0034] In another aspect, the present disclosure relates to a method of inhibiting mast cell activation in a human subject in need thereof comprising topically administering to an eye of the human subject an amount of a Bruton's Tyrosine Kinase (BTK) inhibitor compound effective to inhibit mast cell activation in a meibomian gland in the human subject, wherein the BTK inhibitor compound is 1-(4-(((6-amino-5-(4-phenoxyphenyl)pyrimidin-4-yl)amino)methyl)-4-fluoropiperidin-1-yl)prop-2-en-1-one or a pharmaceutically acceptable salt thereof.

[0035] In another aspect, the present disclosure relates to a method of inhibiting mast cell activation in a lacrimal functional unit in an eye of a human subject in need thereof comprising topically administering to an eye of the human subject an amount of a Bruton's Tyrosine Kinase (BTK) inhibitor compound effective to inhibit mast cell activation in a lacrimal functional unit in the eye of the human subject, wherein the BTK inhibitor compound is 1-(4-(((6-amino-5-(4-phenoxyphenyl)pyrimidin-4-yl)amino)methyl)-4-fluoropiperidin-1-yl)prop-2-en-1-one or a pharmaceutically acceptable salt thereof.

[0036] In another aspect, the present disclosure relates to a method of inhibiting mast cell activation in the surface or glandular epithelia of the cornea in an eye of a human subject in need thereof comprising topically administering to an eye of the human subject an amount of a Bruton's Tyrosine Kinase (BTK) inhibitor compound effective to inhibit mast cell activation in the surface or glandular epithelia of the cornea in the eye of the human subject, wherein the BTK inhibitor compound is 1-(4-(((6-amino-5-(4-phenoxyphenyl)pyrimidin-4-yl)amino)methyl)-4-fluoropiperidin-1-yl)prop-2-en-1-one or a pharmaceutically acceptable salt thereof.

[0037] In another aspect, the present disclosure relates to a method of reducing trafficking of cells to sites of inflammation in a human subject in need thereof comprising topically administering to an eye of the human subject an amount of a Bruton's Tyrosine Kinase (BTK) inhibitor compound effective to reduce trafficking of cells to sites of inflammation in the human subject, wherein the BTK inhibitor compound is 1-(4-(((6-amino-5-(4-phenoxyphenyl)pyrimidin-4-yl)amino)methyl)-4-fluoropiperidin-1-

yl)prop-2-en-1-one or a pharmaceutically acceptable salt thereof. In an embodiment, the cells are mast cells. In an embodiment, the cells are B cells.

[0038] In an embodiment, the human subject has dry eye disease.

[0039] In an embodiment, the human subject has allergic conjunctivitis.

[0040] In an embodiment, the amount of BTK inhibitor compound administered is effective to reduce inflammation in the eye of the human subject compared to pre-treatment.

[0041] In an embodiment, the amount of BTK inhibitor compound administered is effective to reduce ocular redness in the eye of the human subject compared to pre-treatment.

[0042] In an embodiment, the amount of BTK inhibitor compound administered is effective to increase tear volume in the eye of the human subject compared to pre-treatment.

[0043] In another aspect, the present disclosure relates to a method of reducing or alleviating a sign or symptom of dry eye disease, the method comprising administering to a human subject with dry eye disease an amount of a Bruton's Tyrosine Kinase (BTK) inhibitor compound effective to reduce at least one symptom of dry eye disease wherein the reducing or alleviating of a sign or symptom of dry eye disease accompanies at least one of reduced total corneal fluorescein staining score, reduced central corneal fluorescein staining score, reduced inferior corneal fluorescein staining score, reduced superior corneal fluorescein staining score, increased Schirmer's unanesthetized test score, reduced conjunctival lissamine staining score, reduced tear osmolarity, increased tear break-up time, reduced conjunctival redness, reduced ocular discomfort severity (ODS) score, reduced ocular discomfort and four-symptom (OD4S) score, reduced ocular surface disease index (OSDI) score, reduced visual analog scale (VAS) ocular discomfort score, reduced inflammation of an eye, reduced ocular redness, reduced ocular itching score, increased tear volume in an eye, or any combination thereof, and the BTK inhibitor compound is 1-(4-(((6-amino-5-(4-phenoxyphenyl)pyrimidin-4-yl)amino)methyl)-4-fluoropiperidin-1-yl)prop-2-en-1-one or a pharmaceutically acceptable salt thereof.

[0044] In an embodiment, the dry eye disease is aqueous-deficient dry eye disease.

[0045] In an embodiment, the dry eye disease is hyper-evaporative dry eye disease.

[0046] In an embodiment, the dry eye disease is mixed aqueous-deficient and hyper-evaporative dry eye disease.

[0047] In an embodiment, the human subject also has allergic conjunctivitis.

[0048] In another aspect, the present disclosure relates to a method of reducing or alleviating a sign or symptom of allergic conjunctivitis, the method comprising administering to a human subject with allergic conjunctivitis an amount of a Bruton's Tyrosine Kinase (BTK) inhibitor compound effective to reduce at least one sign or symptom of allergic conjunctivitis wherein the reducing or alleviating of a sign or symptom of allergic conjunctivitis comprises reduced conjunctival redness, a reduced ocular itching score, or a combination thereof, and the BTK inhibitor compound is 1-(4-(((6-amino-5-(4-phenoxyphenyl)pyrimidin-4-yl)amino)methyl)-4-fluoropiperidin-1-yl)prop-2-en-1-one or a pharmaceutically acceptable salt thereof.

[0049] In an embodiment, the administering occurs at a frequency of twice daily.

[0050] In an embodiment, the administering occurs at a frequency of once daily.

[0051] In an embodiment, the administering occurs for at least one day.

[0052] In an embodiment, the administering occurs for at least seven days.

[0053] In an embodiment, the administering occurs for at least fourteen days.

[0054] In an embodiment, the administering occurs for at least twenty-eight days.

[0055] In an embodiment, the human subject also has dry eye disease.

[0056] In an embodiment, the administering occurs seasonally.

[0057] In an embodiment, the administering occurs perennially.

[0058] In an embodiment, the BTK inhibitor compound is present in an ophthalmic composition comprising one or more pharmaceutically acceptable excipients formulated for topical administration.

[0059] In an embodiment, the ophthalmic composition is administered as an eye drop.

[0060] In an embodiment, the ophthalmic composition is an oil-in-water microemulsion comprising: about 0.1% (1.0 mg/ml) of 1-(4-(((6-amino-5-(4-phenoxyphenyl)pyrimidin-4-yl)amino)methyl)-4-fluoropiperidin-1-yl)prop-2-en-1-one or a pharmaceutically acceptable salt thereof; about 8.43% polysorbate 20 (w/w); about 16.19% polysorbate 80 (w/w); about 1.77% isopropyl myristate (w/w); and phosphate buffered saline.

[0061] In an embodiment, the eye drop is administered by instilling a first eye drop in each eye, waiting a period of time, and then instilling a second eye drop in each eye.

[0062] In an embodiment, the period of time is 10 minutes $\pm$ 1 minute.

- [0063] In an embodiment, the period of time is 9 minutes $\pm$ 1 minute.
- [0064] In an embodiment, the period of time is 8 minutes $\pm$ 1 minute.
- [0065] In an embodiment, the period of time is 7 minutes $\pm$ 1 minute.
- [0066] In an embodiment, the period of time is 6 minutes $\pm$ 1 minute.
- [0067] In an embodiment, the period of time is 5 minutes $\pm$ 1 minute.
- [0068] In an embodiment, the period of time is 4 minutes $\pm$ 1 minute.
- [0069] In an embodiment, the period of time is 3 minutes $\pm$ 1 minute.
- [0070] In an embodiment, the method further comprises administering a loading dose via at least one eye drop in each eye prior to instilling the first eye drop.
- [0071] In an embodiment, the loading dose comprises one dose administered 12 hours $\pm$ 1.5 hours apart.
- [0072] In an embodiment, the loading dose comprises one dose administered 24 hours $\pm$ 1.5 hours apart.
- [0073] In an embodiment, the loading dose comprises one dose administered less than 12 hours apart $\pm$ 1.5 hours.
- [0074] In an embodiment, the loading dose comprises one dose administered more than 24 hours apart $\pm$ 1.5 hours.
- [0075] In an embodiment, the loading dose comprises two doses administered 12 hours $\pm$ 1.5 hours apart.
- [0076] In an embodiment, the loading dose comprises two doses administered 24 hours $\pm$ 1.5 hours apart.
- [0077] In an embodiment, the loading dose comprises two doses administered less than 12 hours apart $\pm$ 1.5 hours.
- [0078] In an embodiment, the loading dose comprises two doses administered more than 24 hours apart $\pm$ 1.5 hours.
- [0079] In another aspect, the present disclosure relates to a method of treating allergic conjunctivitis in a human subject in need thereof comprising administering as an eye drop to an eye of the human

subject an amount of a Bruton's Tyrosine Kinase (BTK) inhibitor compound effective to treat the allergic conjunctivitis in the human subject, wherein the eye drop is administered by instilling at least one first eye drop in each eye, waiting at least 5 minutes $\pm$ 1 minute, and then instilling at least one second eye drop in each eye; and the BTK inhibitor compound is 1-(4-(((6-amino-5-(4-phenoxyphenyl)pyrimidin-4-yl)amino)methyl)-4-fluoropiperidin-1-yl)prop-2-en-1-one or a pharmaceutically acceptable salt thereof.

[0080] In an embodiment, the methods described herein further comprise administering a loading dose prior to instilling the first eye drop, wherein the loading dose comprises one dose administered 12 hours apart $\pm$ 1.5 hours.

[0081] In an embodiment, the methods described herein further comprise administering a loading dose prior to instilling the first eye drop, wherein the loading dose comprises one dose administered 24 hours apart $\pm$ 1.5 hours.

[0082] In an embodiment, the methods described herein further comprise administering a loading dose prior to instilling the first eye drop, wherein the loading dose comprises one dose administered less than 12 hours apart $\pm$ 1.5 hours.

[0083] In an embodiment, the methods described herein further comprise administering a loading dose prior to instilling the first eye drop, wherein the loading dose comprises one dose administered more than 24 apart $\pm$ 1.5 hours.

[0084] In an embodiment, the methods described herein further comprise administering a loading dose prior to instilling the first eye drop, wherein the loading dose comprises two doses administered 12 hours apart $\pm$ 1.5 hours.

[0085] In an embodiment, the methods described herein further comprise administering a loading dose prior to instilling the first eye drop, wherein the loading dose comprises two doses administered 24 hours apart $\pm$ 1.5 hours.

[0086] In an embodiment, the methods described herein further comprise administering a loading dose prior to instilling the first eye drop, wherein the loading dose comprises two doses administered less than 12 hours apart $\pm$ 1.5 hours.

[0087] In an embodiment, the methods described herein further comprise administering a loading dose prior to instilling the first eye drop, wherein the loading dose comprises two doses administered more than 24 hours apart $\pm$ 1.5 hours.

[0088] In an embodiment, the methods described herein further comprise administering cyclosporine to the eye of the human subject.

[0089] In an embodiment, the cyclosporine is formulated as a cyclosporine ophthalmic microemulsion.

[0090] In an embodiment, the methods described herein further comprise administering an integrin LFA-1 inhibitor to the eye of a human subject.

[0091] In an embodiment, the integrin LFA-1 inhibitor is (S)-2-(2-(benzofuran-6-carbonyl)-5,7-dichloro-1,2,3,4-tetrahydroisoquinoline-6-carboxamido)-3-(3-(methylsulfonyl)phenyl)propanoic acid.

[0092] In an embodiment, the LFA-1 inhibitor is formulated as an ophthalmic solution.

[0093] In an embodiment, the methods described herein further comprise administering a wild-type KIT inhibitor to the eye of the human subject.

[0094] In an embodiment, the wild-type KIT inhibitor is formulated as an ophthalmic microemulsion.

[0095] In an embodiment, the methods described herein further comprise administering an antihistamine to the eye of the human subject.

[0096] In an embodiment, the antihistamine is formulated as an ophthalmic microemulsion.

[0097] In another aspect, the present disclosure relates to an ophthalmic composition comprising: about 0.1% (1.0 mg/ml) of 1-(4-(((6-amino-5-(4-phenoxyphenyl)pyrimidin-4-yl)amino)methyl)-4-fluoropiperidin-1-yl)prop-2-en-1-one or a pharmaceutically acceptable salt thereof; about 8.43% polysorbate 20 (w/w); about 16.19% polysorbate 80 (w/w); about 1.77% isopropyl myristate (w/w); and phosphate buffered saline; wherein the ophthalmic composition is an oil-in-water microemulsion.

[0098] In an embodiment, the ophthalmic composition is formulated as an eye drop.

[0099] In an embodiment, the ophthalmic composition does not contain any preservatives.

BRIEF DESCRIPTION OF THE DRAWINGS

[0100] The following abbreviations are used in the drawings: EC₅₀, half maximal effective concentration; EC₉₀, 90% maximal effective concentration; IL, interleukin; MC-1, mast cell donor 1; MC-2, mast cell donor 2; MC-3, mast cell donor 3; MC4, mast cell donor 4; MC5, mast cell donor 5; MC6, mast cell donor 6; MCP-1, monocyte chemoattractant protein 1; MFI, median fluorescent intensity; MIP-

1a, macrophage inflammatory protein-1 alpha; pBTK, phosphorylated Bruton's tyrosine kinase; unstim, unstimulated levels; CP-128, Compound 128 listed in Table 1.

[0101] Figure 1 is a graph showing the level of BTK phosphorylation in antigen-stimulated human mast cells after exposure to different concentrations of a BTK inhibitor.

[0102] Figure 2 is a graph showing surface expression of CD63 on antigen-stimulated human mast cells after exposure to different concentrations of a BTK inhibitor. CD63 has been identified as an activation and degranulation marker for mast cells (He SH, et al., Acta Pharmacol Sin. 2013;34(10):1270–83).

[0103] Figure 3 is a graph showing calcium flux in antigen-stimulated human mast cells after exposure to different concentrations of a BTK inhibitor.

[0104] Figure 4 is a graph showing histamine release from antigen-stimulated human mast cells after exposure to different concentrations of a BTK inhibitor.

[0105] Figure 5 is a graph showing production of cytokines by antigen-stimulated mast cells after exposure to a BTK inhibitor.

[0106] Figure 6 is a graph showing BTK inhibitor exposure to relevant target tissues.

[0107] Figure 7 is a graph showing BTK occupancy after exposure to a BTK inhibitor.

[0108] Figure 8 is a graph showing inhibition of signaling nodes important for mast cell activation, including PKC phosphorylation after exposure to a BTK inhibitor.

[0109] Figure 9 is a graph showing BTK inhibitor exposure resulting in inhibition of antigen-induced chemoattractant activity.

[0110] Figure 10 demonstrates the role of BTK in dry eye disease.

[0111] Figure 11 demonstrates the role of BTK and mast cells in allergic conjunctivitis.

DETAILED DESCRIPTION

[0112] While preferred embodiments of the disclosure are shown and described herein, such embodiments are provided by way of example only and are not intended to otherwise limit the scope of the disclosure. Various alternatives to the described embodiments may be employed in practicing the disclosure.

[0113] Unless defined otherwise, all technical and scientific terms used herein have the same meaning as is commonly understood by one of skill in the art to which this disclosure belongs.

[0114] The term “amount effective to” or “effective amount” or “therapeutically effective amount” or “amount sufficient” refers to that amount of an active pharmaceutical ingredient or combination of active pharmaceutical ingredients as described herein that is sufficient to effect the intended application including, but not limited to, disease treatment. A therapeutically effective amount may vary depending upon the intended application (*in vitro* or *in vivo*), or the subject and disease condition being treated (*e.g.* the weight, age and gender of the subject), the severity of the disease condition, the manner of administration, and other factors which can readily be determined by one of ordinary skill in the art. The term also applies to a dose that will induce a particular response in target cells, (*e.g.* the reduction of platelet adhesion and/or cell migration). The specific dose will vary depending on the particular compounds chosen, the dosing regimen to be followed, whether the compound is administered in combination with other compounds, timing of administration, the tissue to which it is administered, and the physical delivery system in which the compound is carried.

[0115] A “therapeutic effect” as that term is used herein, encompasses a therapeutic benefit and/or a prophylactic benefit as described above. A prophylactic effect includes delaying or eliminating the appearance of a disease or condition, delaying or eliminating the onset of signs or symptoms of a disease or condition, slowing, halting, or reversing the progression of a disease or condition, or any combination thereof.

[0116] The terms “QD,” “qd,” or “q.d.” means *quaque die*, once a day, or once daily. The terms “BID,” “bid,” or “b.i.d.” mean *bis in die*, twice a day, or twice daily. The terms “TID,” “tid,” or “t.i.d.” mean *ter in die*, three times a day, or three times daily. The terms “QID,” “qid,” or “q.i.d.” mean *quater in die*, four times a day, or four times daily.

[0117] The term “Polydispersity Index (PDI)” is defined as the square of the ratio of standard deviation (σ) of the particle diameter distribution divided by the mean particle diameter ($2a$), as illustrated by the formula: $PDI = (\sigma/2a)^2$. PDI is used to estimate the degree of non-uniformity of a size distribution of nanoparticles, and larger PDI values correspond to a larger size distribution in the particle sample. PDI can also indicate particle aggregation along with the consistency and efficiency of particle surface modifications. A sample is considered monodisperse when the PDI value is less than 0.1.

[0118] The term “pharmaceutically acceptable salt” refers to salts derived from a variety of organic and inorganic counter ions known in the art. Pharmaceutically acceptable acid addition salts can be

formed with inorganic acids and organic acids. Inorganic acids from which salts can be derived include, for example, hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid and phosphoric acid. Organic acids from which salts can be derived include, for example, acetic acid, propionic acid, glycolic acid, pyruvic acid, oxalic acid, maleic acid, malonic acid, succinic acid, fumaric acid, tartaric acid, citric acid, benzoic acid, cinnamic acid, mandelic acid, methanesulfonic acid, ethanesulfonic acid, *p*-toluenesulfonic acid and salicylic acid. Pharmaceutically acceptable base addition salts can be formed with inorganic and organic bases. Inorganic bases from which salts can be derived include, for example, sodium, potassium, lithium, ammonium, calcium, magnesium, iron, zinc, copper, manganese and aluminum. Organic bases from which salts can be derived include, for example, primary, secondary, and tertiary amines, substituted amines including naturally occurring substituted amines, cyclic amines and basic ion exchange resins. Specific examples include isopropylamine, trimethylamine, diethylamine, triethylamine, tripropylamine, and ethanolamine. In selected embodiments, the pharmaceutically acceptable base addition salt is chosen from ammonium, potassium, sodium, calcium, and magnesium salts.

[0119] “Pharmaceutically acceptable carrier” or “pharmaceutically acceptable excipient” is intended to include any and all solvents, dispersion media, coatings, antibacterial and antifungal agents, isotonic, and absorption delaying agents. The use of such media and agents for active pharmaceutical ingredients is well known in the art. Except insofar as any conventional media or agent is incompatible with the active pharmaceutical ingredient, its use in the therapeutic compositions of the disclosure is contemplated. Supplementary active ingredients can also be incorporated into the described compositions.

[0120] “Solvate” refers to a compound in physical association with one or more molecules of a pharmaceutically acceptable solvent.

[0121] Compounds of the disclosure also include crystalline and amorphous forms of the compounds listed in Table 1, including, for example, polymorphs, pseudopolymorphs, solvates, hydrates, unsolvated polymorphs (including anhydrides), conformational polymorphs, and amorphous forms of the compounds, as well as mixtures thereof.

[0122] When ranges are used herein to describe, for example, physical or chemical properties such as molecular weight or chemical formulae, all combinations and subcombinations of ranges and specific embodiments therein are intended to be included. Use of the term “about” when referring to a number or a numerical range means that the number or numerical range referred to is an approximation within

experimental variability (or within statistical experimental error), and thus the number or numerical range may vary from, for example, between 1% and 15% of the stated number or numerical range. The term “comprising” (and related terms such as “comprise” or “comprises” or “having” or “including”) includes those embodiments such as, for example, an embodiment of any composition of matter, method or process that “consist of” or “consist essentially of” the described features.

Methods of Reducing Ocular Mast Cell Degranulation and/or Ocular Mast Cell Cytokine Production with BTK Inhibitors

[0123] In certain aspects, the present disclosure relates to a method of reducing ocular mast cell degranulation and/or ocular mast cell cytokine production comprising the step of topically administering to an eye of a human subject in need thereof a Bruton’s Tyrosine Kinase (BTK) inhibitor compound. The BTK inhibitor compound is administered in an amount effective to reduce the ocular mast cell degranulation, and/or ocular mast cell cytokine production in the human subject. In an embodiment, the reduction in ocular mast cell degranulation and/or ocular mast cell cytokine production occurs in the meibomian gland.

[0124] In an embodiment, the human subject has an ophthalmic condition including, but not limited to, dry eye disease or allergic conjunctivitis. In an embodiment, the human subject has dry eye disease. In an embodiment, the dry eye disease is aqueous-deficient dry eye disease. In an embodiment, the dry eye disease is hyper-evaporative dry eye disease. In an embodiment, the dry eye disease is mixed aqueous-deficient and hyper-evaporative dry eye disease. In an embodiment, the human subject has allergic conjunctivitis. In an embodiment, the human subject has dry eye disease and allergic conjunctivitis.

[0125] In an embodiment, the amount of BTK inhibitor compound administered is effective to reduce inflammation in the eye of the human subject compared to pre-treatment. In an embodiment, the amount of BTK inhibitor compound administered is effective to reduce ocular redness in the eye of the human subject compared to pre-treatment. In an embodiment, the amount of BTK inhibitor compound administered is effective to increase tear volume in the eye of the human subject compared to pre-treatment.

[0126] In an embodiment, the administering occurs at a frequency of twice daily. In an embodiment, the administering occurs at a frequency of once daily. In an embodiment, the administering occurs for at least one day. In an embodiment, the administering occurs at a frequency of twice daily for at least one day. In an embodiment, the administering occurs at a frequency of once daily for at least one day. In an

embodiment, the administering occurs for at least seven days. In an embodiment, the administering occurs at a frequency of twice daily for at least seven days. In an embodiment, the administering occurs at a frequency of once daily for at least seven days. In an embodiment, the administering occurs for at least fourteen days. In an embodiment, the administering occurs at a frequency of twice daily for at least fourteen days. In an embodiment, the administering occurs at a frequency of once daily for at least fourteen days. In an embodiment, the administering occurs for at least twenty-eight days. In an embodiment, the administering occurs at a frequency of twice daily for at least twenty-eight days. In an embodiment, the administering occurs at a frequency of once daily for at least twenty-eight days. In an embodiment, the administering occurs seasonally. In an embodiment, the administering occurs perennially.

[0127] In certain aspects, the present disclosure relates to a method of reducing ocular mast cell degranulation and/or ocular mast cell cytokine production comprising the step of topically administering to an eye of a human subject in need thereof an ophthalmic composition comprising the BTK inhibitor compound. The BTK inhibitor compound is administered in an amount effective to reduce the ocular mast cell degranulation and/or ocular mast cell cytokine production in the human subject.

[0128] In an embodiment, the BTK inhibitor compound is present in an ophthalmic composition comprising one or more pharmaceutically acceptable excipients formulated for topical administration. In an embodiment, the ophthalmic composition is administered as an eye drop. In an embodiment, the ophthalmic composition is an oil-in-water microemulsion. In an embodiment, the ophthalmic composition is an oil-in-water microemulsion administered as an eye drop. In an embodiment, the ophthalmic composition is an oil-in-water microemulsion (including an oil-in-water microemulsion administered as an eye drop) comprising: the BTK inhibitor compound; polysorbate 20; polysorbate 80; isopropyl myristate; and phosphate buffered saline. In an embodiment, the ophthalmic composition is an oil-in-water microemulsion (including an oil-in-water microemulsion administered as an eye drop) comprising: about 0.05% to about 0.2% (w/w) of 1-(4-(((6-amino-5-(4-phenoxyphenyl)pyrimidin-4-yl)amino)methyl)-4-fluoropiperidin-1-yl)prop-2-en-1-one or a pharmaceutically acceptable salt thereof; about 5% to about 10% polysorbate 20 (w/w); about 10% to about 20% polysorbate 80 (w/w); about 1% to about 3% isopropyl myristate (w/w); and phosphate buffered saline. In an embodiment, the ophthalmic composition is an oil-in-water microemulsion (including an oil-in-water microemulsion administered as an eye drop) comprising: about 0.1% (1.0 mg/ml) of 1-(4-(((6-amino-5-(4-phenoxyphenyl)pyrimidin-4-yl)amino)methyl)-4-fluoropiperidin-1-yl)prop-2-en-1-one or a

pharmaceutically acceptable salt thereof; about 7% to about 10% polysorbate 20 (w/w); about 14% to about 18% polysorbate 80 (w/w); about 1.5% to about 2% isopropyl myristate (w/w); and phosphate buffered saline. In an embodiment, the ophthalmic composition is an oil-in-water microemulsion (including an oil-in-water microemulsion administered as an eye drop) comprising: about 0.1% (1.0 mg/ml) of 1-(4-(((6-amino-5-(4-phenoxyphenyl)pyrimidin-4-yl)amino)methyl)-4-fluoropiperidin-1-yl)prop-2-en-1-one or a pharmaceutically acceptable salt thereof; about 8.43% polysorbate 20 (w/w); about 16.19% polysorbate 80 (w/w); about 1.77% isopropyl myristate (w/w); and phosphate buffered saline. In an embodiment, the ophthalmic composition does not contain any preservatives.

[0129] In an embodiment, the eye drop is administered by instilling a first eye drop in each eye, waiting a period of time, and then instilling a second eye drop in each eye. In an embodiment, the period of time is 3 minutes $\pm$ 1 minute to 10 minutes $\pm$ 1 minute. In an embodiment, the period of time is 3 minutes $\pm$ 1 minute to 9 minutes $\pm$ 1 minute. In an embodiment, the period of time is 4 minutes $\pm$ 1 minute to 8 minutes $\pm$ 1 minute. In an embodiment, the period of time is 5 minutes $\pm$ 1 minute to 7 minutes $\pm$ 1 minute. In an embodiment, the period of time is 10 minutes $\pm$ 1 minute. In an embodiment, the period of time is 9 minutes $\pm$ 1 minute. In an embodiment, the period of time is 8 minutes $\pm$ 1 minute. In an embodiment, the period of time is 7 minutes $\pm$ 1 minute. In an embodiment, the period of time is 6 minutes $\pm$ 1 minute. In an embodiment, the period of time is 5 minutes $\pm$ 1 minute. In an embodiment, the period of time is 4 minutes $\pm$ 1 minute. In an embodiment, the period of time is 3 minutes $\pm$ 1 minute.

[0130] In an embodiment, the method further comprises administering a loading dose via at least one eye drop in each eye prior to instilling the first eye drop. In an embodiment, the loading dose comprises two doses administered 12 hours $\pm$ 1.5 hours apart. In an embodiment, the loading dose comprises two doses administered 24 hours $\pm$ 1.5 hours apart. In an embodiment, the loading dose comprises two doses administered less than 12 hours apart $\pm$ 1.5 hours. In an embodiment, the loading dose comprises two doses administered more than 24 hours apart $\pm$ 1.5 hours.

[0131] In an embodiment, the method further comprises administering cyclosporine to the eye of the human subject. In an embodiment, the cyclosporine is formulated as a cyclosporine ophthalmic microemulsion.

[0132] In an embodiment, the method further comprises administering a wild-type KIT inhibitor to the eye of the human subject. In an embodiment, the wild-type KIT inhibitor is formulated as an ophthalmic microemulsion.

[0133] In an embodiment, the method further comprises administering an integrin LFA-1 inhibitor to the eye of a human subject. In an embodiment, the integrin LFA-1 inhibitor is (S)-2-(2-(benzofuran-6-carbonyl)-5,7-dichloro-1,2,3,4-tetrahydroisoquinoline-6-carboxamido)-3-(3-(methylsulfonyl)phenyl)propanoic acid. In an embodiment, the LFA-1 inhibitor is formulated as an ophthalmic solution.

[0134] In an embodiment, the method further comprises administering an antihistamine to the eye of the human subject. In an embodiment, the antihistamine is formulated as an ophthalmic microemulsion.

Mechanism of BTK Inhibitors in Regulation of Mast Cells and Dry Eye Disease

[0135] Mast cells are sentinel cells that induce inflammation via release of pre-formed granules containing histamine and other pro-inflammatory mediators (i.e. degranulation). Mast cells reside in vascularized tissue compartments including, but not limited to, mucosal, cutaneous, connective, and ocular, and are activated by stimuli that trigger degranulation such as allergens. BTK is an important signaling protein of the FCεRI pathway, regulating IgE-mediated mast cell activation and cytokine-driven inflammation. Without wishing to be bound by theory, it is believed that BTK inhibitors block mast cell degranulation and cytokine production (e.g. pro-inflammatory cytokine production) through the inhibition of FCεRI-induced calcium release and immune response.

[0136] In B cells, immune responses to antigens are mediated through BTK interaction with the B cell receptor (BCR). When B cells recognize antigens through BCR, BTK interacts with BCR and initiates a signaling cascade critical to the production of proinflammatory cytokines and chemokines, as well as influencing antigen presentation on B cells. These actions allow the immune system to selectively target antigens for destruction. BTK is tyrosine phosphorylated and activated upon B cell antigen receptor (BCR) stimulation. Activated BTK phosphorylates phospholipase C gamma (PLCγ) thereby activating PLCγ to hydrolyze phosphatidylinositol 4,5-bisphosphate, yielding the second messenger diacylglycerol (DAG) and inositol 1,4,5-trisphosphate (IP3). PLCγ also binds phosphoinositol 3,4,5-trisphosphate (PIP3) produced by PI3K at the plasma membrane. BTK activation of PLCγ leads to Ca²⁺ mobilization and activation of NF-κB and MAP kinase pathways, which induces chemotaxis of B cells towards sites of inflammation.

[0137] Figure 10 demonstrates the role of BTK in dry eye disease. Lacrimal gland dysfunction occurs with age-related autoimmunity caused by dysregulated mast cell aggregation in the lacrimal gland of the eye. Chronic mast cell degranulation results in lacrimal gland (acinar cell) atrophy, fibrosis, and

inflammation. Mast cell-driven lacrimal unit dysfunction with desiccating stress on the ocular surface results in cytokine-mediated inflammation and ocular tissue damage. See Elbasiony, NPJ Aging, 2023, 9:2. Inhibition of BTK blocks activation and degranulation of mast cells and mast cell cytokine production in the lacrimal functional unit. Inhibition of BTK also inhibits activation of B cells and inflammatory cytokines leading to prevention, recruitment and activation of effector T cells. In this process, B cells recruit naïve T cells to produce an inflammatory response.

[0138] Age-related autoimmunity causes dysregulated mast cell aggregation in the lacrimal gland of the eye. Chronic mast cell degranulation results in lacrimal gland (acinar cell) atrophy, fibrosis, and inflammation. Mast cell-driven lacrimal unit dysfunction with desiccating stress on the ocular surface results in cytokine-mediated inflammation and ocular tissue damage. Without wishing to be bound by theory, it is believed that BTK inhibitors block activation and degranulation of mast cells in the lacrimal functional unit, inhibit activation of B cells and inflammatory cytokines, and prevent recruitment and activation of effector T cells.

Methods of Inhibiting Ocular Mast Cell Activation in a Lacrimal Functional Unit with BTK Inhibitors

[0139] The present disclosure relates to a method of inhibiting ocular mast cell activation in a lacrimal functional unit of a human subject comprising the step of topically administering to an eye of the human subject in need thereof a Bruton's Tyrosine Kinase (BTK) inhibitor compound. The BTK inhibitor compound is administered in an amount effective to inhibit ocular mast cell activation in the lacrimal functional unit of the human subject. In an embodiment, the lacrimal functional unit is a lacrimal gland. In an embodiment, the inhibition of ocular mast cell activation occurs in the surface and glandular epithelia of the cornea, in the conjunctiva, in the lacrimal gland or accessory lacrimal glands, and/or in the meibomian gland. In an embodiment, the inhibition of ocular mast cell activation occurs in the surface and glandular epithelia of the cornea. In an embodiment, the inhibition of ocular mast cell activation occurs in the conjunctiva. In an embodiment, the inhibition of ocular mast cell activation occurs in the lacrimal gland or accessory lacrimal glands. In an embodiment, the inhibition of ocular mast cell activation occurs in the meibomian gland.

[0140] In an embodiment, the human subject has an ophthalmic condition including, but not limited to, dry eye disease or allergic conjunctivitis. In an embodiment, the human subject has dry eye disease. In an embodiment, the dry eye disease is aqueous-deficient dry eye disease. In an embodiment, the dry eye disease is hyper-evaporative dry eye disease. In an embodiment, the dry eye disease is mixed aqueous-deficient and hyper-evaporative dry eye disease. In an embodiment, the human subject has

allergic conjunctivitis. In an embodiment, the human subject has dry eye disease and allergic conjunctivitis.

[0141] In an embodiment, the amount of BTK inhibitor compound administered is effective to reduce inflammation in the eye of the human subject compared to pre-treatment. In an embodiment, the amount of BTK inhibitor compound administered is effective to reduce ocular redness in the eye of the human subject compared to pre-treatment. In an embodiment, the amount of BTK inhibitor compound administered is effective to increase tear volume in the eye of the human subject compared to pre-treatment.

[0142] In an embodiment, the administering occurs at a frequency of twice daily. In an embodiment, the administering occurs at a frequency of once daily. In an embodiment, the administering occurs for at least one day. In an embodiment, the administering occurs at a frequency of twice daily for at least one day. In an embodiment, the administering occurs at a frequency of once daily for at least one day. In an embodiment, the administering occurs for at least seven days. In an embodiment, the administering occurs at a frequency of twice daily for at least seven days. In an embodiment, the administering occurs at a frequency of once daily for at least seven days. In an embodiment, the administering occurs for any of one, two, three, four, five, six, seven, eight, nine, ten, eleven, twelve, thirteen or fourteen days. In an embodiment, the administering occurs at a frequency of twice daily for occurs for any of one, two, three, four, five, six, seven, eight, nine, ten, eleven, twelve, thirteen or fourteen days. In an embodiment, the administering occurs at a frequency of once daily for at least seven days. In an embodiment, the administering occurs at a frequency of once daily for at least fourteen days. In an embodiment, the administering occurs for at least twenty-eight days. In an embodiment, the administering occurs at a frequency of twice daily for at least twenty-eight days. In an embodiment, the administering occurs at a frequency of once daily for at least twenty-eight days. In an embodiment, the administering occurs seasonally. In an embodiment, the administering occurs perennially.

[0143] The present disclosure relates to a method of inhibiting ocular mast cell activation in a lacrimal functional unit of a human subject comprising the step of topically administering to an eye of the human subject in need thereof an ophthalmic composition comprising the BTK inhibitor compound. The BTK inhibitor compound is administered in an amount effective inhibit ocular mast cell activation in a lacrimal functional unit of the human subject.

[0144] In an embodiment, the BTK inhibitor compound is present in an ophthalmic composition comprising one or more pharmaceutically acceptable excipients formulated for topical administration. In

an embodiment, the ophthalmic composition is administered as an eye drop. In an embodiment, the ophthalmic composition is an oil-in-water microemulsion. In an embodiment, the ophthalmic composition is an oil-in-water microemulsion administered as an eye drop. In an embodiment, the ophthalmic composition is an oil-in-water microemulsion (including an oil-in-water microemulsion administered as an eye drop) comprising: the BTK inhibitor compound; polysorbate 20; polysorbate 80; isopropyl myristate; and phosphate buffered saline. In an embodiment, the ophthalmic composition is an oil-in-water microemulsion (including an oil-in-water microemulsion administered as an eye drop) comprising: about 0.05% to about 0.2% (w/w) of 1-(4-(((6-amino-5-(4-phenoxyphenyl)pyrimidin-4-yl)amino)methyl)-4-fluoropiperidin-1-yl)prop-2-en-1-one or a pharmaceutically acceptable salt thereof; about 5% to about 10% polysorbate 20 (w/w); about 10% to about 20% polysorbate 80 (w/w); about 1% to about 3% isopropyl myristate (w/w); and phosphate buffered saline. In an embodiment, the ophthalmic composition is an oil-in-water microemulsion (including an oil-in-water microemulsion administered as an eye drop) comprising: about 0.1% (1.0 mg/ml) of 1-(4-(((6-amino-5-(4-phenoxyphenyl)pyrimidin-4-yl)amino)methyl)-4-fluoropiperidin-1-yl)prop-2-en-1-one or a pharmaceutically acceptable salt thereof; about 7% to about 10% polysorbate 20 (w/w); about 14% to about 18% polysorbate 80 (w/w); about 1.5% to about 2% isopropyl myristate (w/w); and phosphate buffered saline. In an embodiment, the ophthalmic composition is an oil-in-water microemulsion (including an oil-in-water microemulsion administered as an eye drop) comprising: about 0.1% (1.0 mg/ml) of 1-(4-(((6-amino-5-(4-phenoxyphenyl)pyrimidin-4-yl)amino)methyl)-4-fluoropiperidin-1-yl)prop-2-en-1-one or a pharmaceutically acceptable salt thereof; about 8.43% polysorbate 20 (w/w); about 16.19% polysorbate 80 (w/w); about 1.77% isopropyl myristate (w/w); and phosphate buffered saline. In an embodiment, the ophthalmic composition does not contain any preservatives.

[0145] In an embodiment, the eye drop is administered by instilling a first eye drop in each eye, waiting a period of time, and then instilling a second eye drop in each eye. In an embodiment, the period of time is 3 minutes $\pm$ 1 minute to 10 minutes $\pm$ 1 minute. In an embodiment, the period of time is 3 minutes $\pm$ 1 minute to 9 minutes $\pm$ 1 minute. In an embodiment, the period of time is 4 minutes $\pm$ 1 minute to 8 minutes $\pm$ 1 minute. In an embodiment, the period of time is 5 minutes $\pm$ 1 minute to 7 minutes $\pm$ 1 minute. In an embodiment, the period of time is 10 minutes $\pm$ 1 minute. In an embodiment, the period of time is 9 minutes $\pm$ 1 minute. In an embodiment, the period of time is 8 minutes $\pm$ 1 minute. In an embodiment, the period of time is 7 minutes $\pm$ 1 minute. In an embodiment, the period of time is 6 minutes $\pm$ 1 minute. In an embodiment, the period of time is 5 minutes $\pm$ 1 minute. In an

embodiment, the period of time is 4 minutes $\pm$ 1 minute. In an embodiment, the period of time is 3 minutes $\pm$ 1 minute.

[0146] In an embodiment, the method further comprises administering a loading dose via at least one eye drop in each eye prior to instilling the first eye drop. In an embodiment, the loading dose comprises two doses administered 12 hours $\pm$ 1.5 hours apart. In an embodiment, the loading dose comprises two doses administered 24 hours $\pm$ 1.5 hours apart. In an embodiment, the loading dose comprises two doses administered less than 12 hours apart $\pm$ 1.5 hours. In an embodiment, the loading dose comprises two doses administered more than 24 hours apart $\pm$ 1.5 hours.

[0147] In an embodiment, the method further comprises administering cyclosporine to the eye of the human subject. In an embodiment, the cyclosporine is formulated as a cyclosporine ophthalmic microemulsion.

[0148] In an embodiment, the method further comprises administering a wild-type KIT inhibitor to the eye of the human subject. In an embodiment, the wild-type KIT inhibitor is formulated as an ophthalmic microemulsion.

[0149] In an embodiment, the method further comprises administering an integrin LFA-1 inhibitor to the eye of a human subject. In an embodiment, the integrin LFA-1 inhibitor is (S)-2-(2-(benzofuran-6-carbonyl)-5,7-dichloro-1,2,3,4-tetrahydroisoquinoline-6-carboxamido)-3-(3-(methylsulfonyl)phenyl)propanoic acid. In an embodiment, the LFA-1 inhibitor is formulated as an ophthalmic solution.

[0150] In an embodiment, the method further comprises administering an antihistamine to the eye of the human subject. In an embodiment, the antihistamine is formulated as an ophthalmic microemulsion.

Methods of Treating Meibomian Gland Dysfunction with BTK Inhibitors

[0151] In certain aspects, the present disclosure relates to a method of treating meibomian gland dysfunction comprising the step of topically administering to an eye of a human subject in need thereof a Bruton's Tyrosine Kinase (BTK) inhibitor compound. The BTK inhibitor compound is administered in an amount effective to treat the meibomian gland dysfunction in the human subject.

[0152] In an embodiment, the human subject has an ophthalmic condition including, but not limited to, dry eye disease or allergic conjunctivitis. In an embodiment, the human subject has dry eye disease. In an embodiment, the dry eye disease is aqueous-deficient dry eye disease. In an embodiment, the dry

eye disease is hyper-evaporative dry eye disease. In an embodiment, the dry eye disease is mixed aqueous-deficient and hyper-evaporative dry eye disease. In an embodiment, the human subject has allergic conjunctivitis. In an embodiment, the human subject has dry eye disease and allergic conjunctivitis.

[0153] In an embodiment, the amount of BTK inhibitor compound administered is effective to reduce inflammation in the eye of the human subject compared to pre-treatment. In an embodiment, the amount of BTK inhibitor compound administered is effective to reduce ocular redness in the eye of the human subject compared to pre-treatment. In an embodiment, the amount of BTK inhibitor compound administered is effective to increase tear volume in the eye of the human subject compared to pre-treatment.

[0154] In an embodiment, the administering occurs at a frequency of twice daily. In an embodiment, the administering occurs at a frequency of once daily. In an embodiment, the administering occurs for at least one day. In an embodiment, the administering occurs at a frequency of twice daily for at least one day. In an embodiment, the administering occurs at a frequency of once daily for at least one day. In an embodiment, the administering occurs for at least seven days. In an embodiment, the administering occurs at a frequency of twice daily for at least seven days. In an embodiment, the administering occurs at a frequency of once daily for at least seven days. In an embodiment, the administering occurs for at least fourteen days. In an embodiment, the administering occurs at a frequency of twice daily for at least fourteen days. In an embodiment, the administering occurs at a frequency of once daily for at least fourteen days. In an embodiment, the administering occurs for at least twenty-eight days. In an embodiment, the administering occurs at a frequency of twice daily for at least twenty-eight days. In an embodiment, the administering occurs at a frequency of once daily for at least twenty-eight days. In an embodiment, the administering occurs seasonally. In an embodiment, the administering occurs perennially.

[0155] In certain aspects, the present disclosure relates to a method of treating meibomian gland dysfunction comprising the step of topically administering to an eye of a human subject in need thereof an ophthalmic composition comprising the BTK inhibitor compound. The BTK inhibitor compound is administered in an amount effective to treat the meibomian gland dysfunction in the human subject.

[0156] In an embodiment, the BTK inhibitor compound is present in an ophthalmic composition comprising one or more pharmaceutically acceptable excipients formulated for topical administration. In an embodiment, the ophthalmic composition is administered as an eye drop. In an embodiment, the

ophthalmic composition is an oil-in-water microemulsion. In an embodiment, the ophthalmic composition is an oil-in-water microemulsion administered as an eye drop. In an embodiment, the ophthalmic composition is an oil-in-water microemulsion (including an oil-in-water microemulsion administered as an eye drop) comprising: the BTK inhibitor compound; polysorbate 20; polysorbate 80; isopropyl myristate; and phosphate buffered saline. In an embodiment, the ophthalmic composition is an oil-in-water microemulsion (including an oil-in-water microemulsion administered as an eye drop) comprising: about 0.05% to about 0.2% (w/w) of 1-(4-(((6-amino-5-(4-phenoxyphenyl)pyrimidin-4-yl)amino)methyl)-4-fluoropiperidin-1-yl)prop-2-en-1-one or a pharmaceutically acceptable salt thereof; about 5% to about 10% polysorbate 20 (w/w); about 10% to about 20% polysorbate 80 (w/w); about 1% to about 3% isopropyl myristate (w/w); and phosphate buffered saline. In an embodiment, the ophthalmic composition is an oil-in-water microemulsion (including an oil-in-water microemulsion administered as an eye drop) comprising: about 0.1% (1.0 mg/ml) of 1-(4-(((6-amino-5-(4-phenoxyphenyl)pyrimidin-4-yl)amino)methyl)-4-fluoropiperidin-1-yl)prop-2-en-1-one or a pharmaceutically acceptable salt thereof; about 7% to about 10% polysorbate 20 (w/w); about 14% to about 18% polysorbate 80 (w/w); about 1.5% to about 2% isopropyl myristate (w/w); and phosphate buffered saline. In an embodiment, the ophthalmic composition is an oil-in-water microemulsion (including an oil-in-water microemulsion administered as an eye drop) comprising: about 0.1% (1.0 mg/ml) of 1-(4-(((6-amino-5-(4-phenoxyphenyl)pyrimidin-4-yl)amino)methyl)-4-fluoropiperidin-1-yl)prop-2-en-1-one or a pharmaceutically acceptable salt thereof; about 8.43% polysorbate 20 (w/w); about 16.19% polysorbate 80 (w/w); about 1.77% isopropyl myristate (w/w); and phosphate buffered saline. In an embodiment, the ophthalmic composition does not contain any preservatives.

[0157] In an embodiment, the eye drop is administered by instilling a first eye drop in each eye, waiting a period of time, and then instilling a second eye drop in each eye. In an embodiment, the period of time is 3 minutes $\pm$ 1 minute to 10 minutes $\pm$ 1 minute. In an embodiment, the period of time is 3 minutes $\pm$ 1 minute to 9 minutes $\pm$ 1 minute. In an embodiment, the period of time is 4 minutes $\pm$ 1 minute to 8 minutes $\pm$ 1 minute. In an embodiment, the period of time is 5 minutes $\pm$ 1 minute to 7 minutes $\pm$ 1 minute. In an embodiment, the period of time is 10 minutes $\pm$ 1 minute. In an embodiment, the period of time is 9 minutes $\pm$ 1 minute. In an embodiment, the period of time is 8 minutes $\pm$ 1 minute. In an embodiment, the period of time is 7 minutes $\pm$ 1 minute. In an embodiment, the period of time is 6 minutes $\pm$ 1 minute. In an embodiment, the period of time is 5 minutes $\pm$ 1 minute. In an embodiment, the period of time is 4 minutes $\pm$ 1 minute. In an embodiment, the period of time is 3 minutes $\pm$ 1 minute.

[0158] In an embodiment, the method further comprises administering a loading dose via at least one eye drop in each eye prior to instilling the first eye drop. In an embodiment, the loading dose comprises two doses administered 12 hours $\pm$ 1.5 hours apart. In an embodiment, the loading dose comprises two doses administered 24 hours $\pm$ 1.5 hours apart. In an embodiment, the loading dose comprises two doses administered less than 12 hours apart $\pm$ 1.5 hours. In an embodiment, the loading dose comprises two doses administered more than 24 hours apart $\pm$ 1.5 hours.

[0159] In an embodiment, the method further comprises administering cyclosporine to the eye of the human subject. In an embodiment, the cyclosporine is formulated as a cyclosporine ophthalmic microemulsion.

[0160] In an embodiment, the method further comprises administering a wild-type KIT inhibitor to the eye of the human subject. In an embodiment, the wild-type KIT inhibitor is formulated as an ophthalmic microemulsion.

[0161] In an embodiment, the method further comprises administering an integrin LFA-1 inhibitor to the eye of a human subject. In an embodiment, the integrin LFA-1 inhibitor is (S)-2-(2-(benzofuran-6-carbonyl)-5,7-dichloro-1,2,3,4-tetrahydroisoquinoline-6-carboxamido)-3-(3-(methylsulfonyl)phenyl)propanoic acid. In an embodiment, the LFA-1 inhibitor is formulated as an ophthalmic solution.

[0162] In an embodiment, the method further comprises administering an antihistamine to the eye of the human subject. In an embodiment, the antihistamine is formulated as an ophthalmic microemulsion.

Methods of Inhibiting Mast Cell Activation with BTK Inhibitors

[0163] In certain aspects, the present disclosure relates to a method of inhibiting mast cell activation in a human subject comprising the step of topically administering to an eye of the human subject in need thereof a Bruton's Tyrosine Kinase (BTK) inhibitor compound. The BTK inhibitor compound is administered in an amount effective to inhibit mast cell activation in the human subject.

[0164] In an embodiment, the human subject has an ophthalmic condition including, but not limited to, dry eye disease or allergic conjunctivitis. In an embodiment, the human subject has dry eye disease. In an embodiment, the dry eye disease is aqueous-deficient dry eye disease. In an embodiment, the dry eye disease is hyper-evaporative dry eye disease. In an embodiment, the dry eye disease is mixed aqueous-deficient and hyper-evaporative dry eye disease. In an embodiment, the human subject has

allergic conjunctivitis. In an embodiment, the human subject has dry eye disease and allergic conjunctivitis.

[0165] In an embodiment, the amount of BTK inhibitor compound administered is effective to reduce inflammation in the eye of the human subject compared to pre-treatment. In an embodiment, the amount of BTK inhibitor compound administered is effective to reduce ocular redness in the eye of the human subject compared to pre-treatment. In an embodiment, the amount of BTK inhibitor compound administered is effective to increase tear volume in the eye of the human subject compared to pre-treatment.

[0166] In an embodiment, the administering occurs at a frequency of twice daily. In an embodiment, the administering occurs at a frequency of once daily. In an embodiment, the administering occurs for at least one day. In an embodiment, the administering occurs at a frequency of twice daily for at least one day. In an embodiment, the administering occurs at a frequency of once daily for at least one day. In an embodiment, the administering occurs for at least seven days. In an embodiment, the administering occurs at a frequency of twice daily for at least seven days. In an embodiment, the administering occurs at a frequency of once daily for at least seven days. In an embodiment, the administering occurs for at least fourteen days. In an embodiment, the administering occurs at a frequency of twice daily for at least fourteen days. In an embodiment, the administering occurs at a frequency of once daily for at least fourteen days. In an embodiment, the administering occurs for at least twenty-eight days. In an embodiment, the administering occurs at a frequency of twice daily for at least twenty-eight days. In an embodiment, the administering occurs at a frequency of once daily for at least twenty-eight days. In an embodiment, the administering occurs seasonally. In an embodiment, the administering occurs perennally.

[0167] The present disclosure relates to a method of inhibiting mast cell activation in a human subject comprising the step of topically administering to an eye of the human subject in need thereof an ophthalmic composition comprising the BTK inhibitor compound. The BTK inhibitor compound is administered in an amount effective inhibit mast cell activation in the human subject.

[0168] In an embodiment, the BTK inhibitor compound is present in an ophthalmic composition comprising one or more pharmaceutically acceptable excipients formulated for topical administration. In an embodiment, the ophthalmic composition is administered as an eye drop. In an embodiment, the ophthalmic composition is an oil-in-water microemulsion. In an embodiment, the ophthalmic composition is an oil-in-water microemulsion administered as an eye drop. In an embodiment, the

ophthalmic composition is an oil-in-water microemulsion (including an oil-in-water microemulsion administered as an eye drop) comprising: the BTK inhibitor compound; polysorbate 20; polysorbate 80; isopropyl myristate; and phosphate buffered saline. In an embodiment, the ophthalmic composition is an oil-in-water microemulsion (including an oil-in-water microemulsion administered as an eye drop) comprising: about 0.05% to about 0.2% (w/w) of 1-(4-(((6-amino-5-(4-phenoxyphenyl)pyrimidin-4-yl)amino)methyl)-4-fluoropiperidin-1-yl)prop-2-en-1-one or a pharmaceutically acceptable salt thereof; about 5% to about 10% polysorbate 20 (w/w); about 10% to about 20% polysorbate 80 (w/w); about 1% to about 3% isopropyl myristate (w/w); and phosphate buffered saline. In an embodiment, the ophthalmic composition is an oil-in-water microemulsion (including an oil-in-water microemulsion administered as an eye drop) comprising: about 0.1% (1.0 mg/ml) of 1-(4-(((6-amino-5-(4-phenoxyphenyl)pyrimidin-4-yl)amino)methyl)-4-fluoropiperidin-1-yl)prop-2-en-1-one or a pharmaceutically acceptable salt thereof; about 7% to about 10% polysorbate 20 (w/w); about 14% to about 18% polysorbate 80 (w/w); about 1.5% to about 2% isopropyl myristate (w/w); and phosphate buffered saline. In an embodiment, the ophthalmic composition is an oil-in-water microemulsion (including an oil-in-water microemulsion administered as an eye drop) comprising: about 0.1% (1.0 mg/ml) of 1-(4-(((6-amino-5-(4-phenoxyphenyl)pyrimidin-4-yl)amino)methyl)-4-fluoropiperidin-1-yl)prop-2-en-1-one or a pharmaceutically acceptable salt thereof; about 8.43% polysorbate 20 (w/w); about 16.19% polysorbate 80 (w/w); about 1.77% isopropyl myristate (w/w); and phosphate buffered saline. In an embodiment, the ophthalmic composition does not contain any preservatives.

[0169] In an embodiment, the eye drop is administered by instilling a first eye drop in each eye, waiting a period of time, and then instilling a second eye drop in each eye. In an embodiment, the period of time is 3 minutes $\pm$ 1 minute to 10 minutes $\pm$ 1 minute. In an embodiment, the period of time is 3 minutes $\pm$ 1 minute to 9 minutes $\pm$ 1 minute. In an embodiment, the period of time is 4 minutes $\pm$ 1 minute to 8 minutes $\pm$ 1 minute. In an embodiment, the period of time is 5 minutes $\pm$ 1 minute to 7 minutes $\pm$ 1 minute. In an embodiment, the period of time is 10 minutes $\pm$ 1 minute. In an embodiment, the period of time is 9 minutes $\pm$ 1 minute. In an embodiment, the period of time is 8 minutes $\pm$ 1 minute. In an embodiment, the period of time is 7 minutes $\pm$ 1 minute. In an embodiment, the period of time is 6 minutes $\pm$ 1 minute. In an embodiment, the period of time is 5 minutes $\pm$ 1 minute. In an embodiment, the period of time is 4 minutes $\pm$ 1 minute. In an embodiment, the period of time is 3 minutes $\pm$ 1 minute.

[0170] In an embodiment, the method further comprises administering a loading dose via at least one eye drop in each eye prior to instilling the first eye drop. In an embodiment, the loading dose comprises two doses administered 12 hours $\pm$ 1.5 hours apart. In an embodiment, the loading dose comprises two doses administered 24 hours $\pm$ 1.5 hours apart. In an embodiment, the loading dose comprises two doses administered less than 12 hours apart $\pm$ 1.5 hours. In an embodiment, the loading dose comprises two doses administered more than 24 hours apart $\pm$ 1.5 hours.

[0171] In an embodiment, the method further comprises administering cyclosporine to the eye of the human subject. In an embodiment, the cyclosporine is formulated as a cyclosporine ophthalmic microemulsion.

[0172] In an embodiment, the method further comprises administering a wild-type KIT inhibitor to the eye of the human subject. In an embodiment, the wild-type KIT inhibitor is formulated as an ophthalmic microemulsion.

[0173] In an embodiment, the method further comprises administering an integrin LFA-1 inhibitor to the eye of a human subject. In an embodiment, the integrin LFA-1 inhibitor is (S)-2-(2-(benzofuran-6-carbonyl)-5,7-dichloro-1,2,3,4-tetrahydroisoquinoline-6-carboxamido)-3-(3-(methylsulfonyl)phenyl)propanoic acid. In an embodiment, the LFA-1 inhibitor is formulated as an ophthalmic solution.

[0174] In an embodiment, the method further comprises administering an antihistamine to the eye of the human subject. In an embodiment, the antihistamine is formulated as an ophthalmic microemulsion.

Methods of Reducing or Alleviating a Sign or Symptom of Dry Eye Disease with BTK Inhibitors

[0175] In certain aspects, the present disclosure relates to a method of reducing or alleviating a sign or symptom of dry eye disease comprising the step of administering to a human subject with dry eye disease a Bruton's Tyrosine Kinase (BTK) inhibitor compound. In an embodiment, the BTK inhibitor compound is topically administered to an eye of the human subject. The BTK inhibitor compound is administered in an amount effective to reduce or alleviate at least one sign or symptom of dry eye disease in the human subject. The reducing or alleviating of a sign or symptom of dry eye disease accompanies at least one of reduced total corneal fluorescein staining score, reduced central corneal fluorescein staining score, reduced inferior corneal fluorescein staining score, reduced superior corneal fluorescein staining score, increased Schirmer's unanesthetized test score, reduced conjunctival

lissamine staining score, reduced tear osmolarity, increased tear break-up time, reduced conjunctival redness, reduced ocular discomfort severity (ODS) score, reduced ocular discomfort and four-symptom (OD4S) score, reduced ocular surface disease index (OSDI) score, reduced visual analog scale (VAS) ocular discomfort score, reduced inflammation of an eye, reduced ocular redness, reduced ocular itching score, increased tear volume in an eye, or any combination thereof. In an embodiment, the reduction of at least one sign or symptom is about a 1% reduction, a 5% reduction, a 10% reduction, a 15% reduction, a 20% reduction, a 25% reduction, a 30% reduction, a 35% reduction, a 40% reduction, a 45% reduction, a 50% reduction, a 55% reduction, a 60% reduction, a 65% reduction, a 70% reduction, a 75% reduction, a 80% reduction, a 85% reduction, a 90% reduction, a 95% reduction, a 96% reduction, a 97% reduction, a 98% reduction, or a 99% or greater reduction.

[0176] In an embodiment, the dry eye disease is aqueous-deficient dry eye disease. In an embodiment, the dry eye disease is hyper-evaporative dry eye disease. In an embodiment, the dry eye disease is mixed aqueous-deficient and hyper-evaporative dry eye disease.

[0177] In an embodiment, the administering occurs at a frequency of twice daily. In an embodiment, the administering occurs at a frequency of once daily. In an embodiment, the administering occurs for at least one day. In an embodiment, the administering occurs at a frequency of twice daily for at least one day. In an embodiment, the administering occurs at a frequency of once daily for at least one day. In an embodiment, the administering occurs for at least seven days. In an embodiment, the administering occurs at a frequency of twice daily for at least seven days. In an embodiment, the administering occurs at a frequency of once daily for at least seven days. In an embodiment, the administering occurs for at least fourteen days. In an embodiment, the administering occurs at a frequency of twice daily for at least fourteen days. In an embodiment, the administering occurs at a frequency of once daily for at least fourteen days. In an embodiment, the administering occurs for at least twenty-eight days. In an embodiment, the administering occurs at a frequency of twice daily for at least twenty-eight days. In an embodiment, the administering occurs at a frequency of once daily for at least twenty-eight days. In an embodiment, the administering occurs seasonally. In an embodiment, the administering occurs perennially.

[0178] In certain aspects, the present disclosure relates to a method of reducing or alleviating a sign or symptom of dry eye disease comprising the step of administering to a human subject with dry eye disease an ophthalmic composition comprising the BTK inhibitor compound. In an embodiment, the BTK inhibitor compound is administered topically to an eye of the human subject. The BTK inhibitor

compound is administered in an amount effective to reduce or alleviate at least one sign or symptom of dry eye disease in the human subject. The reducing or alleviating of a sign or symptom of dry eye disease accompanies at least one of reduced total corneal fluorescein staining score, reduced central corneal fluorescein staining score, reduced inferior corneal fluorescein staining score, reduced superior corneal fluorescein staining score, increased Schirmer's unanesthetized test score, reduced conjunctival lissamine staining score, reduced tear osmolarity, increased tear break-up time, reduced conjunctival redness, reduced ocular discomfort severity (ODS) score, reduced ocular discomfort and four-symptom (OD4S) score, reduced ocular surface disease index (OSDI) score, reduced visual analog scale (VAS) ocular discomfort score, reduced inflammation of an eye, reduced ocular redness, reduced ocular itching score, increased tear volume in an eye, or any combination thereof. In an embodiment, the reduction of at least one sign or symptom is about a 1% reduction, a 5% reduction, a 10% reduction, a 15% reduction, a 20% reduction, a 25% reduction, a 30% reduction, a 35% reduction, a 40% reduction, a 45% reduction, a 50% reduction, a 55% reduction, a 60% reduction, a 65% reduction, a 70% reduction, a 75% reduction, a 80% reduction, a 85% reduction, a 90% reduction, a 95% reduction, a 96% reduction, a 97% reduction, a 98% reduction, or a 99% or greater reduction.

[0179] In an embodiment, the BTK inhibitor compound is present in an ophthalmic composition comprising one or more pharmaceutically acceptable excipients formulated for topical administration. In an embodiment, the ophthalmic composition is administered as an eye drop. In an embodiment, the ophthalmic composition is an oil-in-water microemulsion. In an embodiment, the ophthalmic composition is an oil-in-water microemulsion administered as an eye drop. In an embodiment, the ophthalmic composition is an oil-in-water microemulsion (including an oil-in-water microemulsion administered as an eye drop) comprising: the BTK inhibitor compound; polysorbate 20; polysorbate 80; isopropyl myristate; and phosphate buffered saline. In an embodiment, the ophthalmic composition is an oil-in-water microemulsion (including an oil-in-water microemulsion administered as an eye drop) comprising: about 0.05% to about 0.2% (w/w) of 1-(4-(((6-amino-5-(4-phenoxyphenyl)pyrimidin-4-yl)amino)methyl)-4-fluoropiperidin-1-yl)prop-2-en-1-one or a pharmaceutically acceptable salt thereof; about 5% to about 10% polysorbate 20 (w/w); about 10% to about 20% polysorbate 80 (w/w); about 1% to about 3% isopropyl myristate (w/w); and phosphate buffered saline. In an embodiment, the ophthalmic composition is an oil-in-water microemulsion (including an oil-in-water microemulsion administered as an eye drop) comprising: about 0.1% (1.0 mg/ml) of 1-(4-(((6-amino-5-(4-phenoxyphenyl)pyrimidin-4-yl)amino)methyl)-4-fluoropiperidin-1-yl)prop-2-en-1-one or a pharmaceutically acceptable salt thereof; about 7% to about 10% polysorbate 20 (w/w); about 14% to

about 18% polysorbate 80 (w/w); about 1.5% to about 2% isopropyl myristate (w/w); and phosphate buffered saline. In an embodiment, the ophthalmic composition is an oil-in-water microemulsion (including an oil-in-water microemulsion administered as an eye drop) comprising: about 0.1% (1.0 mg/ml) of 1-(4-(((6-amino-5-(4-phenoxyphenyl)pyrimidin-4-yl)amino)methyl)-4-fluoropiperidin-1-yl)prop-2-en-1-one or a pharmaceutically acceptable salt thereof; about 8.43% polysorbate 20 (w/w); about 16.19% polysorbate 80 (w/w); about 1.77% isopropyl myristate (w/w); and phosphate buffered saline. In an embodiment, the ophthalmic composition does not contain any preservatives.

[0180] In an embodiment, the eye drop is administered by instilling a first eye drop in each eye, waiting a period of time, and then instilling a second eye drop in each eye. In an embodiment, the period of time is 3 minutes $\pm$ 1 minute to 10 minutes $\pm$ 1 minute. In an embodiment, the period of time is 3 minutes $\pm$ 1 minute to 9 minutes $\pm$ 1 minute. In an embodiment, the period of time is 4 minutes $\pm$ 1 minute to 8 minutes $\pm$ 1 minute. In an embodiment, the period of time is 5 minutes $\pm$ 1 minute to 7 minutes $\pm$ 1 minute. In an embodiment, the period of time is 10 minutes $\pm$ 1 minute. In an embodiment, the period of time is 9 minutes $\pm$ 1 minute. In an embodiment, the period of time is 8 minutes $\pm$ 1 minute. In an embodiment, the period of time is 7 minutes $\pm$ 1 minute. In an embodiment, the period of time is 6 minutes $\pm$ 1 minute. In an embodiment, the period of time is 5 minutes $\pm$ 1 minute. In an embodiment, the period of time is 4 minutes $\pm$ 1 minute. In an embodiment, the period of time is 3 minutes $\pm$ 1 minute.

[0181] In an embodiment, the method further comprises administering a loading dose via at least one eye drop in each eye prior to instilling the first eye drop. In an embodiment, the loading dose comprises two doses administered 12 hours $\pm$ 1.5 hours apart. In an embodiment, the loading dose comprises two doses administered 24 hours $\pm$ 1.5 hours apart. In an embodiment, the loading dose comprises two doses administered less than 12 hours apart $\pm$ 1.5 hours. In an embodiment, the loading dose comprises two doses administered more than 24 hours apart $\pm$ 1.5 hours.

[0182] In an embodiment, the method further comprises administering cyclosporine to the eye of the human subject. In an embodiment, the cyclosporine is formulated as a cyclosporine ophthalmic microemulsion.

[0183] In an embodiment, the method further comprises administering a wild-type KIT inhibitor to the eye of the human subject. In an embodiment, the wild-type KIT inhibitor is formulated as an ophthalmic microemulsion.

[0184] In an embodiment, the method further comprises administering an integrin LFA-1 inhibitor to the eye of a human subject. In an embodiment, the integrin LFA-1 inhibitor is (S)-2-(2-(benzofuran-6-carbonyl)-5,7-dichloro-1,2,3,4-tetrahydroisoquinoline-6-carboxamido)-3-(3-(methylsulfonyl)phenyl)propanoic acid. In an embodiment, the LFA-1 inhibitor is formulated as an ophthalmic solution.

[0185] In an embodiment, the method further comprises administering an antihistamine to the eye of the human subject. In an embodiment, the antihistamine is formulated as an ophthalmic microemulsion.

Mechanism of BTK Inhibitors in Allergic Conjunctivitis

[0186] Allergic conjunctivitis is a mast cell-driven condition caused by allergic reactions to allergens such as pollen, ragweed, and animal dander. Associated redness and ocular itching may impact quality of life, especially in those resistant to standard of care. When exposed to allergens, IgE crosslinks with FcεRI, activating downstream signaling proteins such as BTK. BTK is an important signaling protein of the FcεRI pathway that regulates IgE-mediated mast cell activation and degranulation (e.g. CD63+). Without wishing to be bound by theory, it is believed that BTK inhibitors block mast cell degranulation through the inhibition of calcium signaling, halting acute and late phase cytokine-driven inflammation.

[0187] Figure 11 demonstrates the role of BTK in allergic conjunctivitis. Mast cells are sentinel cells that induce inflammation via release of pre-formed granules containing histamine and other pro-inflammatory mediators during degranulation. BTK is an important signaling protein of the FcεRI pathway, regulating IgE-mediated mast cell activation and cytokine-driven inflammation following binding of allergen to IgA. Inhibition of BTK blocks mast cell degranulation and inflammation through inhibition of FcεRI-induced calcium release and an inflammatory response. These mast cells reside in vascularized tissue compartments (e.g. mucosal, cutaneous, connective, ocular) and are activated by stimuli that trigger degranulation (e.g. allergens). Inhibition of BTK-mediated calcium release is important to inhibiting this inflammatory response.

Methods of Reducing or Alleviating a Sign or Symptom of Allergic Conjunctivitis with BTK Inhibitors

[0188] In certain aspects, the present disclosure relates to a method of reducing or alleviating a sign or symptom of allergic conjunctivitis comprising the step of administering to a human subject with allergic conjunctivitis a Bruton's Tyrosine Kinase (BTK) inhibitor compound. In an embodiment, the BTK inhibitor compound is topically administered to an eye of the human subject. The BTK inhibitor

compound is administered in an amount effective to reduce at least one sign or symptom of allergic conjunctivitis. The reducing or alleviating of a sign or symptom of allergic conjunctivitis comprises reduced conjunctival redness, a reduced ocular itching score, or a combination thereof. In an embodiment, a reduced conjunctival redness score is assessed on a scale of 0 (none) to 4 (extremely severe) in 0.5 unit increments. In an embodiment, conjunctival redness is assessed using the Ora Calibra Ocular Hyperemia Scale. In an embodiment, an ocular itching score is assessed as a patient-reported score from 0 (no itching) to 4 (incapacitating itch) in 0.5 unit increments.

[0189] In an embodiment, the inhibition of BTK-mediated calcium release mediates a reduced inflammatory response. In an embodiment, the inhibition of BTK-mediated cytokine production mediates a reduced inflammatory response. In an embodiment, the inhibition of BTK reduces dysregulation of the cytokine production and subsequent inflammatory response. In an embodiment, inhibition of BTK blocks mast cell degranulation and inflammation through inhibition of FcεRI-induced calcium release and the subsequent inflammatory response.

[0190] In an embodiment, the administering occurs at a frequency of twice daily. In an embodiment, the administering occurs at a frequency of once daily. In an embodiment, the administering occurs for at least one day. In an embodiment, the administering occurs at a frequency of twice daily for at least one day. In an embodiment, the administering occurs at a frequency of once daily for at least one day. In an embodiment, the administering occurs for at least seven days. In an embodiment, the administering occurs at a frequency of twice daily for at least seven days. In an embodiment, the administering occurs at a frequency of once daily for at least seven days. In an embodiment, the administering occurs for at least fourteen days. In an embodiment, the administering occurs at a frequency of twice daily for at least fourteen days. In an embodiment, the administering occurs at a frequency of once daily for at least fourteen days. In an embodiment, the administering occurs for at least twenty-eight days. In an embodiment, the administering occurs at a frequency of twice daily for at least twenty-eight days. In an embodiment, the administering occurs at a frequency of once daily for at least twenty-eight days. In an embodiment, the administering occurs seasonally. In an embodiment, the administering occurs perennially.

[0191] In certain aspects, the present disclosure relates to a method of reducing or alleviating a sign or symptom of allergic conjunctivitis comprising the step of administering to a human subject with allergic conjunctivitis an ophthalmic composition comprising the BTK inhibitor compound. In an embodiment, the BTK inhibitor compound is administered topically to an eye of the human subject. The

BTK inhibitor compound is administered in an amount effective to reduce or alleviate at least one sign or symptom of allergic conjunctivitis in the human subject. The reducing or alleviating of a sign or symptom of allergic conjunctivitis comprises reduced conjunctival redness, a reduced ocular itching score, or a combination thereof.

[0192] In an embodiment, the BTK inhibitor compound is present in an ophthalmic composition comprising one or more pharmaceutically acceptable excipients formulated for topical administration. In an embodiment, the ophthalmic composition is administered as an eye drop. In an embodiment, the ophthalmic composition is an oil-in-water microemulsion. In an embodiment, the ophthalmic composition is an oil-in-water microemulsion administered as an eye drop. In an embodiment, the ophthalmic composition is an oil-in-water microemulsion (including an oil-in-water microemulsion administered as an eye drop) comprising: the BTK inhibitor compound; polysorbate 20; polysorbate 80; isopropyl myristate; and phosphate buffered saline. In an embodiment, the ophthalmic composition is an oil-in-water microemulsion (including an oil-in-water microemulsion administered as an eye drop) comprising: about 0.05% to about 0.2% (w/w) of 1-(4-(((6-amino-5-(4-phenoxyphenyl)pyrimidin-4-yl)amino)methyl)-4-fluoropiperidin-1-yl)prop-2-en-1-one or a pharmaceutically acceptable salt thereof; about 5% to about 10% polysorbate 20 (w/w); about 10% to about 20% polysorbate 80 (w/w); about 1% to about 3% isopropyl myristate (w/w); and phosphate buffered saline. In an embodiment, the ophthalmic composition is an oil-in-water microemulsion (including an oil-in-water microemulsion administered as an eye drop) comprising: about 0.1% (1.0 mg/ml) of 1-(4-(((6-amino-5-(4-phenoxyphenyl)pyrimidin-4-yl)amino)methyl)-4-fluoropiperidin-1-yl)prop-2-en-1-one or a pharmaceutically acceptable salt thereof; about 7% to about 10% polysorbate 20 (w/w); about 14% to about 18% polysorbate 80 (w/w); about 1.5% to about 2% isopropyl myristate (w/w); and phosphate buffered saline. In an embodiment, the ophthalmic composition is an oil-in-water microemulsion (including an oil-in-water microemulsion administered as an eye drop) comprising: about 0.1% (1.0 mg/ml) of 1-(4-(((6-amino-5-(4-phenoxyphenyl)pyrimidin-4-yl)amino)methyl)-4-fluoropiperidin-1-yl)prop-2-en-1-one or a pharmaceutically acceptable salt thereof; about 8.43% polysorbate 20 (w/w); about 16.19% polysorbate 80 (w/w); about 1.77% isopropyl myristate (w/w); and phosphate buffered saline. In an embodiment, the ophthalmic composition does not contain any preservatives.

[0193] In an embodiment, the eye drop is administered by instilling a first eye drop in each eye, waiting a period of time, and then instilling a second eye drop in each eye. In an embodiment, the period of time is 3 minutes $\pm$ 1 minute to 10 minutes $\pm$ 1 minute. In an embodiment, the period of time

is 3 minutes $\pm$ 1 minute to 9 minutes $\pm$ 1 minute. In an embodiment, the period of time is 4 minutes $\pm$ 1 minute to 8 minutes $\pm$ 1 minute. In an embodiment, the period of time is 5 minutes $\pm$ 1 minute to 7 minutes $\pm$ 1 minute. In an embodiment, the period of time is 10 minutes $\pm$ 1 minute. In an embodiment, the period of time is 9 minutes $\pm$ 1 minute. In an embodiment, the period of time is 8 minutes $\pm$ 1 minute. In an embodiment, the period of time is 7 minutes $\pm$ 1 minute. In an embodiment, the period of time is 6 minutes $\pm$ 1 minute. In an embodiment, the period of time is 5 minutes $\pm$ 1 minute. In an embodiment, the period of time is 4 minutes $\pm$ 1 minute. In an embodiment, the period of time is 3 minutes $\pm$ 1 minute.

[0194] In an embodiment, the method further comprises administering a loading dose via at least one eye drop in each eye prior to instilling the first eye drop. In an embodiment, the loading dose comprises two doses administered 12 hours $\pm$ 1.5 hours apart. In an embodiment, the loading dose comprises two doses administered 24 hours $\pm$ 1.5 hours apart. In an embodiment, the loading dose comprises two doses administered less than 12 hours apart $\pm$ 1.5 hours. In an embodiment, the loading dose comprises two doses administered more than 24 hours apart $\pm$ 1.5 hours.

[0195] In an embodiment, the method further comprises administering cyclosporine to the eye of the human subject. In an embodiment, the cyclosporine is formulated as a cyclosporine ophthalmic microemulsion.

[0196] In an embodiment, the method further comprises administering a wild-type KIT inhibitor to the eye of the human subject. In an embodiment, the wild-type KIT inhibitor is formulated as an ophthalmic microemulsion.

[0197] In an embodiment, the method further comprises administering an integrin LFA-1 inhibitor to the eye of a human subject. In an embodiment, the integrin LFA-1 inhibitor is (S)-2-(2-(benzofuran-6-carbonyl)-5,7-dichloro-1,2,3,4-tetrahydroisoquinoline-6-carboxamido)-3-(3-(methylsulfonyl)phenyl)propanoic acid. In an embodiment, the LFA-1 inhibitor is formulated as an ophthalmic solution.

[0198] In an embodiment, the method further comprises administering an antihistamine to the eye of the human subject. In an embodiment, the antihistamine is formulated as an ophthalmic microemulsion.

Methods of Treating Allergic Conjunctivitis with BTK Inhibitors

[0199] In certain aspects, the present disclosure relates to a method of treating allergic conjunctivitis comprising the step of administering as an eye drop to an eye of a human subject in need thereof a Bruton's Tyrosine Kinase (BTK) inhibitor compound. In an embodiment, BTK inhibitor compound is administered topically. The BTK inhibitor compound is administered in an amount effective to treat the allergic conjunctivitis in the human subject. The eye drop is administered by instilling at least one first eye drop in each eye, waiting a period of time, and then instilling at least one second eye drop in each eye. In an embodiment, the period of time is 5 minutes $\pm$ 1 minute to 10 minutes $\pm$ 1 minute. In an embodiment, the period of time is 6 minutes $\pm$ 1 minute to 10 minutes $\pm$ 1 minute. In an embodiment, the period of time is 7 minutes $\pm$ 1 minute to 10 minutes $\pm$ 1 minute. In an embodiment, the period of time is 8 minutes $\pm$ 1 minute to 10 minutes $\pm$ 1 minute. In an embodiment, the period of time is at least 5 minutes $\pm$ 1 minute. In an embodiment, the period of time is at least 6 minutes $\pm$ 1 minute. In an embodiment, the period of time is at least 7 minutes $\pm$ 1 minute. In an embodiment, the period of time is at least 8 minutes $\pm$ 1 minute. In an embodiment, the period of time is at least 9 minutes $\pm$ 1 minute. In an embodiment, the period of time is 10 minutes $\pm$ 1 minute. In an embodiment, the period of time is 9 minutes $\pm$ 1 minute. In an embodiment, the period of time is 8 minutes $\pm$ 1 minute. In an embodiment, the period of time is 7 minutes $\pm$ 1 minute. In an embodiment, the period of time is 6 minutes $\pm$ 1 minute. In an embodiment, the period of time is 5 minutes $\pm$ 1 minute.

[0200] In an embodiment, human subject also has dry eye disease.

[0201] In an embodiment, the administering occurs at a frequency of twice daily. In an embodiment, the administering occurs at a frequency of once daily. In an embodiment, the administering occurs for at least one day. In an embodiment, the administering occurs at a frequency of twice daily for at least one day. In an embodiment, the administering occurs at a frequency of once daily for at least one day. In an embodiment, the administering occurs for at least seven days. In an embodiment, the administering occurs at a frequency of twice daily for at least seven days. In an embodiment, the administering occurs at a frequency of once daily for at least seven days. In an embodiment, the administering occurs for at least fourteen days. In an embodiment, the administering occurs at a frequency of twice daily for at least fourteen days. In an embodiment, the administering occurs at a frequency of once daily for at least fourteen days. In an embodiment, the administering occurs for at least twenty-eight days. In an embodiment, the administering occurs at a frequency of twice daily for at least twenty-eight days. In an embodiment, the administering occurs at a frequency of once daily for at least twenty-eight days. In an

embodiment, the administering occurs seasonally. In an embodiment, the administering occurs perennially.

[0202] The present disclosure relates to a method of treating allergic conjunctivitis comprising the step of administering as an eye drop to an eye of a human subject in need thereof an ophthalmic composition comprising the BTK inhibitor compound. In an embodiment, the BTK inhibitor compound is administered topically. The BTK inhibitor compound is administered in an amount effective to treat the allergic conjunctivitis in the human subject.

[0203] In an embodiment, the BTK inhibitor compound is present in an ophthalmic composition comprising one or more pharmaceutically acceptable excipients formulated for topical administration. In an embodiment, the ophthalmic composition is administered as an eye drop. In an embodiment, the ophthalmic composition is an oil-in-water microemulsion. In an embodiment, the ophthalmic composition is an oil-in-water microemulsion administered as an eye drop. In an embodiment, the ophthalmic composition is an oil-in-water microemulsion (including an oil-in-water microemulsion administered as an eye drop) comprising: the BTK inhibitor compound; polysorbate 20; polysorbate 80; isopropyl myristate; and phosphate buffered saline. In an embodiment, the ophthalmic composition is an oil-in-water microemulsion (including an oil-in-water microemulsion administered as an eye drop) comprising: about 0.05% to about 0.2% (w/w) of 1-(4-(((6-amino-5-(4-phenoxyphenyl)pyrimidin-4-yl)amino)methyl)-4-fluoropiperidin-1-yl)prop-2-en-1-one or a pharmaceutically acceptable salt thereof; about 5% to about 10% polysorbate 20 (w/w); about 10% to about 20% polysorbate 80 (w/w); about 1% to about 3% isopropyl myristate (w/w); and phosphate buffered saline. In an embodiment, the ophthalmic composition is an oil-in-water microemulsion (including an oil-in-water microemulsion administered as an eye drop) comprising: about 0.1% (1.0 mg/ml) of 1-(4-(((6-amino-5-(4-phenoxyphenyl)pyrimidin-4-yl)amino)methyl)-4-fluoropiperidin-1-yl)prop-2-en-1-one or a pharmaceutically acceptable salt thereof; about 7% to about 10% polysorbate 20 (w/w); about 14% to about 18% polysorbate 80 (w/w); about 1.5% to about 2% isopropyl myristate (w/w); and phosphate buffered saline. In an embodiment, the ophthalmic composition is an oil-in-water microemulsion (including an oil-in-water microemulsion administered as an eye drop) comprising: about 0.1% (1.0 mg/ml) of 1-(4-(((6-amino-5-(4-phenoxyphenyl)pyrimidin-4-yl)amino)methyl)-4-fluoropiperidin-1-yl)prop-2-en-1-one or a pharmaceutically acceptable salt thereof; about 8.43% polysorbate 20 (w/w); about 16.19% polysorbate 80 (w/w); about 1.77% isopropyl myristate (w/w); and phosphate buffered saline. In an embodiment, the ophthalmic composition does not contain any preservatives.

[0204] In an embodiment, the method further comprises administering a loading dose via at least one eye drop in each eye prior to instilling the first eye drop. In an embodiment, the loading dose comprises two doses administered 12 hours $\pm$ 1.5 hours apart. In an embodiment, the loading dose comprises two doses administered 24 hours $\pm$ 1.5 hours apart. In an embodiment, the loading dose comprises two doses administered less than 12 hours apart $\pm$ 1.5 hours. In an embodiment, the loading dose comprises two doses administered more than 24 hours apart $\pm$ 1.5 hours.

[0205] In an embodiment, the method further comprises administering cyclosporine to the eye of the human subject. In an embodiment, the cyclosporine is formulated as a cyclosporine ophthalmic microemulsion.

[0206] In an embodiment, the method further comprises administering a wild-type KIT inhibitor to the eye of the human subject. In an embodiment, the wild-type KIT inhibitor is formulated as an ophthalmic microemulsion.

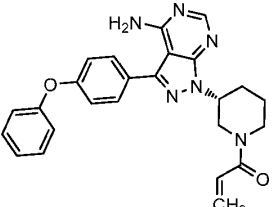
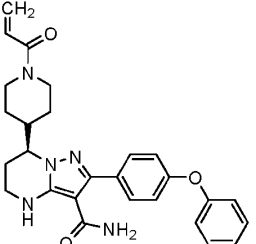
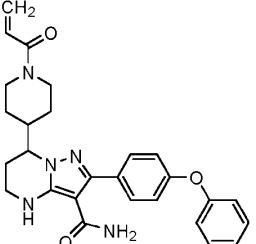
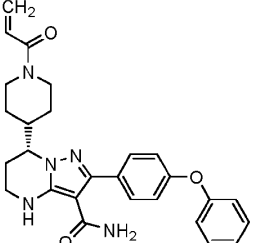
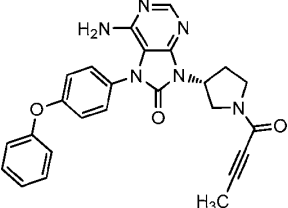
[0207] In an embodiment, the method further comprises administering an integrin LFA-1 inhibitor to the eye of a human subject. In an embodiment, the integrin LFA-1 inhibitor is (S)-2-(2-(benzofuran-6-carbonyl)-5,7-dichloro-1,2,3,4-tetrahydroisoquinoline-6-carboxamido)-3-(3-(methylsulfonyl)phenyl)propanoic acid. In an embodiment, the LFA-1 inhibitor is formulated as an ophthalmic solution.

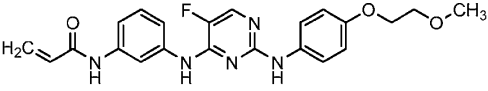
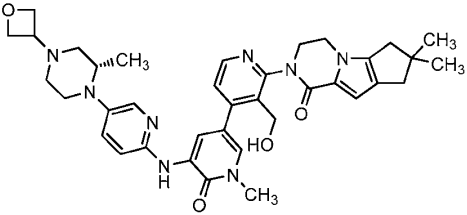
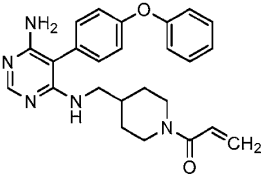
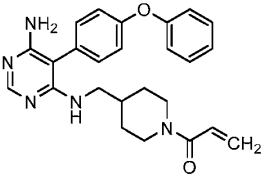
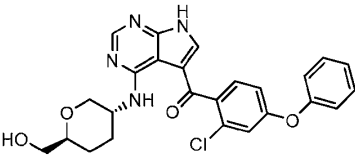
[0208] In an embodiment, the method further comprises administering an antihistamine to the eye of the human subject. In an embodiment, the antihistamine is formulated as an ophthalmic microemulsion.

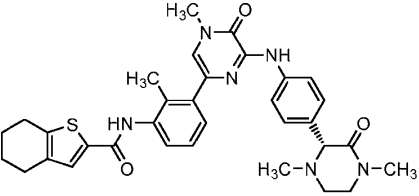
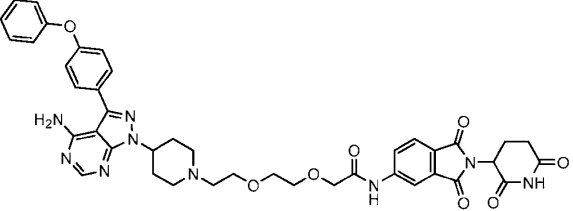
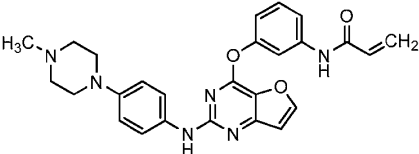
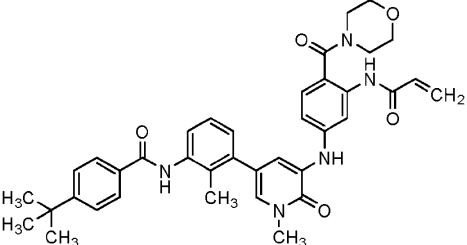
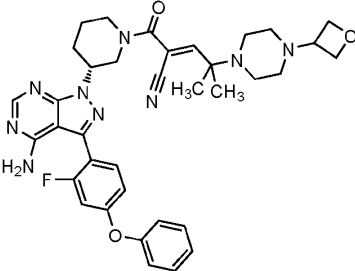
[0209] In an embodiment, the BTK inhibitor compound is selected from the compounds listed in Table 1 or a pharmaceutically acceptable salt thereof:

Table 1: BTK Inhibitors

No.	IUPAC Name	Structure
1.	Acalabrutinib ((S)-4-(8-amino-3-(1-(but-2-ynoyl)pyrrolidin-2-yl)imidazo[1,5-a]pyrazin-1-yl)-N-(pyridin-2-yl)benzamide)	

No.	IUPAC Name	Structure
2.	Ibrutinib (1-[(3R)-3-[4-amino-3-(4-phenoxyphenyl)pyrazolo[3,4-d]pyrimidin-1-yl]piperidin-1-yl]prop-2-en-1-one)	
3.	(7S)-2-(4-phenoxyphenyl)-7-(1-prop-2-enoylpiperidin-4-yl)-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrimidine-3-carboxamide	
4.	2-(4-phenoxyphenyl)-7-(1-prop-2-enoylpiperidin-4-yl)-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrimidine-3-carboxamide	
5.	(7R)-2-(4-phenoxyphenyl)-7-(1-prop-2-enoylpiperidin-4-yl)-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrimidine-3-carboxamide	
6.	6-amino-9-[(3R)-1-but-2-ynoylpyrrolidin-3-yl]-7-(4-phenoxyphenyl)purin-8-one	

No.	IUPAC Name	Structure
7.	N-[3-[[5-fluoro-2-[4-(2-methoxyethoxy)anilino]pyrimidin-4-yl]amino]phenyl]prop-2-enamide	
8.	Fenebrutinib (10-[3-(hydroxymethyl)-4-[1-methyl-5-[[5-[(2S)-2-methyl-4-(oxetan-3-yl)piperazin-1-yl]pyridin-2-yl]amino]-6-oxopyridin-3-yl]pyridin-2-yl]-4,4-dimethyl-1,10-diazatricyclo[6.4.0.0 ^{2,6}]dodeca-2(6),7-dien-9-one)	
9.	1-[4-[[[6-amino-5-(4-phenoxyphenyl)pyrimidin-4-yl]amino]methyl]piperidin-1-yl]prop-2-en-1-one	
10.	1-[4-[[[6-amino-5-(4-phenoxyphenyl)pyrimidin-4-yl]amino]methyl]piperidin-1-yl]prop-2-en-1-one	
11.	(2-chloro-4-phenoxyphenyl)-[4-[[[(3R,6S)-6-(hydroxymethyl)oxan-3-yl]amino]-7H-pyrrolo[2,3-d]pyrimidin-5-yl]methanone	

No.	IUPAC Name	Structure
12.	N-[3-[6-[4-[(2R)-1,4-dimethyl-3-oxopiperazin-2-yl]anilino]-4-methyl-5-oxopyrazin-2-yl]-2-methylphenyl]-4,5,6,7-tetrahydro-1-benzothiophene-2-carboxamide	
13.	2-[2-[2-[4-[4-amino-3-(4-phenoxyphenyl)pyrazolo[3,4-d]pyrimidin-1-yl]piperidin-1-yl]ethoxy]ethoxy]-N-[2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisindol-5-yl]acetamide	
14.	N-[3-[2-[4-(4-methylpiperazin-1-yl)anilino]furo[3,2-d]pyrimidin-4-yl]oxyphenyl]prop-2-enamide	
15.	4-tert-butyl-N-[2-methyl-3-[1-methyl-5-[4-(morpholine-4-carbonyl)-3-(prop-2-enoylamino)anilino]-6-oxopyridin-3-yl]phenyl]benzamide	
16.	(R,E)-2-{3-[4-amino-3-(2-fluoro-4-phenoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl]piperidine-1-carbonyl}-4-methyl-4-(4-(oxetan-3-yl)piperazin-1-yl)pent-2-enenitrile	

No.	IUPAC Name	Structure
17.	Branebrutinib ((S)-4-(3-(but-2-ynamido)piperidin-1-yl)-5-fluoro-2,3-dimethyl-1H-indole-7-carboxamide)	
18.	4-(tert-Butyl)-N-(2-methyl-3-(4-methyl-6-((4-(morpholine-4-carbonyl)phenyl)amino)-5-oxo-4,5-dihydropyrazin-2-yl)phenyl)benzamide	
19.	N-(1-(7H-Pyrrolo[2,3-d] pyrimidin-4-yl)piperidin-3-yl)-2-((3-chlorophenyl)amino) acetamide	
20.	6-cyclopropyl-8-fluoro-2-[2-(hydroxymethyl)-3-[1-methyl-5-[[5-(4-methylpiperazin-1-yl)pyridin-2-yl]amino]-6-oxopyridin-3-yl]phenyl]isoquinolin-1-one	
21.	N-[5-[9-[4-(methanesulfonamido)phenyl]-2-oxobenzo[h][1,6]naphthyridin-1-yl]-2-methylphenyl]prop-2-enamide	
22.	4-(4-((4-((3-acrylamidophenyl)amino)-5-fluoropyrimidin-2-yl)amino)phenoxy)-N-methylpicolinamide	

No.	IUPAC Name	Structure
23.	(7S)-3-fluoro-4-[3-(8-fluoro-1-methyl-2,4-dioxoquinazolin-3-yl)-2-methylphenyl]-7-(2-hydroxypropan-2-yl)-6,7,8,9-tetrahydro-5H-carbazole-1-carboxamide	
24.	1-[3-fluoro-4-[7-(5-methyl-1H-imidazol-2-yl)-1-oxo-2,3-dihydroisindol-4-yl]phenyl]-3-[3-(trifluoromethyl)phenyl]urea	
25.	9-(1-methylpyrazol-4-yl)-1-(1-prop-2-enoyl-2,3-dihydroindol-6-yl)benzo[h][1,6]naphthyridin-2-one	
26.	7-(2-hydroxypropan-2-yl)-4-[2-methyl-3-(4-oxoquinazolin-3-yl)phenyl]-9H-carbazole-1-carboxamide	
27.	10-[2-(Hydroxymethyl)-3-[1-methyl-6-oxo-5-(pyrimidin-4-ylamino)pyridin-3-yl]phenyl]-4,4-dimethyl-7-thia-10-azatricyclo[6.4.0.0.2,6]dodeca-1(8),2(6)-dien-9-one	
28.	(S)-5-amino-1-(1-cyanopiperidin-3-yl)-3-(4-(2,4-difluorophenoxy)phenyl)-1H-pyrazole-4-carboxamide	

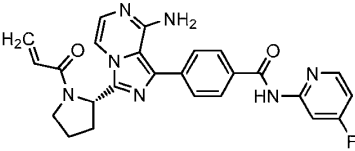
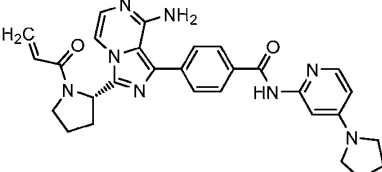
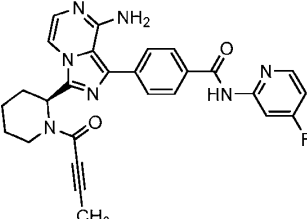
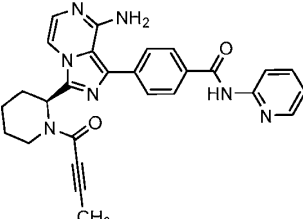
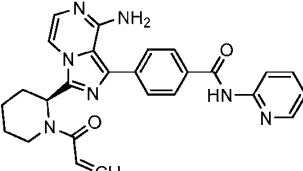
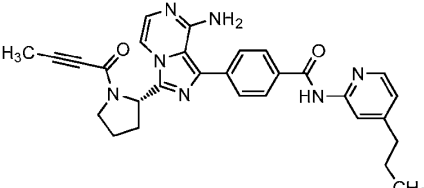
No.	IUPAC Name	Structure
29.	(S)-4-(3-(1-Acryloylpyrrolidin-2-yl)-8-aminoimidazo[1,5-a]pyrazin-1-yl)-N-(pyridin-2-yl)benzamide	
30.	(S,E)-4-(8-Amino-3-(1-(4-(dimethylamino)but-2-en-1-yl)pyrrolidin-2-yl)imidazo[1,5-a]pyrazin-1-yl)-N-(pyridin-2-yl)benzamide	
31.	(S)-4-(8-Amino-3-(1-but-2-yn-1-ylpyrrolidin-2-yl)imidazo[1,5-a]pyrazin-1-yl)-N-(4-methylpyridin-2-yl)benzamide	
32.	(S,E)-4-(8-Amino-3-(1-(4-methoxybut-2-en-1-yl)pyrrolidin-2-yl)imidazo[1,5-a]pyrazin-1-yl)-N-(4-propylpyridin-2-yl)benzamide	
33.	(S)-4-(8-Amino-3-(1-but-2-yn-1-ylpyrrolidin-2-yl)imidazo[1,5-a]pyrazin-1-yl)-N-(4-(trifluoromethyl)pyridin-2-yl)benzamide	
34.	(S)-4-(8-Amino-3-(1-but-2-yn-1-ylpyrrolidin-2-yl)imidazo[1,5-a]pyrazin-1-yl)-N-(4,5,6,7-tetrahydrobenzo[d]thiazol-2-yl)benzamide	

No.	IUPAC Name	Structure
35.	(S)-4-(3-(1-acryloylpyrrolidin-2-yl)-8-aminoimidazo[1,5-a]pyrazin-1-yl)-2-fluoro-N-(pyridin-2-yl)benzamide	
36.	(S)-4-(3-(1-Acryloylpyrrolidin-2-yl)-8-aminoimidazo[1,5-a]pyrazin-1-yl)-2-methoxy-N-(pyridin-2-yl)benzamide	
37.	(S, E)-4-(8-Amino-3-(1-(4-(dimethylamino)but-2-enoyl)pyrrolidin-2-yl)imidazo[1,5-a]pyrazin-1-yl)-N-(thiazol-2-yl)benzamide	
38.	(S)-4-(3-(1-Acryloylpiperidin-2-yl)-8-aminoimidazo[1,5-a]pyrazin-1-yl)-N-(4-fluoropyridin-2-yl)benzamide	
39.	(S)-4-(3-(1-Acryloylpiperidin-2-yl)-8-aminoimidazo[1,5-a]pyrazin-1-yl)-N-(4-cyanopyridin-2-yl)benzamide	
40.	(S)-4-(8-Amino-3-(1-(vinylsulfonyl)piperidin-2-yl)imidazo[1,5-a]pyrazin-1-yl)-N-(4-(trifluoromethyl)pyridin-2-yl)benzamide	
41.	(S)-4-(3-(1-Acryloylpiperidin-2-yl)-8-aminoimidazo[1,5-a]pyrazin-1-yl)-N-(pyrimidin-2-yl)benzamide	

No.	IUPAC Name	Structure
42.	(S)-4-(3-(1-Acryloylpiperidin-2-yl)-8-aminoimidazo[1,5-a]pyrazin-1-yl)-N-(4-methylpyrimidin-2-yl)benzamide	
43.	(S)-4-(8-Amino-3-(1-but-2-ynoylpiperidin-2-yl)imidazo[1,5-a]pyrazin-1-yl)-N-(pyrimidin-4-yl)benzamide	
44.	(S)-4-(8-Amino-3-(1-but-2-ynoylpiperidin-2-yl)imidazo[1,5-a]pyrazin-1-yl)-N-(pyridazin-3-yl)benzamide	
45.	(S, E)-4-(8-Amino-3-(1-(4-methoxybut-2-enoyl)piperidin-2-yl)imidazo[1,5-a]pyrazin-1-yl)-N-(5-ethylthiazol-2-yl)benzamide	
46.	(S)-4-(3-(1-Acryloylpiperidin-2-yl)-8-aminoimidazo[1,5-a]pyrazin-1-yl)-2-fluoro-N-(4-propylpyridin-2-yl)benzamide	
47.	(S, E)-4-(8-Amino-3-(1-(4-(dimethylamino)but-2-enoyl)piperidin-2-yl)imidazo[1,5-a]pyrazin-1-yl)-2-methoxy-N-(4-propylpyridin-2-yl)benzamide	

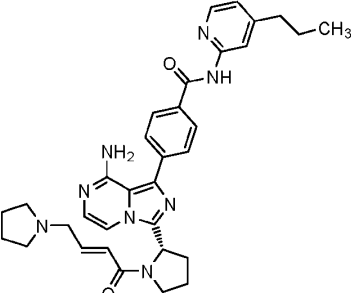
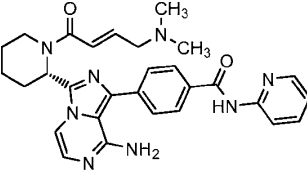
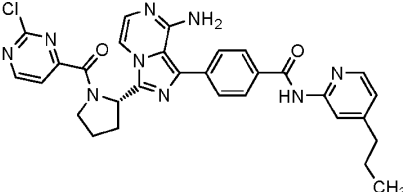
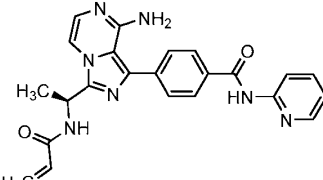
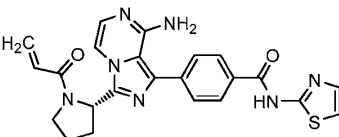
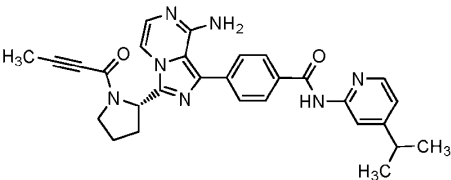
No.	IUPAC Name	Structure
48.	4-(8-Amino-3-((S)-1-but-2-ynoylpiperidin-2-yl)imidazo[1,5-a]pyrazin-1-yl)-3-methyl-N-(pyridin-2-yl)benzamide	
49.	4-(3-(Acrylamidomethyl)-8-aminoimidazo[1,5-a]pyrazin-1-yl)-N-(pyridin-2-yl)benzamide	
50.	(S)-4-(8-Amino-3-(1-but-2-ynamidoethyl)imidazo[1,5-a]pyrazin-1-yl)-N-(pyridin-2-yl)benzamide	
51.	(S)-S-(2-(2-(8-amino-1-(4-(pyridin-2-ylcarbamoyl)phenyl)imidazo[1,5-a]pyrazin-3-yl)pyrrolidin-1-yl)-2-oxoethyl) ethanethioate	
52.	(S)-4-(8-Amino-3-(1-(4-hydroxy-4-methylpent-2-ynoyl)pyrrolidin-2-yl)imidazo[1,5-a]pyrazin-1-yl)-N-(pyridin-2-yl)benzamide	
53.	(S)-4-(8-Amino-3-(1-(6-chloropyrimidine-4-carbonyl)pyrrolidin-2-yl)imidazo[1,5-a]pyrazin-1-yl)-N-(pyridin-2-yl)benzamide	

No.	IUPAC Name	Structure
54.	(S)-4-(8-Amino-3-(1-pent-2-ynoylpyrrolidin-2-yl)imidazo[1,5-a]pyrazin-1-yl)-N-(pyridin-2-yl)benzamide	
55.	(S)-4-(8-Amino-3-(1-(3-cyclopropylpropioloyl)pyrrolidin-2-yl)imidazo[1,5-a]pyrazin-1-yl)-N-(pyridin-2-yl)benzamide	
56.	(S)-4-(8-Amino-3-(1-hex-2-ynoylpyrrolidin-2-yl)imidazo[1,5-a]pyrazin-1-yl)-N-(pyridin-2-yl)benzamide	
57.	4-(3-(1-Acryloylazepan-2-yl)-8-aminoimidazo[1,5-a]pyrazin-1-yl)-N-(pyridin-2-yl)benzamide	
58.	(R)-4-(8-Amino-3-(4-but-2-ynoylmorpholin-3-yl)imidazo[1,5-a]pyrazin-1-yl)-N-(pyridin-2-yl)benzamide	
59.	(S)-4-(8-amino-3-(1-(N-methylbut-2-ynamido)ethyl)imidazo[1,5-a]pyrazin-1-yl)-N-(4-(trifluoromethyl)pyridin-2-yl)benzamide	

No.	IUPAC Name	Structure
60.	(S)-4-(3-(1-acryloylpyrrolidin-2-yl)-8-aminoimidazo[1,5-a]pyrazin-1-yl)-N-(4-fluoropyridin-2-yl)benzamide	
61.	(S)-4-(3-(1-acryloylpyrrolidin-2-yl)-8-aminoimidazo[1,5-a]pyrazin-1-yl)-N-(4-(pyrrolidin-1-yl)pyridin-2-yl)benzamide	
62.	(S)-4-(8-amino-3-(1-but-2-ynoyl)piperidin-2-yl)imidazo[1,5-a]pyrazin-1-yl)-N-(4-fluoropyridin-2-yl)benzamide	
63.	(S)-4-(8-amino-3-(1-but-2-ynoyl)piperidin-2-yl)imidazo[1,5-a]pyrazin-1-yl)-N-(pyridine-2-yl)benzamide	
64.	(S)-4-(3-(1-acryloylpiperidin-2-yl)-8-aminoimidazo[1,5-a]pyrazin-1-yl)-N-(pyridine-2-yl)benzamide	
65.	(S)-4-(8-amino-3-(1-but-2-ynoylpyrrolidin-2-yl)imidazo[1,5-a]pyrazin-1-yl)-N-(4-propylpyridin-2-yl)benzamide	

No.	IUPAC Name	Structure
66.	(S,E)-4-(8-amino-3-(1-(4-methoxy-N-methylbut-2-enamido)ethyl)imidazo[1,5-a]pyrazin-1-yl)-N-(4-propylpyridin-2-yl)benzamide	
67.	(S)-4-(8-amino-3-(1-(vinylsulfonyl)piperidin-2-yl)imidazo[1,5-a]pyrazin-1-yl)-N-(4-propylpyridin-2-yl)benzamide	
68.	(S)-4-(3-(1-acryloylpiperidin-2-yl)-8-aminoimidazo[1,5-a]pyrazin-1-yl)-N-(4-propylpyridin-2-yl)benzamide	
69.	(S)-4-(3-(1-acryloylpyrrolidin-2-yl)-8-aminoimidazo[1,5-a]pyrazin-1-yl)-N-(4-(trifluoromethyl)pyridin-2-yl)benzamide	
70.	(S)-4-(8-amino-3-(1-but-2-ynoylpiperidin-2-yl)imidazo[1,5-a]pyrazin-1-yl)-N-(4-(trifluoromethyl)pyridin-2-yl)benzamide	
71.	(S)-4-(8-amino-3-(1-but-2-ynoylpiperidin-2-yl)imidazo[1,5-a]pyrazin-1-yl)-N-(4-propylpyridin-2-yl)benzamide	

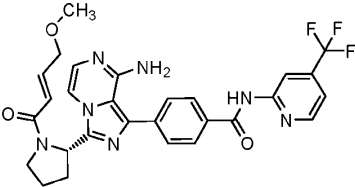
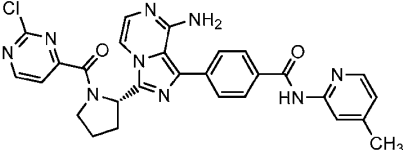
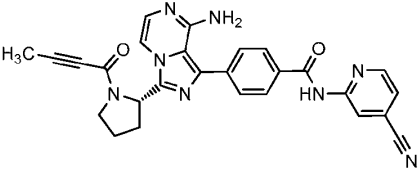
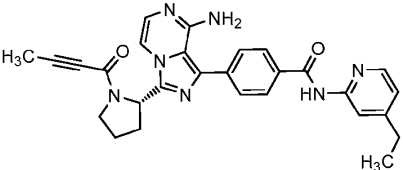
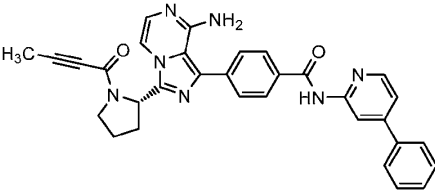
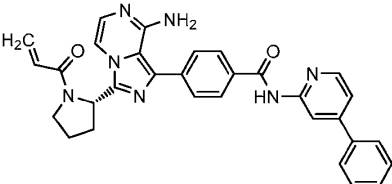
No.	IUPAC Name	Structure
72.	(S,E)-4-(8-amino-3-(1-(4-(dimethylamino)but-2-enoyl)pyrrolidin-2-yl)imidazo[1,5-a]pyrazin-1-yl)-N-(4-isopropylpyridin-2-yl)benzamide	
73.	4-(8-amino-3-((S)-1-(vinylsulfonyl)piperidin-2-yl)imidazo[1,5-a]pyrazin-1-yl)-3-methyl-N-(pyridin-2-yl)benzamide	
74.	(S)-4-(8-amino-3-(1-but-2-ynoylpiperidin-2-yl)imidazo[1,5-a]pyrazin-1-yl)-2-fluoro-N-(4-propylpyridin-2-yl)benzamide	
75.	(S,E)-4-(8-amino-3-(1-(4-methoxy-N-methylbut-2-enamido)ethyl)imidazo[1,5-a]pyrazin-1-yl)-N-(4-(trifluoromethyl)pyridin-2-yl)benzamide	
76.	(S,E)-4-(8-amino-3-(1-(4-(dimethylamino)-N-methylbut-2-enamido)ethyl)imidazo[1,5-a]pyrazin-1-yl)-N-(4-propylpyridin-2-yl)benzamide	

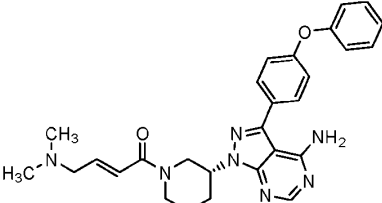
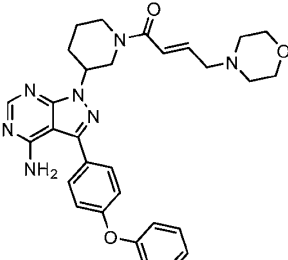
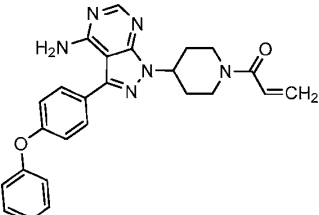
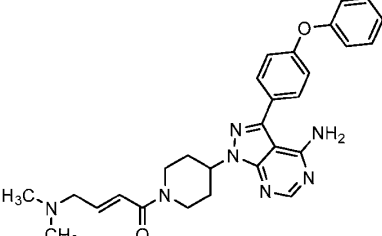
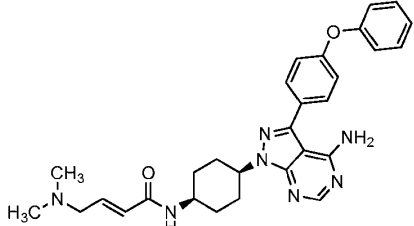
No.	IUPAC Name	Structure
77.	(S,E)-4-(8-amino-3-(1-(4-(pyrrolidin-1-yl)but-2-enoyl)pyrrolidin-2-yl)imidazo[1,5-a]pyrazin-1-yl)-N-(4-propylpyridin-2-yl)benzamide	
78.	(S,E)-4-(8-amino-3-(1-(4-(dimethylamino)but-2-enoyl)piperidin-2-yl)imidazo[1,5-a]pyrazin-1-yl)-N-(pyridin-2-yl)benzamide	
79.	(S)-4-(8-amino-3-(1-(2-chloropyrimidine-4-carbonyl)pyrrolidin-2-yl)imidazo[1,5-a]pyrazin-1-yl)-N-(4-propylpyridin-2-yl)benzamide	
80.	(S)-4-(3-(1-(acrylamidoethyl)-8-aminoimidazo[1,5-a]pyrazin-1-yl)-N-(pyridin-2-yl)benzamide	
81.	(S)-4-(3-(1-(acryloylpyrrolidin-2-yl)-8-aminoimidazo[1,5-a]pyrazin-1-yl)-N-(thiazol-2-yl)benzamide	
82.	(S)-4-(8-amino-3-(1-but-2-ynoylpyrrolidin-2-yl)imidazo[1,5-a]pyrazin-1-yl)-N-(4-isopropylpyridin-2-yl)benzamide	

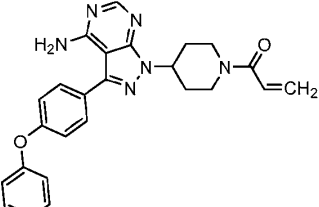
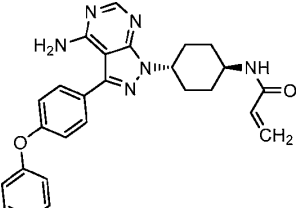
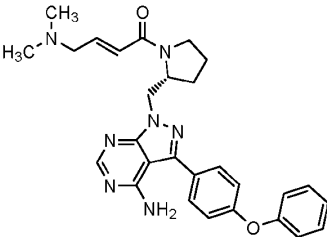
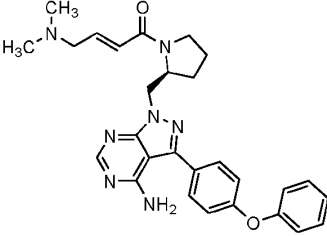
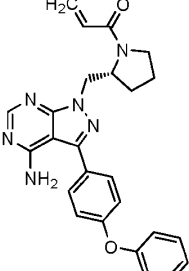
No.	IUPAC Name	Structure
83.	(S)-4-(8-amino-3-(1-(2-chloropyrimidin-4-carbonyl)piperidin-2-yl)imidazo[1,5-a]pyrazin-1-yl)-N-(4-propylpyridin-2-yl)benzamide	
84.	(S, E)-4-(8-amino-3-(1-(4-methoxybut-2-enoyl)piperidin-2-yl)imidazo[1,5-a]pyrazin-1-yl)-N-(4-(trifluoromethyl)pyridin-2-yl)benzamide	
85.	(S)-4-(3-(1-acryloylpiperidin-2-yl)-8-aminoimidazo[1,5-a]pyrazin-1-yl)-N-(4-(trifluoromethyl)pyridin-2-yl)benzamide	
86.	(S)-4-(8-amino-3-(1-but-2-ynoylpiperidin-2-yl)imidazo[1,5-a]pyrazin-1-yl)-2-methoxy-N-(4-propylpyridin-2-yl)benzamide	
87.	(S,E)-4-(8-amino-3-(1-(4-methoxybut-2-enoyl)piperidin-2-yl)imidazo[1,5-a]pyrazin-1-yl)-2-methoxy-N-(4-propylpyridin-2-yl)benzamide	

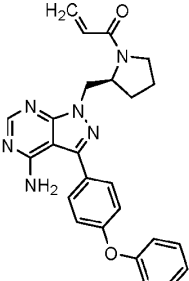
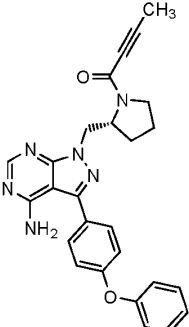
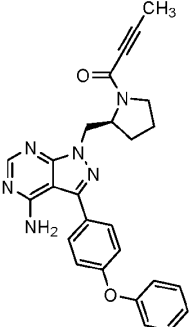
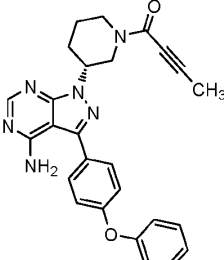
No.	IUPAC Name	Structure
88.	(S)-4-(8-amino-3-(1-(2-chloropyrimidine-4-carbonyl)piperidin-2-yl)imidazo[1,5-a]pyrazin-1-yl)-N-(4-(trifluoromethyl)pyridin-2-yl)benzamide	
89.	(S)-4-(8-amino-3-(1-but-2-ynoylpiperidin-2-yl)imidazo[1,5-a]pyrazin-1-yl)-N-(5-ethylthiazol-2-yl)benzamide	
90.	(S)-4-(3-(1-acryloylpiperidin-2-yl)-8-aminoimidazo[1,5-a]pyrazin-1-yl)-N-(5-ethylthiazol-2-yl)benzamide	
91.	(S)-4-(8-amino-3-(1-(2-chloropyrimidine-4-carbonyl)piperidin-2-yl)imidazo[1,5-a]pyrazin-1-yl)-N-(5-ethylthiazol-2-yl)benzamide	
92.	(R,E)-4-(8-amino-3-(4-(4-methoxybut-2-enoyl)morpholin-3-yl)imidazo[1,5-a]pyrazin-1-yl)-N-(pyridin-2-yl)benzamide	
93.	(S,E)-4-(8-amino-3-(1-(4-methoxybut-2-enoyl)piperidin-2-yl)imidazo[1,5-a]pyrazin-1-yl)-N-(4-propylpyridin-2-yl)benzamide	

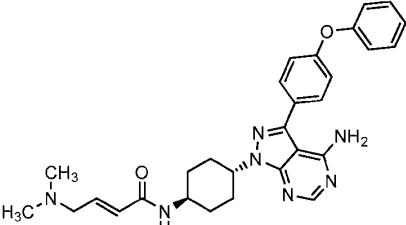
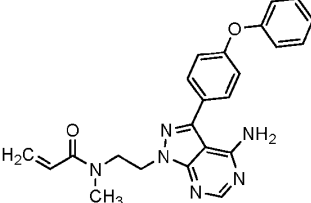
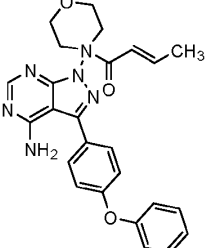
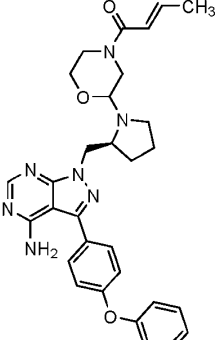
No.	IUPAC Name	Structure
94.	(S)-4-(3-(1-acryloylpyrrolidin-2-yl)-8-aminoimidazo[1,5-a]pyrazin-1-yl)-N-(4-cyanopyridin-2-yl)benzamide	
95.	(S)-4-(8-amino-3-(1-but-2-ynoylpyrrolidin-2-yl)imidazo[1,5-a]pyrazin-1-yl)-N-(4-methoxypyridin-2-yl)benzamide	
96.	(S)-4-(3-(1-acryloylpyrrolidin-2-yl)-8-aminoimidazo[1,5-a]pyrazin-1-yl)-N-(4-methylpyridin-2-yl)benzamide	
97.	(S)-4-(3-(1-acryloylpyrrolidin-2-yl)-8-aminoimidazo[1,5-a]pyrazin-1-yl)-N-(4-propylpyridin-2-yl)benzamide	
98.	(S)-4-(3-(1-acryloylpyrrolidin-2-yl)-8-aminoimidazo[1,5-a]pyrazin-1-yl)-N-(4-ethylpyridin-2-yl)benzamide	
99.	(S,E)-4-(8-amino-3-(1-(4-(dimethylamino)but-2-enoyl)pyrrolidin-2-yl)imidazo[1,5-a]pyrazin-1-yl)-N-(pyridin-2-yl)benzamide	

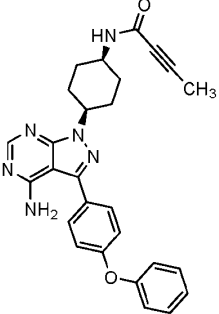
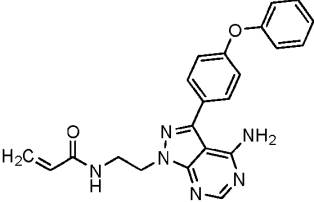
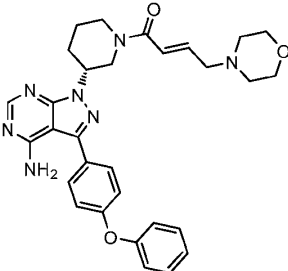
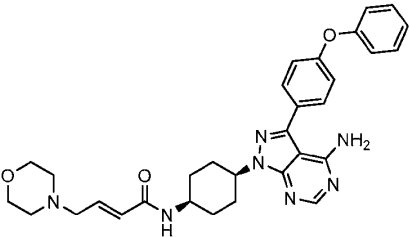
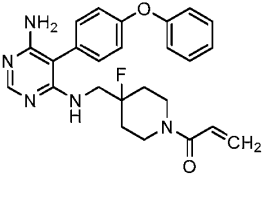
No.	IUPAC Name	Structure
100.	(S,E)-4-(8-amino-3-(1-(4-methoxybut-2-enoyl)pyrrolidin-2-yl)imidazo[1,5-a]pyrazin-1-yl)-N-(4-(trifluoromethyl)pyridin-2-yl)benzamide	
101.	(S)-4-(8-amino-3-(1-(2-chloropyrimidine-4-carbonyl)pyrrolidin-2-yl)imidazo[1,5-a]pyrazin-1-yl)-N-(4-methylpyridin-2-yl)benzamide	
102.	(S)-4-(8-amino-3-(1-but-2-ynoylpyrrolidin-2-yl)imidazo[1,5-a]pyrazin-1-yl)-N-(4-cyanopyridin-2-yl)benzamide	
103.	(S)-4-(8-amino-3-(1-but-2-ynoylpyrrolidin-2-yl)imidazo[1,5-a]pyrazin-1-yl)-N-(4-ethylpyridin-2-yl)benzamide	
104.	(S)-4-(8-amino-3-(1-but-2-ynoylpyrrolidin-2-yl)imidazo[1,5-a]pyrazin-1-yl)-N-(4-phenylpyridin-2-yl)benzamide	
105.	(S)-4-(3-(1-acryloylpyrrolidin-2-yl)-8-aminoimidazo[1,5-a]pyrazin-1-yl)-N-(4-phenylpyridin-2-yl)benzamide	

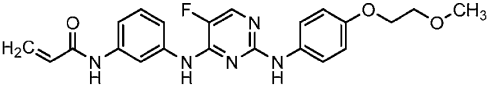
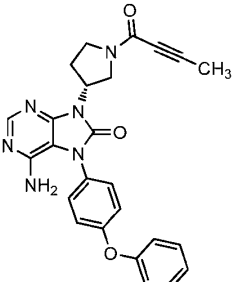
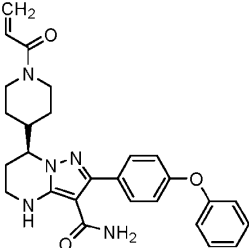
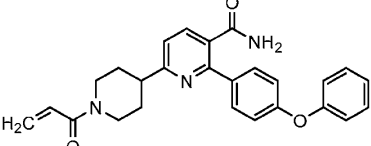
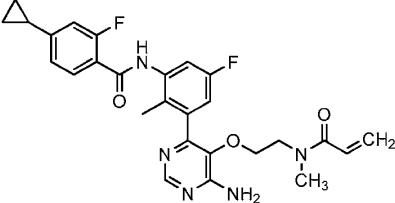
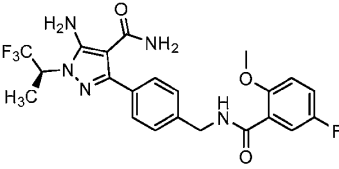
No.	IUPAC Name	Structure
106.	(R,E)-1-(3-(4-amino-3-(4-phenoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)piperidin-1-yl)-4-(dimethylamino)but-2-en-1-one	
107.	(E)-1-(3-(4-amino-3-(4-phenoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)piperidin-1-yl)-4-morpholinobut-2-en-1-one	
108.	1-(4-(4-amino-3-(4-phenoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)piperidin-1-yl)prop-2-en-1-one	
109.	(E)-1-(4-(4-amino-3-(4-phenoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)piperidin-1-yl)-4-(dimethylamino)but-2-en-1-one	
110.	(E)-N-((1s,4s)-4-(4-amino-3-(4-phenoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)cyclohexyl)-4-(dimethylamino)but-2-enamide	

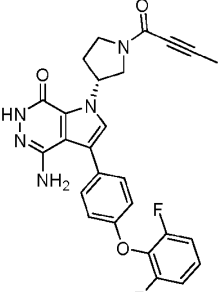
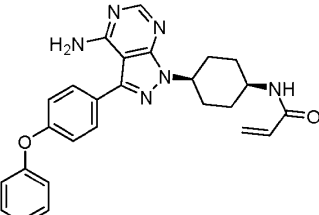
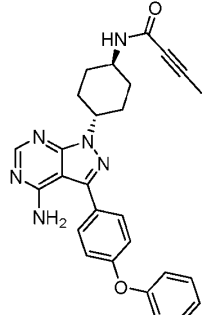
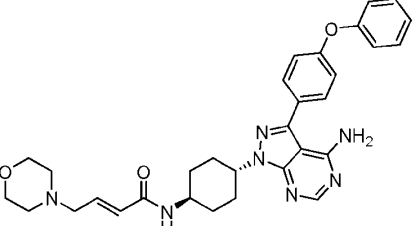
No.	IUPAC Name	Structure
111.	1-(4-(4-amino-3-(4-phenoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)piperidin-1-yl)prop-2-en-1-one	
112.	N-((1r,4r)-4-(4-amino-3-(4-phenoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)cyclohexyl)acrylamide	
113.	(E)-1-((R)-2-((4-amino-3-(4-phenoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)methyl)pyrrolidin-1-yl)-4-(dimethylamino)but-2-en-1-one	
114.	(E)-1-((S)-2-((4-amino-3-(4-phenoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)methyl)pyrrolidin-1-yl)-4-(dimethylamino)but-2-en-1-one	
115.	1-((R)-2-((4-amino-3-(4-phenoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)methyl)pyrrolidin-1-yl)prop-2-en-1-one	

No.	IUPAC Name	Structure
116.	1-((S)-2-((4-amino-3-(4-phenoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)methyl)pyrrolidin-1-yl)prop-2-en-1-one	
117.	1-((R)-2-((4-amino-3-(4-phenoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)methyl)pyrrolidin-1-yl)but-2-yn-1-one	
118.	1-((S)-2-((4-amino-3-(4-phenoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)methyl)pyrrolidin-1-yl)but-2-yn-1-one	
119.	1-((R)-3-(4-amino-3-(4-phenoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)piperidin-1-yl)but-2-yn-1-one	

No.	IUPAC Name	Structure
120.	(E)-N-((1r,4r)-4-(4-amino-3-(4-phenoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)cyclohexyl-4-(dimethylamino))but-2-enamide	
121.	N-(2-(4-amino-3-(4-phenoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)ethyl)-N-methylacrylamide	
122.	(E)-1-(4-(4-amino-3-(4-phenoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)-4-morpholino)but-2-en-1-one	
123.	(E)-1-(2-((S)-2-((4-amino-3-(4-phenoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)methyl)pyrrolidin-1-yl)morpholino)but-2-en-1-one	

No.	IUPAC Name	Structure
124.	N-((1s,4s)-4-(4-amino-3-(4-phenoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)cyclohexyl)but-2-ynamide	
125.	N-(2-(4-amino-3-(4-phenoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)ethyl)acrylamide	
126.	(E)-1-((R)-3-(4-amino-3-(4-phenoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)piperidin-1-yl)-4-morpholinobut-2-en-1-one	
127.	(E)-N-((1s,4s)-4-(4-amino-3-(4-phenoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)cyclohexyl)-4-morpholinobut-2-enamide	
128.	1-(4-(((6-amino-5-(4-phenoxyphenyl)pyrimidin-4-yl)amino)methyl)-4-fluoropiperidin-1-yl)prop-2-en-1-one	

No.	IUPAC Name	Structure
129.	N-[3-[[5-fluoro-2-[4-(2-methoxyethoxy)anilino]pyrimidin-4-yl]amino]phenyl]prop-2-enamide	
130.	6-amino-9-[(3 <i>R</i>)-1-but-2-ynoylpyrrolidin-3-yl]-7-(4-phenoxyphenyl)purin-8-one	
131.	(7 <i>S</i>)-2-(4-phenoxyphenyl)-7-(1-prop-2-enoylpiperidin-4-yl)-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrimidine-3-carboxamide	
132.	Orelabrutinib (2-(4-phenoxyphenyl)-6-(1-prop-2-enoylpiperidin-4-yl)pyridine-3-carboxamide)	
133.	Remibrutinib (N-[3-[6-amino-5-[2-[methyl(prop-2-enoyl)amino]ethoxy]pyrimidin-4-yl]-5-fluoro-2-methylphenyl]-4-cyclopropyl-2-fluorobenzamide)	
134.	Loxo-305 (1 <i>H</i> -Pyrazole-4-carboxamide, 5-amino-3-[4-[[[5-fluoro-2-methoxybenzoyl]amino]methyl]phenyl]-1-[(1 <i>S</i>)-2,2,2-trifluoro-1-methylethyl])	

No.	IUPAC Name	Structure
135.	TG-1701 (4-amino-1-[(3R)-1-but-2-ynoylpyrrolidin-3-yl]-3-[4-(2,6-difluorophenoxy)phenyl]-6H-pyrrolo[2,3-d]pyridazin-7-one)	
136.	N-((1s,4s)-4-(4-amino-3-(4-phenoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)cyclohexyl)acrylamide	
137.	N-((1r,4r)-4-(4-amino-3-(4-phenoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)cyclohexyl)but-2-ynamide	
138.	(E)-N-((1r,4r)-4-(4-amino-3-(4-phenoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)cyclohexyl)-4-morpholinobut-2-enamide	

No.	IUPAC Name	Structure
139.	2-[3-[2-amino-6-[1-(oxetan-3-yl)-3,6-dihydro-2H-pyridin-4-yl]-7H-pyrrolo[2,3-d]pyrimidin-4-yl]-2-(hydroxymethyl)phenyl]-6-cyclopropyl-8-fluoroisoquinolin-1-one	

[0210] In an embodiment, the BTK inhibitor is a BTK-targeted proteolysis targeting chimera (PROTAC) (Arthur (2020) *Explor Target Antitumor Ther.* 1, 131–152). In an embodiment, the BTK-targeted PROTAC comprises a BTK inhibitor moiety covalently coupled through a linker moiety to an ubiquitin protein ligase (E3) ligase-recruiting moiety. In an embodiment, the BTK inhibitor moiety comprises a BTK inhibitor selected from the group consisting of the compounds listed in Table 1 or pharmaceutically-acceptable salt thereof. In an embodiment, the BTK inhibitor moiety is derived from a BTK inhibitor selected from the group consisting of the compounds listed in Table 1 or pharmaceutically-acceptable salt thereof. In an embodiment, the linker comprises polyethylene glycol (PEG). In an embodiment, the linker is 9 to 14 atoms in length, 10 to 12 atoms in length, or 11 atoms in length. In an embodiment, the E3 ligase-recruiting moiety comprises pomalidomide. In an embodiment, the E3 ligase-recruiting moiety is derived from pomalidomide. In an embodiment, the E3 ligase-recruiting moiety comprises lenalidomide. In an embodiment, the E3 ligase-recruiting moiety is derived from lenalidomide. In an embodiment, the E3 ligase-recruiting moiety comprises RG-71120. In an embodiment, the E3 ligase-recruiting moiety is derived from RG-71120. In an embodiment, the E3 ligase-recruiting moiety targets cereblon (CRBN). In an embodiment, the E3 ligase-recruiting moiety targets murine double-minute 2 (MDM2). In an embodiment, the E3 ligase-recruiting moiety targets Von Hippel-Landau (VHL). In an embodiment, the E3 ligase-recruiting moiety targets inhibitor of apoptosis protein (IAP).

[0211] In an embodiment, the BTK inhibitor or a pharmaceutically acceptable salt thereof is a reversible BTK inhibitor. In an embodiment, the BTK inhibitor or a pharmaceutically acceptable salt thereof is an irreversible covalent BTK inhibitor.

[0212] In an embodiment, the BTK inhibitor is 1-(4-(((6-amino-5-(4-phenoxyphenyl)pyrimidin-4-yl)amino)methyl)-4-fluoropiperidin-1-yl)prop-2-en-1-one or a pharmaceutically-acceptable salt thereof.

Ophthalmic compositions for Topical Administration

[0213] Ophthalmic compositions for topical ophthalmic administration of this disclosure may be formulated in conventional ophthalmic compatible vehicles, such as, for example, an ointment, cream, suspension, lotion, powder, solution, paste, gel, hydrogel, spray, aerosol or oil.

[0214] The formulation may be one of many topical formulation types containing water as the major ingredient, including solutions, gels, hydrogel, creams, sprays and foams. In an embodiment, the formulation may be in the form of an aqueous gel. Accordingly, the formulation of the disclosure for topical ophthalmic administration may contain a gelling or thickening agent. Any gelling agent that is water-dispersible is suitable for use in the composition of the disclosure. One preferred gelling agent is hydroxypropylcellulose, such as that sold under the tradename KLUCEL® (Hercules Incorporated). Another preferred gelling agent is hydroxyethylcellulose, such as that sold under the tradename NATROSOL® (Hercules Incorporated). Other suitable gelling agents include carboxyvinyl polymers, also known as carbomers, such as are sold under the tradename CARBOPOL® 934, 940, 941, 980, and 981 (B.F. Goodrich), ETD 2020™, and ULTREZ® (Noveon). Additional suitable gelling agents are polyvinyl alcohol, polyethylene oxides, propylene glycol alginates, methylcellulose, hydroxypropylmethylcellulose and natural polymeric gums such as xanthan, and carrageenan. The concentration of gelling agent in the composition may be varied depending on several factors, including the desired degree of stabilization of the suspension and desired viscosity of the gel composition.

[0215] If desired, the formulation of the disclosure may further include additional pharmaceutically acceptable excipients typically used in formulations and known to those skilled in the art. Such excipients include, for example, humectants, emollients, pH stabilizing agents, preservatives, chelating agents, and anti-oxidants.

[0216] The formulation of the disclosure for topical ophthalmic administration may be made by any means by which the components of the disclosure are combined to provide a pharmaceutical formulation. For example, a suspension of benzoyl peroxide may be made by combining water, the water-miscible organic solvent, and benzoyl peroxide. Preferably, the combination is mixed, such as by stirring, sonicating, milling, and/or shaking, to produce a uniform suspension of benzoyl peroxide particles in the water and organic solvent. Additional ingredients, such as a gelling agent and other excipients, may be added either before or after the uniform suspension is obtained.

[0217] Gels comprising polymers can swell in water and then interact in such a way as to thicken the water and increase viscosity. Polymers may interact physically, by chain entanglement, or by ionic or

hydrophobic/hydrophilic interactions. In each case, the polymers form a matrix that increases the viscosity of the water and allows for (1) physical stabilization and prevention of migration of suspended BTK inhibitor, (2) maintenance of product homogeneity throughout the shelf life, (3) clean, no drip, no mess transfer of the product from the primary package to the skin surface and (4) easy spreading and acceptable aesthetics.

[0218] In an embodiment, the composition for topical ophthalmic administration comprises matrix builder, such as high molecular weight polyvinylpyrrolidones (e.g. Kollidon® 90F), thickening polymers and biopolymers; poloxamers, emulsifiers, stably suspending oils in gels and solubilizers. The composition for topical ophthalmic administration may have sensory modifiers such as isopropyl myristate. In an exemplary embodiment, the sensory modifier is present at a concentration range of about 0.1% to about 5%, such as about 0.1% to about 0.5%, such as about 0.5% to about 1%, such as about 1% to about 2%, such as about 2% to about 3%, such as about 1% to about 3%, such as about 3% to about 5%. The solubility in an aqueous matrix can be enhanced by the use of water miscible solvents like propylene glycol, polyethylene glycols, triacetin, poloxamers, and low molecular weight polyvinylpyrrolidone.

[0219] In an embodiment, the composition for topical ophthalmic administration comprises the BTK inhibitor suspended in a hydrogel. A hydrogel is a colloidal gel formed as a dispersion in water or other aqueous medium. Thus a hydrogel is formed upon formation of a colloid in which a dispersed phase (the polymer) has combined with a continuous phase (i.e. water) to produce a viscous jellylike product; for example, coagulated silicic acid. A hydrogel is a three-dimensional network of hydrophilic polymer chains that are cross-linked through either chemical or physical bonding. Because of the hydrophilic nature of the polymer chains, hydrogels absorb water and swell (unless they have already absorbed their maximum amount of water). The swelling process is the same as the dissolution of non-cross-linked hydrophilic polymers. By definition, water constitutes at least 10% of the total weight (or volume) of a hydrogel.

[0220] Examples of hydrogels include synthetic polymers such as polyhydroxy ethyl methacrylate, and chemically or physically cross-linked polyvinyl alcohol, polyacrylamide, poly(N-vinyl pyrrolidone), polyethylene oxide, and hydrolysed polyacrylonitrile. Examples of hydrogels which are organic polymers include covalent or ionically cross-linked polysaccharide-based hydrogels such as the polyvalent metal salts of alginate, pectin, carboxymethyl cellulose, heparin, hyaluronate and hydrogels from chitin,

chitosan, pullulan, gellan and xanthan. The preferred hydrogels includes a cellulose compound (i.e. hydroxypropylmethylcellulose [HPMC]) and/or a high molecular weight hyaluronic acid (HA).

[0221] The ophthalmic compositions according to the disclosure for topical ophthalmic administration may also contain inert additives or combinations of these additives, such as wetting agents; mucoadhesive agents; flavor enhancers; preservatives such as para-hydroxybenzoic acid esters; stabilizers; moisture regulators; pH regulators; osmotic pressure modifiers; emulsifiers; UV-A and UV-B screening agents; and antioxidants, such as α -tocopherol, butylhydroxyanisole or butylhydroxytoluene, superoxide dismutase, ubiquinol or certain metal chelating agents.

[0222] The formulations for topical ophthalmic administration, after sterilization, may be packaged, stored and used directly. In an exemplary embodiment, the formulations are in drop form in the manner typically used to apply eye drops. The normal squeeze-type liquid drop application devices are perfectly suited for use in applying the ophthalmic formulations of the disclosure. In an exemplary embodiment, the formulations are conveniently administered by dropwise addition of the formulations into the affected eye(s) of the user.

[0223] The formulations of the present disclosure for topical ophthalmic administration containing preservatives are especially advantageous for use in multi-dose containers. Multi-dose containers, as used herein, refer to containers which allow two or more separate applications of the ophthalmic formulation present within the container. Such containers are resealable - i.e. the container cap may be removed for a first application, and then the cap may be replaced onto the container, thereby providing a substantially liquid impermeable seal again. In various exemplary embodiments, an antimicrobial preservative is present in an amount sufficient to reduce microbial concentrations for a period of about 12 hours to about 1 month, such as about 12 hours to about 3 weeks, such as about 12 hours to about 2 weeks, such as about 12 hours to about 1 week, such as about 12 hours to about 3 days, such as about 12 hours to about 48 hours, such as about 12 hours to about 24 hours.

[0224] In an exemplary embodiment, those formulations containing no preservative are packaged in a unit dose container - i.e. where only a single dose can be provided by a given container. Such preservative-free compositions are subject to uncontrolled microbial growth once the consumer initially breaks the container seal. Accordingly, the consumer is instructed to dispose of the container after the first dose. An appropriate unit-dose system such as blow-fill-seal unit dose preservative-free packaging system is typically used for the preservative-free formulations.

[0225] The concentration of the BTK inhibitor or pharmaceutically acceptable salt thereof for topical ophthalmic administration is typically about 0.01% to about 10.0 % by weight, about 0.02% to about 9.0 % by weight, about 0.03% to about 8.0 % by weight, about 0.04% to about 7.0 % by weight, about 0.05% to about 8.0 % by weight, about 0.06% to about 7.0 % by weight, about 0.07% to about 6.0 % by weight, about 0.08% to about 5.0 % by weight, about 0.09% to about 4.0 % by weight, about 0.1% to about 3.0 % by weight, about 0.2% to about 2.0 % by weight, about 0.3% to about 1.0 % by weight, about 0.4% to about 5.0 % by weight, or about 0.5% to about 5.0 % by weight.

[0226] The concentration of the BTK inhibitor or pharmaceutically acceptable salt thereof for topical ophthalmic administration is typically about 0.01% by weight, about 0.02% by weight, about 0.03% by weight, about 0.04% by weight, about 0.05% by weight, about 0.06% by weight, about 0.07% by weight, about 0.08% by weight, about 0.09% by weight, about 0.10% by weight, about 0.15% by weight, about 0.20% by weight, about 0.25% by weight, about 0.30% by weight, about 0.35% by weight, about 0.40% by weight, about 0.45% by weight, about 0.50% by weight, about 0.55% by weight, about 0.6% by weight, about 0.65% by weight, about 0.7% by weight, about 0.75% by weight, about 0.8% by weight, about 0.85% by weight, about 0.9% by weight, about 0.95% by weight, about 1% by weight, about 2% by weight, about 3% by weight, about 4% by weight, about 5% by weight, about 6% by weight, about 7% by weight, about 8% by weight, about 9% by weight, or about 10% by weight.

[0227] In various exemplary embodiments, the BTK inhibitor or pharmaceutically acceptable salt thereof is employed at a concentration of about 0.1 to about 10% w/v, such as about 0.1 to about 4.5% w/v, such as about 0.1 to about 4.0% w/v, such as about 0.1 to about 3.5% w/v, such as about 0.1 to about 3.0% w/v, such as about 0.1 to about 2.5% w/v, such as about 0.1 to about 2.0% w/v, such as about 0.1 to about 1.5% w/v, such as about 0.1 to about 1.0% w/v, such as about 0.1 to about 0.8% w/v, such as about 0.1 to about 0.7% w/v, such as about 0.1 to about 0.6% w/v, such as about 0.1 to about 0.5% w/v, such as about 0.1 to about 0.4% w/v, such as about 0.1 to about 0.3% w/v, such as about 0.1 to about 0.2% w/v.

[0228] Optionally, the formulations for topical ophthalmic administration contain a tonicity modifier.

[0229] In an exemplary embodiment, the tonicity modifier is non-ionic. The tonicity modifier may be selected from, but is not limited to, mannitol, sorbitol, dextrose, sucrose, urea, glycerol, polyethylene glycol and any mixtures thereof. In an exemplary embodiment, the tonicity modifier is present in amount sufficient to generate a tonicity of about 250 to about 350 milliosmoles per kilogram

(mOsmol/kg), such as about 265 to about 325 mOsmol/kg, such as about 280 to about 310 mOsmol/kg, such as about 295 to about 315 mOsmol/kg.

[0230] The formulation for topical ophthalmic administration may also contain an ionic salt, selected from, but not limited to, alkali metal halides (such as, for example, NaCl, KCl, NaBr, etc.), in an amount ranging from about 0.3% to about 1% weight percent or sufficient to approximate the salt concentration and/or tonicity of the human tear fluid. Selected salts from this group may also be referred to as ionic tonicity modifiers.

[0231] Where a preservative is used in the formulations for topical ophthalmic administration, an antimicrobial is present in an amount sufficient to generate a microbial barrier to maintain or reduce microbial concentrations for a period of about 12 hours to about 1 month, such as about 12 hours to about 3 weeks, such as about 12 hours to about 2 weeks, such as about 12 hours to about 1 week, such as about 12 hours to about 3 days, such as about 12 hours to about 48 hours, such as about 12 hours to about 24 hours. Suitable preservatives include, but are not limited to, benzalkonium chloride, benzyl alcohol, sorbic acid, chlorobutanol, cetrimonium, methylparaben, propylparaben, polyamino propyl biguanide, phenylethyl alcohol, chlorhexidine, chlorhexidine digluconate, chloroquat, stabilized oxychloro complex or any combination thereof.

[0232] Buffering agents that can be used in the formulations for topical ophthalmic administration include, but are not limited to, buffers prepared from sodium, potassium bicarbonate, phosphate, acetate, citrate, borate salts and/or phosphoric acid, acetic acid, citric acid or boric acid. In an exemplary embodiment, the buffer is sodium dihydrogen phosphate or disodium phosphate or boric acid/sodium borate. In an exemplary embodiment, the buffer is phosphate buffered saline. In certain embodiments, the buffers are present in an amount sufficient to produce and maintain a formulation pH of about 5.0 to about 8.0, such as about 5.5 to about 7.7, such as about 6.0 to about 7.5, such as about 6.3 to about 7.5, such as about 6.7 to 7.5, such as about 6.7 to about 7.1, and including a pH of about 5.7, about 5.9, about 6.1, about 6.3, about 6.5, about 6.7, about 6.9, about 7.1, about 7.3, about 7.5, about 7.7 or about 7.9.

[0233] A surfactant may also be added to the compositions for topical ophthalmic administration. In an exemplary embodiment, the surfactant is present at a concentration range of about 0.001% to about 0.3%, such as about 0.005% to about 0.2%, such as about 0.01% to about 0.1%, such as about 0.05% to about 0.1% to provide enhanced wetting characteristics to the formulation. In another embodiment, the surfactant is present at a concentration range of about 0.3% to about 30%, such as about 0.3% to about

3%, such as about 3% to about 5%, such as about 5% to about 10%, such as about 10% to about 15%, such as about 15% to about 20%, such as about 20% to about 25%, such as about 25% to about 30%, such as about 5% to about 20%. The surfactant may include, but is not limited to, poloxamers, polysorbate 80, polysorbate 20, tyloxapol, polyoxyethylene, Brij 35, Brij 58, Brij 78, Aptet 100, G 1045, Spans 20, 40 and 85, Tweens 20, 40, 80 or 81, sodium lauroyl sarcosinate, lauroyl-L-glutamic acid triethanolamine, sodium myristyl sarcosinate and sodium lauryl sulfate, polyoxyethylene sorbitan fatty acid esters, polyoxyethylene hydrogenated castor oil, polyethylene glycol fatty acid esters (*e.g.* polyoxyl stearate), polyoxyethylene polyoxypropylene alkyl ethers, polyoxyalkylene alkyl phenyl ethers, polyglycerol fatty acids esters (*e.g.* decaglycerol monolaurate), glycerol fatty acid esters, sorbitan fatty acid esters, and polyoxyethylene polyoxypropylene glycol (poloxamer), polyoxyl stearate 40, and/or any combination thereof.

[0234] A stabilizer can also be added to the formulations for topical ophthalmic administration. Suitable stabilizers include, but are not limited to, sodium metabisulfite, sodium bisulfate, acetylcysteine, ascorbic acid, sodium thiosulfate, alpha-tocopherol, carnosine, retinyl palmitate, salts of ethylenediaminetetraacetic acid (EDTA) (such as, for example, the disodium, tetrasodium, calcium or calcium sodium edetate salts), or any combination thereof.

[0235] The mucoadhesive agent, when present in the described formulations, increases corneal contact time, enhances bioavailability and/or produces a lubricating effect, and includes, but is not limited to acrylic acid polymers, methylcellulose, ethylcellulose, Povidone K-30, hydroxypropyl methylcellulose, hydroxyethylcellulose, Carbopol® polymers (such as, for example, Carbopol® 674, 676, 690, 980 NF, EZ-2, EZ-3, EZ-4, Aqua 30 and Novethix™ L-10), hydroxypropyl cellulose, polyvinyl alcohol, gelatin, sodium chondroitin sulfate, or any combination thereof.

[0236] In an embodiment, after administration onto the surface of the eye, the composition enters the conjunctiva and anterior sclera and into the corneal layer. When present, the mucoadhesive agent appears to increase residence time in the cornea so that the drug may diffuse slowly over time to the posterior sclera, resulting in delivery of sustained concentrations of the BTK inhibitor or pharmaceutically acceptable salts thereof in the posterior sclera. The mucoadhesive agent accomplishes this objective by retarding the loss of the drug through, for example, drainage from the nasolachrymal duct due to lachrymation and tear turnover. The mucoadhesive agent also typically possesses viscosity enhancing properties that may result in a desirable soothing or lubricating effect. The penetration enhancer agent which is optionally added to the formulation enhances penetration of the formulation

into the corneal epithelial layers, further enhancing the residence time of the BTK inhibitor or pharmaceutically acceptable salts thereof in the eye. The stabilizing agent may act as an antioxidant or otherwise retard the chemical degradation of the BTK inhibitor formulation. The buffering agent buffers the formulation to a comfortable near-neutral pH compatible with ocular administration. The tonicity modifier in the formulation produces the appropriate osmolality of the ophthalmic formulation.

[0237] The penetration enhancer optionally present in the described formulations for topical ophthalmic administration includes, but is not limited to, laurocapram (azone), bile acids and their alkali metal salts, including chenodeoxycholic acid, cholic acid, taurocholic acid, taurodeoxycholic acid, tauroursodeoxycholic acid or ursodeoxycholic acid, glycocholate, n-dodecyl- β -D-maltoside, sucrose dodecanoate, octyl maltoside, decyl maltoside, tridecyl maltoside, tetradecyl maltoside, hexamethylene lauramide, hexamethylene octanamide, glycerol monolaurate, PGML (polyethylene glycol monolaurate), dimethyl sulfoxide, methylsulfonylmethane, sodium fusidate, saponins, cyclodextrins (CDs) or any combination thereof.

[0238] In addition, a solubilizing or resuspension agent may also be added to the formulations for topical ophthalmic administration. Suitable solubilizing or resuspension agents include, but are not limited to, cyclodextrins (CDs), such as hydroxypropyl γ -cyclodextrin (Cavasol®), sulfobutyl ether 4 β -cyclodextrin (Captisol®), and hydroxypropyl β -cyclodextrin (Kleptose®) (such as 2-hydroxypropyl β -cyclodextrin), Polysorbate 80 (Tween80®) or hyaluronic acid or hyaluronate salts. The cyclodextrins in particular may also exhibit penetration enhancing properties, although in other instances, cyclodextrins are known to retard the uptake of steroidal compounds (such as hydrocortisone) into ocular tissues. Masson, Proc. of the 9th Intl. Symposium on Cyclodextrins, Kluwer Academic Publishers (1999), 363-369; Loftsson, Acta Ophthalmologica Scandinavica (2003), 144-150; International Journal of Pharmaceutics 156 (1997), 201-209.

[0239] An exemplary listing of typical carriers, stabilizers and adjuvants known to those of skill in the art that may be useful in the ophthalmic compositions described herein may be found in Gennaro (2005) Remington: The Science and Practice of Pharmacy, Mack Publishing, 21st ed.

Microemulsion

[0240] Ophthalmic compositions for topical ophthalmic administration of this disclosure may be formulated as an oil-in-water microemulsion. In some embodiments, the oil-in-water microemulsion functions as a pharmaceutical carrier.

[0241] An “oil-in-water microemulsion” is a microemulsion comprised of at least 50 percent (w/w) water or a buffer, at least one organic compound that is substantially immiscible in water (i.e., an oil), and at least two surfactants (sometimes referred to as co-surfactants). The dispersed oil phase is dispersed as droplets in the continuous (water) phase, where the droplets typically have a mean diameter of less than about 300 nm, e.g., about 5 nm to about 200 nm. A microemulsion characteristically has a clear or translucent appearance on visual inspection because the droplets are too small to scatter light of visible wavelengths. Microemulsions typically have viscosities lower than liquid crystals, e.g., about 10-400 mPa·s.

[0242] It is well known that topical delivery of an active pharmaceutical ingredient (API) to the eye is commonly limited by a number of factors, including low residence time, poor penetration and delivery to target tissue, and physiological barriers to delivery. These limiting factors are affecting the effective concentration needed for the treatment of eye diseases, such as dry eye disease and allergic conjunctivitis (AC).

[0243] It is unexpected to discover that the oil-in-water microemulsions described herein are able to deliver a BTK inhibitor for treating eye diseases, such as dry eye disease and allergic conjunctivitis (AC). In some embodiments, the BTK inhibitor is 1-(4-(((6-amino-5-(4-phenoxyphenyl)pyrimidin-4-yl)amino)methyl)-4-fluoropiperidin-1-yl)prop-2-en-1-one or a pharmaceutically acceptable salt thereof. The oil-in-water microemulsions described herein do not cause irritation as the surfactant molecules are ordered in the emulsion droplets in such a way that ocular tissues are only exposed to the hydrophilic component of the surfactant. Further, the oil-in-water microemulsions described herein are stable and do not break down when exposed to the corneal tear film interface. In some embodiment, the BTK inhibitor is any BTK inhibitor listed in Table 1.

[0244] In some embodiments, the oil-in-water microemulsion comprises surfactants, oil, and water or buffer. In some embodiments, the water or buffer represents at least about 50, about 55, about 60, about 65, about 70, about 75, about 80, about 85, about 90, or about 95 percent (w/w) of the oil-water microemulsion.

[0245] In some embodiments, the water or buffer represents at least about 50, about 55, about 60, about 65, about 70, about 75, about 80, about 85, about 90, or about 95 percent (v/v) of the oil-water microemulsion.

[0246] In some embodiments, the oil represents at least about 1% (v/v) of the oil-water microemulsion. In some embodiments, the oil represents at least from about 1% (v/v) to about 5% (v/v)

of the oil-water microemulsion. In some embodiments, the oil represents about 1%, 2%, 3%, 4%, or 5% (v/v) of oil-water microemulsion. In some embodiments, the oil represents 1%, 2%, 3%, 4%, or 5% (v/v) of oil-water microemulsion. In some embodiments, the oil represents at least about 1% (w/w) of the oil-water microemulsion. In some embodiments, the oil represents at least from about 1% (w/w) to about 5% (w/w) of the oil-water microemulsion. In some embodiments, the oil represents about 1%, 2%, 3%, 4%, or 5% (w/w) of oil-water microemulsion. In some embodiments, the oil represents 1%, 2%, 3%, 4%, or 5% (w/w) of oil-water microemulsion. In some embodiments, the oil is selected from the group consisting of isopropyl myristate, isopropyl palmitate, medium chain triglycerides, propylene glycol, oleic acid, palm oil, and combinations thereof. In an embodiment, the oil is isopropyl myristate. In an embodiment, the oil is medium chain triglycerides. In an embodiment, the oil is isopropyl palmitate.

[0247] The term “w/w” as used herein means ratio of weight of component (in grams) to weight of solution (in grams), where weight of solution refers to the total weight of the oil, water, and surfactant. As an example, 1 percent (w/w) isopropyl myristate denotes 1 g isopropyl myristate per 100 g total weight of solution.

[0248] The term “w/v” as used herein means ratio of weight (in grams) to volume (in mL), where volume refers to the final volume. As an example, 1 percent (w/v) isopropyl myristate denotes 1 g isopropyl myristate per 100 mL final volume.

[0249] The term “v/v” as used herein means ratio of volume (in mL) to volume (in mL), where volume refers to the final volume. As an example, 1 percent (v/v) isopropyl myristate in the ophthalmic composition denotes 0.01 mL isopropyl myristate per 1 mL final volume of the ophthalmic composition; 1 percent (v/v) isopropyl myristate in the oil-in-water microemulsion denotes 0.01 mL isopropyl myristate per 1 mL final volume of the oil-in-water microemulsion.

[0250] In some embodiments, the oil-in-water microemulsion further comprises a pair of surfactants. Suitable surfactants include anionic, cationic, and nonionic surfactants, as well as mixtures thereof. Suitable anionic surfactants include but are not limited to alkyl sulfates, alkyl ether sulfates, alkyl sulphonates, alkaryl sulfonates, α -olefin-sulphonates, alkylamide sulphonates, alkarylpolyether sulphates, alkylamidoether sulphates, alkyl monoglyceryl ether sulfates, alkyl monoglyceride sulfates, alkyl monoglyceride sulfonates, alkyl succinates, alkyl sulfosuccinates, alkyl sulfosuccinamates, alkyl ether sulphosuccinates, alkyl amidosulfosuccinates; alkyl sulphoacetates, alkyl phosphates, alkyl ether phosphates, alkyl ether carboxylates, alkyl amidoethercarboxylates, N-alkylamino acids, N-acyl amino acids, alkyl peptides, N-acyl taurates, alkyl isethionates, carboxylate salts wherein the acyl

group is derived from fatty acids; and the alkali metal, alkaline earth metal, ammonium, amine, and triethanolamine salts thereof. Suitable classes of cationic surfactants include but are not limited to alkyl amines, alkyl imidazolines, ethoxylated amines, quaternary compounds, and quaternized esters. Suitable nonionic surfactants include, but are not limited to, aliphatic (C₆-C₁₈) primary or secondary linear or branched chain acids, alcohols or phenols; alkyl ethoxylates; alkyl phenol alkoxylates (especially ethoxylates and mixed ethoxy/propoxy moieties); block alkylene oxide condensates of alkyl phenols; alkylene oxide condensates of alkanols; and ethylene oxide/propylene oxide block copolymers. Other suitable nonionic surfactants include mono- or dialkyl alkanolamides; alkyl polyglucosides (APGs); sorbitan fatty acid esters; polyoxyethylene sorbitan fatty acid esters; polyoxyethylene sorbitol esters; polyoxyethylene acids, and polyoxyethylene alcohols. Other examples of suitable nonionic surfactants include polysorbate 20, 40, 60, and 80, ethoxylated linear alcohols, coco mono- or diethanolamide, coco glucoside, decyl diglucoside, lauryl diglucoside, coco diglucoside, cetearyl alcohol, lanolin alcohol, stearic acid, glyceryl stearate, PEG-100 stearate, laureth 7, and oleyl 20. In some embodiments, non-ionic surfactants include, but are not limited to, alkoxylated methyl glucosides such as, for example, methyl gluceth-10, methyl gluceth-20, PPG-10 methyl glucose ether, and PPG-20 methyl glucose ether, available from Lubrizol Advanced Materials, Inc., under the trade names, Glucam® E10, Glucam® E20, Glucam® P10, and Glucam® P20, respectively; and hydrophobically modified alkoxylated methyl glucosides, such as PEG 120 methyl glucose dioleate, PEG-120 methyl glucose trioleate, and PEG-20 methyl glucose sesquistearate, available from Lubrizol Advanced Materials, Inc., under the trade names, Glucamate® DOE-120, Glucamate™ LT, and Glucamate™ SSE-20, respectively. In some embodiments, the pair of surfactants selected from the group consisting of two polysorbates, a polysorbate and propylene glycol, a polysorbate and glycerol, a polysorbate and triacetin (1,2,3-triacetoxyp propane), cremophor EL (polyethoxylated castor oil) and triacetin (1,2,3-triacetoxyp propane), and cremophor EL (polyethoxylated castor oil) and propylene glycol. In one embodiment, the pair of surfactants is two polysorbates. For example, in one embodiment, the pair of surfactants is polysorbate 20 and polysorbate 80. In one embodiment, the pair of surfactants is a polysorbate and propylene glycol. In one embodiment, the pair of surfactants is a polysorbate and glycerol. In one embodiment, the pair of surfactants is a polysorbate and triacetin (1,2,3-triacetoxyp propane). In one embodiment, the pair of surfactants is cremophor EL (polyethoxylated castor oil) and triacetin (1,2,3-triacetoxyp propane). In one embodiment, the pair of surfactants is cremophor EL (polyethoxylated castor oil) and propylene glycol.

[0251] As used herein, the term “polysorbate” refers generally to a polyoxyethylene derivative of sorbitan fatty acid ester. Common commercial preparations of polysorbates are sold under the name

Tween®, Alkest, or Canarcel. In the nomenclature of polysorbates, the numeric designation following polysorbate (or Tween®) refers to the lipophilic group. For example, polysorbate 20 is a monolaurate ester, and polysorbate 80 is a monooleate ester.

[0252] Cremophor® EL (BASF SE), is a version of polyethoxylated castor oil, the major component of which is glycerol polyethylene glycol ricinoleate. Additional components include free polyethylene glycols and ethoxylated glycerol. It is prepared by reacting 35 moles of ethylene oxide with each mole of castor oil. The product has been given CAS number 61791-12-6.

[0253] In some embodiments, the pair of surfactants represent about 10 to about 50 percent (v/v) of the oil-in-water microemulsion. In some embodiments, the pair of surfactants represent about 15 to about 40 percent (v/v) of the oil-in-water microemulsion. In some embodiments, the pair of surfactants represent about 20 to about 40 percent (v/v) of the oil-in-water microemulsion. In some embodiments, wherein the pair of surfactants represent about 15%, about 20%, about 25%, about 30%, about 35%, about 40%, or about 45% (v/v) of the oil-in-water microemulsion. In some embodiments, wherein the pair of surfactants represent 15%, 20%, 30%, 35%, 40%, or 45% (v/v) of the oil-in-water microemulsion. In some embodiments, wherein the pair of surfactants represent about 15%, about 20%, about 25%, about 30%, about 35%, about 40%, or about 45% (w/w) of the oil-in-water microemulsion. In some embodiments, wherein the pair of surfactants represent 15%, 20%, 30%, 35%, 40%, or 45% (w/w) of the oil-in-water microemulsion.

[0254] In some embodiments, the oil-in-water microemulsion further comprises a buffer. Buffering agents that can be used in the formulations for topical ophthalmic administration include, but are not limited to, buffers prepared from sodium, potassium bicarbonate, phosphate, acetate, citrate, borate salts and/or phosphoric acid, acetic acid, citric acid or boric acid. In an exemplary embodiment, the buffer is sodium dihydrogen phosphate or disodium phosphate or boric acid/sodium borate. In an exemplary embodiment, the buffer is phosphate buffered saline. In some embodiments, the phosphate buffered saline buffer comprises disodium hydrogen phosphate. In some embodiments, the phosphate buffered saline buffer comprises sodium chloride. In some embodiments, the phosphate buffered saline buffer comprises potassium chloride. In some embodiments, the phosphate buffered saline buffer comprises potassium dihydrogen phosphate. In some embodiments, the phosphate buffered saline buffer comprises disodium hydrogen phosphate and sodium chloride. In some embodiments, the phosphate buffered saline buffer comprises potassium chloride and potassium dihydrogen phosphate. In some embodiments, the phosphate buffered saline buffer comprises disodium hydrogen phosphate,

sodium chloride, potassium chloride, and potassium dihydrogen phosphate. In some embodiments, the phosphate buffered saline buffer comprises 0.17% (w/w) disodium hydrogen phosphate, 0.79% (w/w) sodium chloride, 0.02% (w/w) potassium chloride, and 0.025% (w/w) potassium dihydrogen phosphate. In certain embodiments, the buffers are present in an amount sufficient to produce and maintain a formulation pH of about 5.0 to about 8.0, such as about 5.5 to about 7.7, such as about 6.0 to about 7.5, such as about 6.3 to about 7.5, such as about 6.7 to 7.5, such as about 6.7 to about 7.1, and including a pH of about 5.7, about 5.9, about 6.1, about 6.3, about 6.5, about 6.7, about 6.9, about 7.1, about 7.3, about 7.5, about 7.7 or about 7.9.

[0255] In some embodiments, the present disclosure provides a method of treating or preventing an ophthalmic condition in a human subject in need thereof comprising topically administering to an eye of the human subject an ophthalmic composition comprising a Bruton's Tyrosine Kinase (BTK) inhibitor, wherein the BTK inhibitor is 1-(4-(((6-amino-5-(4-phenoxyphenyl)pyrimidin-4-yl)amino)methyl)-4-fluoropiperidin-1-yl)prop-2-en-1-one or a pharmaceutically acceptable salt thereof. In some embodiments, the ophthalmic condition is dry eye disease (DED) or allergic conjunctivitis (AC). In some embodiment, the BTK inhibitor is any BTK inhibitor listed in Table 1. In some embodiment, the ophthalmic composition is an oil-in-water microemulsion described herein. In some embodiments, oil-in-water microemulsion comprises: (i) 1-(4-(((6-amino-5-(4-phenoxyphenyl)pyrimidin-4-yl)amino)methyl)-4-fluoropiperidin-1-yl)prop-2-en-1-one or a pharmaceutically acceptable salt thereof (ii) an oil selected from the group consisting of isopropyl myristate, isopropyl palmitate, and medium chain triglycerides; (iii) a pair of surfactants selected from the group consisting of two polysorbates, a polysorbate and propylene glycol, a polysorbate and glycerol, a polysorbate and 1,2,3-triacetoxyp propane, polyethoxylated castor oil and 1,2,3-triacetoxyp propane, and polyethoxylated castor oil and propylene glycol; and (iv) water or a buffer, wherein: the water or buffer represents 50 to about 95 percent (w/w) of the pharmaceutical carrier; the oil and the pair of surfactants represent substantially all of the remainder of the pharmaceutical carrier; and the ratio of percent (w/w) the pair of surfactants to percent (w/w) the oil is at least about 10:1. In some embodiments, oil-in-water microemulsion comprises: (i) 1-(4-(((6-amino-5-(4-phenoxyphenyl)pyrimidin-4-yl)amino)methyl)-4-fluoropiperidin-1-yl)prop-2-en-1-one or a pharmaceutically acceptable salt thereof (ii) an oil selected from the group consisting of isopropyl myristate, isopropyl palmitate, and medium chain triglycerides; (iii) a pair of surfactants selected from the group consisting of two polysorbates, a polysorbate and propylene glycol, a polysorbate and glycerol, a polysorbate and 1,2,3-triacetoxyp propane, polyethoxylated castor oil and 1,2,3-triacetoxyp propane, and polyethoxylated castor oil and propylene

glycol; and (iv) water or a buffer, wherein: the water or buffer represents 50 to about 95 percent (v/v) of the pharmaceutical carrier; the oil and the pair of surfactants represent substantially all of the remainder of the pharmaceutical carrier; and the ratio of percent (v/v) the pair of surfactants to percent (v/v) the oil is at least about 10:1.

[0256] In some embodiments, the ophthalmic composition comprises about 0.1% (1.0 mg/ml) of 1-(4-(((6-amino-5-(4-phenoxyphenyl)pyrimidin-4-yl)amino)methyl)-4-fluoropiperidin-1-yl)prop-2-en-1-one or a pharmaceutically acceptable salt thereof; about 8.43% polysorbate 20 (w/w); about 16.19% polysorbate 80 (w/w); about 1.77% isopropyl myristate (w/w); and phosphate buffered saline.

[0257] In some embodiments, the ophthalmic composition comprises about 0.09% (w/w) of 1-(4-(((6-amino-5-(4-phenoxyphenyl)pyrimidin-4-yl)amino)methyl)-4-fluoropiperidin-1-yl)prop-2-en-1-one or a pharmaceutically acceptable salt thereof; about 8.43% polysorbate 20 (w/w); about 16.19% polysorbate 80 (w/w); about 1.77% isopropyl myristate (w/w); and phosphate buffered saline.

[0258] In an embodiment, the ophthalmic composition is an oil-in-water microemulsion comprising: about 0.1% (1.0 mg/ml) of 1-(4-(((6-amino-5-(4-phenoxyphenyl)pyrimidin-4-yl)amino)methyl)-4-fluoropiperidin-1-yl)prop-2-en-1-one or a pharmaceutically acceptable salt thereof; about 8% polysorbate 20 (v/v); about 17% polysorbate 80 (v/v); about 2% isopropyl myristate (v/v); and about 73% phosphate buffered saline (v/v).

[0259] In an embodiment, the ophthalmic composition is an oil-in-water microemulsion comprising: about 0.1% (1.0 mg/ml) of 1-(4-(((6-amino-5-(4-phenoxyphenyl)pyrimidin-4-yl)amino)methyl)-4-fluoropiperidin-1-yl)prop-2-en-1-one or a pharmaceutically acceptable salt thereof; about 36% polysorbate 20 (v/v); about 4% polysorbate 80 (v/v); about 3% isopropyl myristate (v/v); and about 57% phosphate buffered saline (v/v).

[0260] In some embodiments, the ophthalmic composition comprises about 0.09% (w/w) of 1-(4-(((6-amino-5-(4-phenoxyphenyl)pyrimidin-4-yl)amino)methyl)-4-fluoropiperidin-1-yl)prop-2-en-1-one or a pharmaceutically acceptable salt thereof; about 36.21% polysorbate 20 (w/w); about 3.88% polysorbate 80 (w/w); about 2.23% isopropyl myristate (w/w); and phosphate buffered saline.

[0261] In an embodiment, the ophthalmic composition is an oil-in-water microemulsion comprising: about 0.1% (1.0 mg/ml) of 1-(4-(((6-amino-5-(4-phenoxyphenyl)pyrimidin-4-yl)amino)methyl)-4-fluoropiperidin-1-yl)prop-2-en-1-one or a pharmaceutically acceptable salt thereof; about 7%

polysorbate 20 (v/v); about 28% polysorbate 80 (v/v); about 3% isopropyl myristate (v/v); and about 62% phosphate buffered saline (v/v).

[0262] In an embodiment, the ophthalmic composition is an oil-in-water microemulsion comprising: about 0.1% (1.0 mg/ml) of 1-(4-(((6-amino-5-(4-phenoxyphenyl)pyrimidin-4-yl)amino)methyl)-4-fluoropiperidin-1-yl)prop-2-en-1-one or a pharmaceutically acceptable salt thereof; about 6% polysorbate 20 (v/v); about 24% polysorbate 80 (v/v); about 3% isopropyl myristate (v/v); and about 67% phosphate buffered saline (v/v).

[0263] In an embodiment, the ophthalmic composition is an oil-in-water microemulsion comprising: about 0.1% (1.0 mg/ml) of 1-(4-(((6-amino-5-(4-phenoxyphenyl)pyrimidin-4-yl)amino)methyl)-4-fluoropiperidin-1-yl)prop-2-en-1-one or a pharmaceutically acceptable salt thereof; about 2% polysorbate 20 (v/v); about 18% polysorbate 80 (v/v); about 2% isopropyl myristate (v/v); and about 78% phosphate buffered saline (v/v).

Dosages and Dosing Regimens

[0264] The amount of a BTK inhibitor or a pharmaceutically acceptable salt thereof administered will be dependent on the human being treated, the severity of the disorder or condition, the rate of administration, the disposition of the compounds and the discretion of the prescribing physician. However, an effective dosage is in the range of about 0.001 to about 100 mg per kg body weight per day, such as about 1 to about 35 mg/kg/day, in single or divided doses. For a 70 kg human, this would amount to about 0.05 to 7 g/day, such as about 0.05 to about 2.5 g/day. In some instances, dosage levels below the lower limit of the aforesaid range may be more than adequate, while in other cases still larger doses may be employed without causing any harmful side effect - *e.g.* by dividing such larger doses into several small doses for administration throughout the day.

[0265] In some embodiments, a BTK inhibitor or a pharmaceutically acceptable salt thereof is administered in a single dose. Multiple daily doses are also embodied, for example, twice daily. Typically, such administration will be by injection - *e.g.* intravenous injection or intravitreal injection, in order to introduce the agents quickly. However, other routes may be used as appropriate. A single dose of a BTK inhibitor or a pharmaceutically acceptable salt thereof may also be used for treatment of an acute condition.

[0266] In some embodiments, a BTK inhibitor or a pharmaceutically acceptable salt thereof is administered in multiple doses for reducing ocular mast cell degranulation and/or ocular mast cell

cytokine production. In some embodiments, a BTK inhibitor or a pharmaceutically acceptable salt thereof is administered in multiple doses for inhibiting ocular mast cell activation. In some embodiments, a BTK inhibitor or a pharmaceutically acceptable salt thereof is administered in multiple doses for treating meibomian gland dysfunction. In some embodiments, a BTK inhibitor or a pharmaceutically acceptable salt thereof is administered in multiple doses for inhibiting mast cell activation. In some embodiments, a BTK inhibitor or a pharmaceutically acceptable salt thereof is administered in multiple doses for reducing or alleviating a sign or symptom of dry eye disease, wherein the reducing or alleviating of a sign or symptom of dry eye disease accompanies at least one of reduced total corneal fluorescein staining score, reduced central corneal fluorescein staining score, reduced inferior corneal fluorescein staining score, reduced superior corneal fluorescein staining score, increased Schirmer's unanesthetized test score, reduced conjunctival lissamine staining score, reduced tear osmolarity, increased tear break-up time, reduced conjunctival redness, reduced ocular discomfort severity (ODS) score, reduced ocular discomfort and four-symptom (OD4S) score, reduced ocular surface disease index (OSDI) score, reduced visual analog scale (VAS) ocular discomfort score, reduced inflammation of an eye, reduced ocular redness, reduced ocular itching score, increased tear volume in an eye, or any combination thereof. In some embodiments, a BTK inhibitor or a pharmaceutically acceptable salt thereof is administered in multiple doses for reducing or alleviating a sign or symptom of allergic conjunctivitis, wherein the reducing or alleviating of a sign or symptom of allergic conjunctivitis comprises reduced conjunctival redness, a reduced ocular itching score, or a combination thereof. In some embodiments, a BTK inhibitor or a pharmaceutically acceptable salt thereof is administered in multiple doses for treating allergic conjunctivitis.

[0267] In an embodiment, a BTK inhibitor or a pharmaceutically acceptable salt thereof is administered in multiple doses. In an embodiment, a BTK inhibitor or a pharmaceutically acceptable salt thereof is administered in multiple doses by injection - *e.g.* intravenous injection or intravitreal injection. In an embodiment, dosing may be once, twice, three times, four times, five times, six times, or more than six times per day. In an embodiment, dosing may be selected from the group consisting of once a day, twice a day, three times a day, four times a day, five times a day, six times a day, once every other day, once weekly, twice weekly, three times weekly, four times weekly, biweekly, and monthly. In other embodiments, a BTK inhibitor or a pharmaceutically acceptable salt thereof is administered about once per day to about six times per day. In some embodiments a BTK inhibitor or a pharmaceutically acceptable salt thereof is administered once daily, while in other embodiments a BTK inhibitor or a pharmaceutically acceptable salt thereof is administered twice daily, and in other embodiments a BTK

inhibitor or a pharmaceutically acceptable salt thereof is administered three times daily. In some embodiments a BTK inhibitor or a pharmaceutically acceptable salt thereof is administered three times a week, including every Monday, Wednesday, and Friday.

[0268] In some embodiments, an ophthalmic composition comprising a BTK inhibitor is administered by intravitreal or intraocular injection to a human subject monthly, bi-monthly, once every three months, quarterly, once every five months, once every six months, or yearly. In some embodiments, the ophthalmic composition comprising a BTK inhibitor is administered by intravitreal or intraocular injection to a human subject monthly for two, three, four, or five months followed by bi-monthly administration.

[0269] In some embodiments, an ophthalmic composition comprising a BTK inhibitor is administered topically to a human subject once a day, twice a day, three times a day, once every other day, weekly, twice weekly, three times weekly, four times weekly, biweekly, or monthly.

[0270] Administration of a BTK inhibitor or a pharmaceutically acceptable salt thereof may continue as long as necessary. In some embodiments, a BTK inhibitor or a pharmaceutically acceptable salt thereof is administered for more than 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31 or more days. In some embodiments, a BTK inhibitor or a pharmaceutically acceptable salt thereof is administered for less than 28, 14, 7, 6, 5, 4, 3, 2, or 1 day. In some embodiments, a BTK inhibitor or a pharmaceutically acceptable salt thereof is administered for about 14 days, about 21 days, about 28 days, about 35 days, about 42 days, about 49 days, or about 56 days. In some embodiments, a BTK inhibitor or a pharmaceutically acceptable salt thereof is administered chronically on an ongoing basis - *e.g.* for the treatment of chronic effects. In another embodiment the administration of a BTK inhibitor or a pharmaceutically acceptable salt thereof continues for less than about 7 days. In yet another embodiment the administration continues for more than about 6, 10, 14, 28 days, two months, three months, four months, five months, six months, seven months, eight months, nine months, ten months, eleven months or one year. In some embodiments, the administration continues for more than about one year, two years, three years, four years, or five years. In some embodiments, continuous dosing is achieved and maintained as long as necessary.

[0271] In some embodiments, an effective dosage of a BTK inhibitor or a pharmaceutically acceptable salt thereof is in the range of about 1 mg to about 600 mg, about 1 mg to about 500 mg, about 10 mg to about 500 mg, about 10 mg to about 300 mg, about 20 mg to about 450 mg, about 20 mg to about 250 mg, about 25 mg to about 200 mg, about 10 mg to about 200 mg, about 20 mg to about 150 mg, about

30 mg to about 120 mg, about 10 mg to about 90 mg, about 20 mg to about 80 mg, about 30 mg to about 70 mg, about 40 mg to about 60 mg, about 45 mg to about 55 mg, about 48 mg to about 52 mg, about 50 mg to about 150 mg, about 60 mg to about 140 mg, about 70 mg to about 130 mg, about 80 mg to about 120 mg, about 90 mg to about 110 mg, about 95 mg to about 105 mg, about 150 mg to about 250 mg, about 160 mg to about 240 mg, about 170 mg to about 230 mg, about 180 mg to about 220 mg, about 190 mg to about 210 mg, about 195 mg to about 205 mg, or about 198 to about 202 mg. In some embodiments, an effective dosage of a BTK inhibitor or a pharmaceutically acceptable salt thereof is about 15 mg, about 25 mg, about 30 mg, about 50 mg, about 50 mg, about 75 mg, about 90 mg, about 100 mg, about 120 mg, about 125 mg, about 150 mg, about 175 mg, about 180 mg, about 200 mg, about 225 mg, about 240 mg, about 250 mg, about 275 mg, about 300 mg, about 325 mg, about 350 mg, about 360 mg, about 375 mg, about 400 mg, about 425 mg, about 450 mg, about 475 mg, about 480 mg, or about 500 mg. In some embodiments, an effective dosage of a BTK inhibitor or a pharmaceutically acceptable salt thereof is 15 mg, 25 mg, 30 mg, 50 mg, 60 mg, 75 mg, 90 mg, 100 mg, 120 mg, 150 mg, 175 mg, 180 mg, 200 mg, 225 mg, 240 mg, 250 mg, 275 mg, 300 mg, 325 mg, 350 mg, 360 mg, 375 mg, and 480 mg.

[0272] In some embodiments, an effective dosage of a BTK inhibitor or a pharmaceutically acceptable salt thereof is in the range of about 0.01 mg/kg to about 4.3 mg/kg, about 0.15 mg/kg to about 3.6 mg/kg, about 0.3 mg/kg to about 3.2 mg/kg, about 0.35 mg/kg to about 2.85 mg/kg, about 0.15 mg/kg to about 2.85 mg/kg, about 0.3 mg to about 2.15 mg/kg, about 0.45 mg/kg to about 1.7 mg/kg, about 0.15 mg/kg to about 1.3 mg/kg, about 0.3 mg/kg to about 1.15 mg/kg, about 0.45 mg/kg to about 1 mg/kg, about 0.55 mg/kg to about 0.85 mg/kg, about 0.65 mg/kg to about 0.8 mg/kg, about 0.7 mg/kg to about 0.75 mg/kg, about 0.7 mg/kg to about 2.15 mg/kg, about 0.85 mg/kg to about 2 mg/kg, about 1 mg/kg to about 1.85 mg/kg, about 1.15 mg/kg to about 1.7 mg/kg, about 1.3 mg/kg to about 1.6 mg/kg, about 1.35 mg/kg to about 1.5 mg/kg, about 2.15 mg/kg to about 3.6 mg/kg, about 2.3 mg/kg to about 3.4 mg/kg, about 2.4 mg/kg to about 3.3 mg/kg, about 2.6 mg/kg to about 3.15 mg/kg, about 2.7 mg/kg to about 3 mg/kg, about 2.8 mg/kg to about 3 mg/kg, or about 2.85 mg/kg to about 2.95 mg/kg. In some embodiments, an effective dosage of a BTK inhibitor or a pharmaceutically acceptable salt thereof is about 0.35 mg/kg, about 0.7 mg/kg, about 1 mg/kg, about 1.4 mg/kg, about 1.8 mg/kg, about 2.1 mg/kg, about 2.5 mg/kg, about 2.85 mg/kg, about 3.2 mg/kg, or about 3.6 mg/kg.

[0273] In some embodiments, a BTK inhibitor or a pharmaceutically acceptable salt thereof is administered at a dosage of 10 to 500 mg BID, including a dosage of 15 mg, 25 mg, 30 mg, 50 mg, 60 mg,

75 mg, 90 mg, 100 mg, 120 mg, 150 mg, 175 mg, 180 mg, 200 mg, 225 mg, 240 mg, 250 mg, 275 mg, 300 mg, 325 mg, 350 mg, 360 mg, 375 mg, and 480 mg BID.

[0274] In some embodiments, a BTK inhibitor or a pharmaceutically acceptable salt thereof is administered at a dosage of 10 to 600 mg QD, including a dosage of 15 mg, 25 mg, 30 mg, 50 mg, 60 mg, 75 mg, 90 mg, 100 mg, 120 mg, 150 mg, 175 mg, 180 mg, 200 mg, 225 mg, 240 mg, 250 mg, 275 mg, 300 mg, 325 mg, 350 mg, 360 mg, 375 mg, and 480 mg QD.

[0275] An effective amount of a BTK inhibitor or a pharmaceutically acceptable salt thereof may be administered in either single or multiple doses by any of the accepted modes of administration of agents having similar utilities, including buccal, sublingual, and transdermal routes, by intra-arterial injection, intravenously, parenterally, intramuscularly, subcutaneously or orally.

[0276] In certain embodiments, the route of delivery used is intraocular injection, direct injection into a given compartment of the eye, such as the vitreous, the cornea, or the retina, application of a patch on the eye, direct application of an ointment, spray, or droppable liquid to the eye, or intraocular implant. In an embodiment, the route of delivery is intravitreal injection.

[0277] In some embodiments, the route of delivery used is topical administration to an eye of a human in need thereof, intraocular injection to an eye of a human in need thereof, intravitreal injection to an eye of a human in need thereof, periocular administration to a human in need thereof, oral administration to a human in need thereof, intravenous injection to a human in need thereof, or a combination thereof.

[0278] In some embodiments, the ophthalmic composition comprising a BTK inhibitor or a pharmaceutically acceptable salt thereof is administered by injection at a dosage of about 0.001 mg/ml, about 0.005 mg/ml, about 0.01 mg/ml, about 0.02 mg/ml, about 0.03 mg/ml, about 0.04 mg/ml, about 0.05 mg/ml, about 0.06 mg/ml, about 0.07 mg/ml, about 0.08 mg/ml, about 0.09 mg/ml, about 0.1 mg/ml, about 0.2 mg/ml, about 0.3 mg/ml, about 0.4 mg/ml, about 0.5 mg/ml, about 0.6 mg/ml, about 0.7 mg/ml, about 0.8 mg/ml, about 0.9 mg/ml, about 1 mg/ml, about 1.1 mg/ml, about 1.2 mg/ml, about 1.3 mg/ml, about 1.4 mg/ml, about 1.5 mg/ml, about 1.6 mg/ml, about 1.7 mg/ml, about 1.8 mg/ml, about 1.9 mg/ml, about 2.0 mg/ml, about 2.1 mg/ml, about 2.2 mg/ml, about 2.3 mg/ml, about 2.4 mg/ml, about 2.5 mg/ml, about 2.6 mg/ml, about 2.7 mg/ml, about 2.8 mg/ml, about 2.9 mg/ml, about 3.0 mg/ml, about 3.1 mg/ml, about 3.2 mg/ml, about 3.3 mg/ml, about 3.4 mg/ml, about 3.5 mg/ml, about 3.6 mg/ml, about 3.7 mg/ml, about 3.8 mg/ml, about 3.9 mg/ml, about 4.0 mg/ml, about 4.1 mg/ml, about 4.2 mg/ml, about 4.3 mg/ml, about 4.4 mg/ml, about 4.5 mg/ml, about 4.6 mg/ml,

about 4.7 mg/ml, about 4.8 mg/ml, about 4.9 mg/ml, about 5.0 mg/ml, about 5.1 mg/ml, about 5.2 mg/ml, about 5.3 mg/ml, about 5.4 mg/ml, about 5.5 mg/ml, about 5.6 mg/ml, about 5.7 mg/ml, about 5.8 mg/ml, about 5.9 mg/ml, about 6.0 mg/ml, about 6.1 mg/ml, about 6.2 mg/ml, about 6.3 mg/ml, about 6.4 mg/ml, about 6.5 mg/ml, about 6.6 mg/ml, about 6.7 mg/ml, about 6.8 mg/ml, about 6.9 mg/ml, about 7.0 mg/ml, about 7.1 mg/ml, about 7.2 mg/ml, about 7.3 mg/ml, about 7.4 mg/ml, about 7.5 mg/ml, about 7.6 mg/ml, about 7.7 mg/ml, about 7.8 mg/ml, about 7.9 mg/ml, about 8.0 mg/ml, about 8.1 mg/ml, about 8.2 mg/ml, about 8.3 mg/ml, about 8.4 mg/ml, about 8.5 mg/ml, about 8.6 mg/ml, about 8.7 mg/ml, about 8.8 mg/ml, about 8.9 mg/ml, about 9 mg/ml, about 9.1 mg/ml, about 9.2 mg/ml, about 9.3 mg/ml, about 9.4 mg/ml, about 9.5 mg/ml, about 9.6 mg/ml, about 9.7 mg/ml, about 9.8 mg/ml, about 9.9 mg/ml, about 10 mg/ml, about 10.5 mg/ml, about 11 mg/ml, about 11.5 mg/ml, about 12 mg/ml, about 12.5 mg/ml, about 13 mg/ml, about 13.5 mg/ml, about 14 mg/ml, about 14.5 mg/ml, about 15 mg/ml, about 16 mg/ml, about 17 mg/ml, about 18 mg/ml, about 19 mg/ml, about 20 mg/ml, about 21 mg/ml, about 22 mg/ml, about 23 mg/ml, about 24 mg/ml, about 25 mg/ml, about 26 mg/ml, about 27 mg/ml, about 28 mg/ml, about 29 mg/ml, about 30 mg/ml, about 31 mg/ml, about 32 mg/ml, about 33 mg/ml, about 34 mg/ml, about 35 mg/ml, about 36 mg/ml, about 37 mg/ml, about 38 mg/ml, about 39 mg/ml, about 40 mg/ml, about 41 mg/ml, about 42 mg/ml, about 43 mg/ml, about 44 mg/ml, about 45 mg/ml, about 46 mg/ml, about 47 mg/ml, about 48 mg/ml, about 49 mg/ml, or about 50 mg/ml.

[0279] In some embodiments, the ophthalmic composition comprising a BTK inhibitor or a pharmaceutically acceptable salt thereof is administered by injection at a volume of about 0.01 ml, about 0.02 ml, about 0.03 ml, about 0.04 ml, about 0.05 ml, about 0.06 ml, about 0.07 ml, about 0.08 ml, about 0.09 ml, about 0.1 ml, about 0.15 ml, about 0.2 ml, about 0.25 ml, about 0.30 ml, about 0.35 ml, about 0.40 ml, about 0.45 ml, about 0.5 ml, about 0.55 ml, about 0.60 ml, about 0.65 ml, about 0.70 ml, about 0.75 ml, about 0.80 ml, about 0.85 ml, about 0.90 ml, about 0.95 ml, about 1.0 ml, about 1.1 ml, about 1.2 ml, about 1.3 ml, about 1.4 ml, about 1.5 ml, about 1.6 ml, about 1.7 ml, about 1.8 ml, about 1.9 ml, about 2.0 ml, about 2.5 ml, about 3.0 ml, about 3.5 ml, about 4.0 ml, about 4.5 ml, about 5.0 ml, about 5.5 ml, about 6.0 ml, about 6.5 ml, about 7.0 ml, about 7.5 ml, about 8.0 ml, about 8.5 ml, about 9.0 ml, about 9.5 ml, about 10.0 ml, about 15.0 ml, about 20.0 ml, about 25.0 ml, about 30.0 ml, about 35.0 ml, about 40.0 ml, about 45.0 ml, or about 50.0 ml.

[0280] In some embodiments, the ophthalmic composition comprising a BTK inhibitor or a pharmaceutically acceptable salt thereof is administered by intravitreal or intraocular injection at a

volume of about 0.001 ml, about 0.005 ml, about 0.010 ml, about 0.015 ml, about 0.020 ml, about 0.025 ml, about 0.030 ml, about 0.035 ml, about 0.040 ml, about 0.045 ml, about 0.05 ml, about 0.055 ml, about 0.06 ml, about 0.065 ml, about 0.07 ml, about 0.075 ml, about 0.08 ml, about 0.085 ml, about 0.09 ml, about 0.095 ml, or about 0.1 ml.

[0281] In some embodiments, a BTK inhibitor or a pharmaceutically acceptable salt thereof is administered to a subject intermittently, known as intermittent administration. By “intermittent administration”, it is meant a period of administration of a therapeutically effective dose of a BTK inhibitor or a pharmaceutically acceptable salt thereof, followed by a time period of discontinuance, which is then followed by another administration period and so on. In each administration period, the dosing frequency can be independently selected from three times daily, twice daily, daily, once weekly, twice weekly, three times weekly, four times weekly, five times weekly, or six times weekly for topical administration to the eye or monthly for intravitreal or intraocular injection to the eye.

[0282] By “period of discontinuance” or “discontinuance period” or “rest period”, it is meant the length of time when discontinuing of the administration of a BTK inhibitor or a pharmaceutically acceptable salt thereof. The time period of discontinuance may be longer or shorter than the administration period or the same as the administration period. During the discontinuance period, other therapeutic agents other than a BTK inhibitor or a pharmaceutically acceptable salt thereof may be administered. The discontinuance period may be necessary to alleviate any toxic effects associated with a particular BTK inhibitor compound.

[0283] In an embodiment, an ophthalmic composition comprising a BTK inhibitor or a pharmaceutically acceptable salt thereof is administered to a human subject in need thereof by intravitreal or intraocular injection for a first administration period, then followed by a discontinuance period, then followed by a second administration period, and so on.

[0284] In an embodiment, an ophthalmic composition comprising a BTK inhibitor or a pharmaceutically acceptable salt thereof is administered topically to a human subject in need thereof for a first administration period, then followed by a discontinuance period, then followed by a second administration period, and so on.

[0285] For topical administration to the eye, the first administration period, the second administration period, and the discontinuance period are independently selected from the group consisting of more than 1 day, 2 days, 3 days, 4 days, 5 days, 6 days, 7 days, 8 days, 9 days, 10 days, 11 days, 12 days, 13 days, 14 days, 15 days, 16 days, 17 days, 18 days, 19 days, 20 days, 21 days, 22 days, 23

days, 24 days, 25 days, 26 days, 27 days, 28 days, 29 days, one month, five weeks, six weeks, seven weeks, two months, nine weeks, ten weeks, eleven weeks, three months, thirteen weeks, fourteen weeks, fifteen weeks, four months, and more days, in which a BTK inhibitor or a pharmaceutically acceptable salt thereof is administered to a subject three times daily, twice daily, daily, once weekly, twice weekly, three times weekly, four times weekly, five times weekly, six times weekly or monthly. In an embodiment, the first administration period is the same length as the second administration period. In an embodiment, the first administration period is shorter than the second administration period. In an embodiment, the first administration period is longer than the second administration period. In an embodiment, the first administration period and the second administration period are about one week, in which a BTK inhibitor or a pharmaceutically acceptable salt thereof is administered to a subject daily; and the discontinuance period is about two weeks. In an embodiment, the first administration period and the second administration period are about three weeks, in which a BTK inhibitor or a pharmaceutically acceptable salt thereof is administered to a subject daily; and the discontinuance period is about two weeks. In an embodiment, the first administration period and the second administration period are about three weeks, in which a BTK inhibitor or a pharmaceutically acceptable salt thereof is administered to a subject weekly; and the discontinuance period is about two weeks. In an embodiment, the first administration period and the second administration period are about four weeks, in which a BTK inhibitor or a pharmaceutically acceptable salt thereof is administered to a subject daily; and the discontinuance period is about two weeks. In an embodiment, the first administration period and the second administration period are about four weeks, in which a BTK inhibitor or a pharmaceutically acceptable salt thereof is administered to a subject weekly; and the discontinuance period is about two weeks.

[0286] For intravitreal or intraocular injection to the eye, the first administration period, the second administration period, and the discontinuance period are independently selected from the group consisting of one month, two months, three months, four months, five months, six months, seven months, eight months, nine months, ten months, eleven months, and a year, in which the ophthalmic composition comprising a BTK inhibitor or a pharmaceutically acceptable salt thereof is administered to a subject monthly, bi-monthly, once every three-month, once every four-month, once every five-month, once every six-month, or yearly. In an embodiment, the first administration period is the same length as the second administration period. In an embodiment, the first administration period is shorter than the second administration period. In an embodiment, the first administration period is longer than the second administration period.

Further embodiments of the invention include the following:

1. An ophthalmic composition for use in treating or preventing dry eye disease (DED) in a human subject in need thereof comprising topically administering to an eye of the human subject the ophthalmic composition comprising a Bruton's Tyrosine Kinase (BTK) inhibitor, wherein the BTK inhibitor is 1-(4-(((6-amino-5-(4-phenoxyphenyl)pyrimidin-4-yl)amino)methyl)-4-fluoropiperidin-1-yl)prop-2-en-1-one or a pharmaceutically acceptable salt thereof.
2. An ophthalmic composition for use treating or preventing allergic conjunctivitis (AC) in a human subject in need thereof comprising topically administering to an eye of the human subject the ophthalmic composition comprising a Bruton's Tyrosine Kinase (BTK) inhibitor, wherein the BTK inhibitor is 1-(4-(((6-amino-5-(4-phenoxyphenyl)pyrimidin-4-yl)amino)methyl)-4-fluoropiperidin-1-yl)prop-2-en-1-one or a pharmaceutically acceptable salt thereof.
3. The ophthalmic composition according to any one of embodiments 1 or 2, wherein the ophthalmic composition is an oil-in-water microemulsion.
4. The ophthalmic composition according to embodiment 3, wherein the oil-in-water microemulsion further comprises:
 - (i) an oil selected from the group consisting of isopropyl myristate, isopropyl palmitate, and medium chain triglycerides;
 - (ii) a pair of surfactants selected from the group consisting of two polysorbates, a polysorbate and propylene glycol, a polysorbate and glycerol, a polysorbate and 1,2,3-triacetoxyp propane, polyethoxylated castor oil and 1,2,3-triacetoxyp propane, and polyethoxylated castor oil and propylene glycol; and (iii) water,wherein: the water represents about 50% to about 95% (v/v) of the oil-in-water microemulsion; and the ratio of percent (v/v) total surfactant to percent (v/v) oil is at least about 10: 1.
5. The ophthalmic composition according to embodiment 4, wherein the pair of surfactants represent about 10% to about 50% (v/v) of the oil-in-water microemulsion.
6. The ophthalmic composition according to embodiment 4, wherein the pair of surfactants represent about 15% to about 40% (v/v) of the oil-in-water microemulsion.

7. The ophthalmic composition according to embodiment 4, wherein the pair of surfactants represent about 20% to about 40% (v/v) of the oil-in-water microemulsion.
8. The ophthalmic composition according to embodiment 4, wherein the pair of surfactants represent about 15%, about 20%, about 25%, about 30%, about 35%, about 40%, or about 45% percent (v/v) of the oil-in-water microemulsion.
9. The ophthalmic composition according to embodiment 4, wherein the oil represents about 1% to about 5% (v/v) of the oil-in-water microemulsion.
10. The ophthalmic composition according to embodiment 4, where the oil represents about 1%, about 2%, about 3%, about 4%, or about 5% (v/v) of the oil-in-water microemulsion.
11. The ophthalmic composition according to embodiment 4, wherein the ratio of the pair of surfactants (v/v) is in a range of about 1:10 to 10:1.
12. The ophthalmic composition according to embodiment 4, wherein the ratio of the pair of surfactants (v/v) is in a range of about 1:4 to 4:1.
13. The ophthalmic composition according to embodiment 4, wherein the ratio of the pair of surfactants (v/v) is in a range of about 1:2 to 2:1.
14. The ophthalmic composition according to embodiment 4, wherein the ratio of the pair of surfactants (v/v) is about 1:1.
15. The ophthalmic composition according to embodiment 4, wherein one of the surfactants is polysorbate 20.
16. The ophthalmic composition according to embodiment 4, wherein one of the surfactants is polysorbate 80.
17. The ophthalmic composition according to embodiment 4, wherein the appearance of the oil-in-water microemulsion is clear.
18. The ophthalmic composition according to embodiment 4, wherein the particle size of the oil-in-water microemulsion is between about 1 nm and 10 nm.
19. The ophthalmic composition according to embodiment 4, wherein the particle size of the oil-in-water microemulsion is between about 1 nm and 8 nm.

20. The ophthalmic composition according to embodiment 4, wherein the particle size of the oil-in-water microemulsion is between about 1 nm and 5 nm.
21. The ophthalmic composition according to embodiment 4, wherein the particle size of the oil-in-water microemulsion is between about 2 nm and 5 nm.
22. The ophthalmic composition according to embodiment 4, wherein the particle size of the oil-in-water microemulsion is between about 2 nm and 3 nm.
23. The ophthalmic composition according to embodiment 4, wherein the particle size of the oil-in-water microemulsion is between about 2 nm and 8 nm.
24. The ophthalmic composition according to embodiment 4, wherein viscosity of the oil-in-water microemulsion is between about 0 to about 500 centipoise.
25. The ophthalmic composition according to embodiment 4, wherein viscosity of the oil-in-water microemulsion is between about 0 to about 400 centipoise.
26. The ophthalmic composition according to embodiment 4, wherein osmolality of the oil-in-water microemulsion is between about 5 to about 100 mOsm/kg at 1:3 dilution.
27. The ophthalmic composition according to embodiment 4, wherein osmolality of the oil-in-water microemulsion is between about 5 to about 50 mOsm/kg at 1:3 dilution.
28. The ophthalmic composition according to embodiment 4, wherein osmolality of the oil-in-water microemulsion is between about 15 to about 40 mOsm/kg at 1:3 dilution.
29. The ophthalmic composition according to embodiment 4, wherein osmolality of the oil-in-water microemulsion is between about 20 to about 30 mOsm/kg at 1:3 dilution.
30. An ophthalmic composition comprising a Bruton's Tyrosine Kinase (BTK) inhibitor, and a pharmaceutical carrier, wherein the BTK inhibitor is 1-(4-(((6-amino-5-(4-phenoxyphenyl)pyrimidin-4-yl)amino)methyl)-4-fluoropiperidin-1-yl)prop-2-en-1-one or a pharmaceutically acceptable salt thereof, wherein the ophthalmic composition is an oil-in-water microemulsion.
31. The ophthalmic composition according to embodiment 30, wherein the oil-in-water microemulsion further comprises:
- (i) an oil selected from the group consisting of isopropyl myristate, isopropyl palmitate, and medium chain triglycerides;

(ii) a pair of surfactants selected from the group consisting of two polysorbates, a polysorbate and propylene glycol, a polysorbate and glycerol, a polysorbate and 1,2,3- triacetoxyp propane, polyethoxylated castor oil and 1,2,3-triacetoxyp propane, and polyethoxylated castor oil and propylene glycol; and (iii) water,

wherein: the water represents about 50 to about 95 percent (v/v) of the oil-in-water microemulsion; and the ratio of percent (v/v) total surfactant to percent (v/v) oil is at least about 10: 1.

32. The ophthalmic composition according to embodiment 31, wherein the pair of surfactants represent about 10% to about 50% (v/v) of the oil-in-water microemulsion.
33. The ophthalmic composition according to embodiment 31, wherein the pair of surfactants represent about 15% to about 40% (v/v) of the oil-in-water microemulsion.
34. The ophthalmic composition according to embodiment 31, wherein the pair of surfactants represent about 20% to about 40% (v/v) of the oil-in-water microemulsion.
35. The ophthalmic composition according to embodiment 31, wherein the pair of surfactants represent about 15%, about 20%, about 25%, about 30%, about 35%, about 40%, or about 45% (v/v) of the oil-in-water microemulsion.
36. The ophthalmic composition according to embodiment 31, wherein the oil represents about 1% to about 5% (v/v) of the oil-in-water microemulsion.
37. The ophthalmic composition according to embodiment 31, where the oil represents about 1%, about 2%, about 3%, about 4%, or about 5% (v/v) of the oil-in-water microemulsion.
38. The ophthalmic composition according to embodiment 31, wherein the ratio of the pair of surfactants (v/v) is in a range of about 1:10 to 10:1.
39. The ophthalmic composition according to embodiment 31, wherein the ratio of the pair of surfactants (v/v) is in a range of about 1:4 to 4:1.
40. The ophthalmic composition according to embodiment 31, wherein the ratio of the pair of surfactants (v/v) is in a range of about 1:2 to 2:1.
41. The ophthalmic composition according to embodiment 31, wherein the ratio of the pair of surfactants (v/v) is about 1:1.

42. The ophthalmic composition according to embodiment 31, wherein one of the surfactants is polysorbate 20.
43. The ophthalmic composition according to embodiment 31, wherein one of the surfactants is polysorbate 80.
44. The ophthalmic composition according to embodiment 31, wherein the appearance of the oil-in-water microemulsion is clear.
45. The ophthalmic composition according to embodiment 31, wherein the particle size of the oil-in-water microemulsion is between about 1 nm and 10 nm.
46. The ophthalmic composition according to embodiment 31, wherein the particle size of the oil-in-water microemulsion is between about 1 nm and 8 nm.
47. The ophthalmic composition according to embodiment 31, wherein the particle size of the oil-in-water microemulsion is between about 1 nm and 5 nm.
48. The ophthalmic composition according to embodiment 31, wherein the particle size of the oil-in-water microemulsion is between about 2 nm and 5 nm.
49. The ophthalmic composition according to embodiment 31, wherein the particle size of the oil-in-water microemulsion is between about 2 nm and 3 nm.
50. The ophthalmic composition according to embodiment 31, wherein the particle size of the oil-in-water microemulsion is between about 2 nm and 8 nm.
51. The ophthalmic composition according to embodiment 31, wherein viscosity of the oil-in-water microemulsion is between about 0 to about 500 centipoise.
52. The ophthalmic composition according to embodiment 31, wherein viscosity of the oil-in-water microemulsion is between about 0 to about 400 centipoise.
53. The ophthalmic composition according to embodiment 31, wherein osmolality of the oil-in-water microemulsion is between about 5 to about 100 mOsm/kg at 1:3 dilution.
54. The ophthalmic composition according to embodiment 31, wherein osmolality of the oil-in-water microemulsion is between about 5 to about 50 mOsm/kg at 1:3 dilution.
55. The ophthalmic composition according to embodiment 31, wherein osmolality of the oil-in-water microemulsion is between about 15 to about 40 mOsm/kg at 1:3 dilution.

56. The ophthalmic composition according to embodiment 31, wherein osmolality of the oil-in-water microemulsion is between about 20 to about 30 mOsm/kg at 1:3 dilution.
57. An ophthalmic composition formulated as an oil-in-water microemulsion comprising:
- 0.1% (1.0 mg/ml) of 1-(4-(((6-amino-5-(4-phenoxyphenyl)pyrimidin-4-yl)amino)methyl)-4-fluoropiperidin-1-yl)prop-2-en-1-one or a pharmaceutically acceptable salt thereof;
 - about 8.43% polysorbate 20 (w/w);
 - about 16.19% polysorbate 80 (w/w);
 - about 1.77% isopropyl myristate (w/w); and
 - phosphate buffered saline.
58. An ophthalmic composition formulated as an oil-in-water microemulsion comprising:
- 0.1% (1.0 mg/ml) of 1-(4-(((6-amino-5-(4-phenoxyphenyl)pyrimidin-4-yl)amino)methyl)-4-fluoropiperidin-1-yl)prop-2-en-1-one or a pharmaceutically acceptable salt thereof;
 - about 8.43% polysorbate 20 (w/w);
 - about 16.19% polysorbate 80 (w/w);
 - about 1.77% isopropyl myristate (w/w); and
 - about 73.52% phosphate buffered saline (w/w).
59. An ophthalmic composition formulated as an oil-in-water microemulsion comprising: about 0.1% (1.0 mg/ml) of 1-(4-(((6-amino-5-(4-phenoxyphenyl)pyrimidin-4-yl)amino)methyl)-4-fluoropiperidin-1-yl)prop-2-en-1-one or a pharmaceutically acceptable salt thereof; about 8% polysorbate 20 (v/v); about 17% polysorbate 80 (v/v); about 2% isopropyl myristate (v/v); and about 73% phosphate buffered saline (v/v).
60. An ophthalmic composition formulated as an oil-in-water microemulsion comprising: about 0.1% (1.0 mg/ml) of 1-(4-(((6-amino-5-(4-phenoxyphenyl)pyrimidin-4-yl)amino)methyl)-4-fluoropiperidin-1-yl)prop-2-en-1-one or a pharmaceutically acceptable salt thereof; about 36%

polysorbate 20 (v/v); about 4% polysorbate 80 (v/v); about 3% isopropyl myristate (v/v); and about 57% phosphate buffered saline (v/v).

61. An ophthalmic composition formulated as an oil-in-water microemulsion comprising: about 0.1% (1.0 mg/ml) of 1-(4-(((6-amino-5-(4-phenoxyphenyl)pyrimidin-4-yl)amino)methyl)-4-fluoropiperidin-1-yl)prop-2-en-1-one or a pharmaceutically acceptable salt thereof; about 7% polysorbate 20 (v/v); about 28% polysorbate 80 (v/v); about 3% isopropyl myristate (v/v); and about 62% phosphate buffered saline (v/v).
62. An ophthalmic composition formulated as an oil-in-water microemulsion comprising: about 0.1% (1.0 mg/ml) of 1-(4-(((6-amino-5-(4-phenoxyphenyl)pyrimidin-4-yl)amino)methyl)-4-fluoropiperidin-1-yl)prop-2-en-1-one or a pharmaceutically acceptable salt thereof; about 6% polysorbate 20 (v/v); about 24% polysorbate 80 (v/v); about 3% isopropyl myristate (v/v); and about 67% phosphate buffered saline (v/v).
63. An ophthalmic composition formulated as oil-in-water microemulsion comprising: about 0.1% (1.0 mg/ml) of 1-(4-(((6-amino-5-(4-phenoxyphenyl)pyrimidin-4-yl)amino)methyl)-4-fluoropiperidin-1-yl)prop-2-en-1-one or a pharmaceutically acceptable salt thereof; about 2% polysorbate 20 (v/v); about 18% polysorbate 80 (v/v); about 2% isopropyl myristate (v/v); and about 78% phosphate buffered saline (v/v).
64. The ophthalmic composition according to any one of the embodiments 57-63 for use in treating or preventing dry eye disease (DED) in a human subject in need thereof comprising topically administering to an eye of the human subject the ophthalmic composition.
65. The ophthalmic composition according to any one of the embodiments 57-63 for use treating or preventing allergic conjunctivitis (AC) in a human subject in need thereof comprising topically administering to an eye of the human subject the ophthalmic composition.
66. The ophthalmic composition according to any one of the embodiments 57-63 for use in treating or preventing dry eye disease (DED) in a human subject in need thereof comprising topically administering to an eye of the human subject the ophthalmic composition twice a day (BID) or three times a day (TID).
67. The ophthalmic composition according to any one of the embodiments 57-63 for use treating or preventing allergic conjunctivitis (AC) in a human subject in need thereof comprising

topically administering to an eye of the human subject the ophthalmic composition twice a day (BID) or three times a day (TID).

68. The ophthalmic composition according to any one of the embodiments 57-63 for use in treating or preventing dry eye disease (DED) in a human subject in need thereof comprising topically administering to an eye of the human subject the ophthalmic composition as one, two or three eye drops twice a day (BID) or three times a day (TID).
69. The ophthalmic composition according to any one of the embodiments 57-63 for use treating or preventing allergic conjunctivitis (AC) in a human subject in need thereof comprising topically administering to an eye of the human subject the ophthalmic composition as one, two or three eye drops twice a day (BID) or three times a day (TID).

EXAMPLES

[0287] The embodiments encompassed herein are now described with reference to the following examples. These examples are provided for the purpose of illustration only and the disclosure encompassed herein should in no way be construed as being limited to these examples, but rather should be construed to encompass any and all variations which become evident as a result of the teachings provided herein, including embodiments in which the administration of a BTK inhibitor to a subject in need thereof results in a reduction, wherein the reduction is about a 1% reduction, a 5% reduction, a 10% reduction, a 15% reduction, a 20% reduction, a 25% reduction, a 30% reduction, a 35% reduction, a 40% reduction, a 45% reduction, a 50% reduction, a 55% reduction, a 60% reduction, a 65% reduction, a 70% reduction, a 75% reduction, a 80% reduction, a 85% reduction, a 90% reduction, a 95% reduction, a 96% reduction, a 97% reduction, a 98% reduction, or a 99% or greater reduction.

Example 1: Topical Administration of BTK Inhibitor in Subjects with Dry Eye Disease

[0288] Dry eye disease is a chronic inflammatory disorder of the lacrimal functional unit, causing ocular discomfort, pain, and visual disturbances. Mast cells, found in the lacrimal functional unit, are initiators and amplifiers of the inflammatory cascade. Bruton's Tyrosine Kinase (BTK) is important for mast cell activation and immune response and was targeted in an approach to treating dry eye disease using an ocular formulation of an irreversible BTK inhibitor. Without wishing to be bound by theory, administration of the BTK inhibitor is believed to prevent mast cell degranulation, reduce mast cell cytokine production, block the inflammatory response, and restore lacrimal functional unit homeostasis. Inhibition of BTK according to the methods described herein is useful for disease modification, including, but not limited to treatment of dry-eye disease.

[0289] A phase 2, multicenter, randomized, double-masked, vehicle-controlled study evaluated Compound 128 in subjects with moderate to severe dry eye disease using the Ora Controlled Adverse Environment (CAE) Challenge Model. After a 2-week, single-masked vehicle run-in, subjects were randomized 1:1 to receive Compound 128 or vehicle bilaterally twice daily for 28 days. The primary objective was safety and the secondary objective was efficacy based on signs and symptoms by an intention-to-treat analysis (pre/post CAE).

[0290] The study randomized 107 subjects across two arms well matched and representative of a dry eye disease population. The most common treatment-emergent adverse event was instillation site irritation. Other safety assessments were unremarkable. On Day 15, mean drop comfort score was 2.6 (Scale: 0-10) in both arms two minutes after instillation. A summary of treatment-emergent adverse

events (TEAEs) is provided in Table 2. The safety population includes all subjects who have been randomized and received at least one dose of Compound 128 or vehicle. Ocular events are summarized for those occurring in at least two subjects. Study Eye was determined as the eye with most severe baseline signs and symptoms.

Table 2

	Study Eye		Fellow Eye	
Summary of TEAEs	Cmpd 128 (n=53)	Vehicle (n=53)	Cmpd 128 (n=53)	Vehicle (n=53)
Any TEAE, n (%)	17 (32)	8 (15)	15 (28)	10 (19)
Grade 1	16 (30)	8 (15)	14 (26)	10 (19)
Grade 2 [§]	1 (2)	0	1 (2)	0
Serious TEAE	0	0	0	0
Related ocular AE	15 (28)	8 (15)	14 (26)	9 (17)
TEAE leading to drug withdrawal	1 (2)	0	1 (2)	0
Preferred Terms, n (%)				
Instillation site irritation	11 (21)	8 (15)	10 (19)	8 (15)
Eye discharge	2 (4)	0	2 (4)	0
Ocular hyperemia	1 (2)	1 (2)	1 (2)	1 (2)
Vision blurred	1 (2)	1 (2)	1 (2)	1 (2)
Conjunctivitis	2 (4)	0	2 (4)	0
Vitreous detachment	0	0	0	2 (4)

[§] Grade 2 conjunctivitis occurred in one subject and was not related to Compound 128.

[0291] After 28 days, Compound 128 significantly improved the signs and symptoms of dry eye disease, including fluorescein staining central ($p=0.01$) and total corneal sum ($p=0.034$). Positive trends were seen in inferior ($p=0.053$) and total sum regions ($p=0.077$). Schirmer's responders ($\geq 10\text{mm}$) were higher with Compound 128 compared to vehicle in both Study and Fellow Eye (13.2% vs 5.6% and 13.2% vs 3.7%, respectively). The intention-to-treat (ITT) efficacy population includes all randomized subjects. Study Eye was determined as the eye with most severe baseline signs and symptoms. The efficacy results for signs of dry eye disease are provided in Tables 3 and 4.

Table 3

		Day 29 Response Rate Mean Change From Baseline			
Endpoint (ITT)	Setting	Cmpd 128 (n=53)	Vehicle (n=54)	Mean Difference (SE) [‡]	p-value [§]
Central fluorescein staining	Post minus Pre CAE	-0.32	0.14	-0.46 (0.17)	0.010
Corneal sum fluorescein staining	Post minus Pre CAE	-1.22	-0.37	-0.85 (0.40)	0.034
Inferior fluorescein staining	Post minus Pre CAE	-0.64	-0.28	-0.36 (0.19)	0.053
Total sum fluorescein staining	Post minus Pre CAE	-1.52	-0.40	-1.12 (0.63)	0.077
Conjunctival redness	Pre CAE	-0.15	0.01	-0.16 (0.12)	0.181

[§] 2-sample t-test was used for all endpoints.

[‡] SE, standard error.

Table 4

		Day 29 Response Rate			
Endpoint (ITT)	Setting	Cmpd 128 (n=53)	Vehicle (n=54)	% Difference	p-value [§]
Schirmer's Test (≥10mm), Study Eye	Post CAE	7 (13.2%)	3 (5.6%)	7.7%	0.202
Schirmer's Test (≥10mm), Fellow Eye	Post CAE	7 (13.2%)	2 (3.7%)	9.5%	0.093

[§] Pearson's Chi-square test was used for Schirmer's test.

[0292] Compound 128 also significantly improved the signs and symptoms of dry eye disease, including Pain (VAS, visual analog scale; p=0.014), Dryness (OD4SQ, Ora Ocular Discomfort 4-symptom Questionnaire; p=0.026), and Burning (OD4SQ; p=0.034), and trended positively on the Ora Ocular Discomfort Scale (p=0.052). The efficacy results for signs and symptoms of dry eye disease are provided in Table 5.

Table 5

		Day 29 Response Rate Mean Change From Baseline			
Endpoint (ITT)	Setting	Cmpd 128 (n=53)	Vehicle (n=54)	Mean Difference (SE) [‡]	p-value [§]
VAS Pain	Post minus Pre CAE	-8.9	1.8	-10.7 (4.27)	0.014
OD4SQ Dryness	Post CAE	-0.4	0.0	-0.4 (0.20)	0.026
OD4SQ Burning	Pre CAE	-0.4	0.0	-0.4 (0.20)	0.034
Ocular Discomfort Score	Pre CAE	-0.3	0.1	-0.4 (0.18)	0.052
OD4SQ Overall Ocular Discomfort	Post CAE	-0.4	0.0	-0.4 (0.19)	0.059

[§] 2-sample t-test was used for all endpoints.

[‡] SE, standard error.

[0293] The results demonstrated the safety and efficacy of Compound 128 topical administration across ocular regions and in different settings (i.e. pre- and post-CAE).

Example 2: Topical Administration of BTK Inhibitor in the Ocular Inflammatory Response

[0294] Mast cells play an early and important role in the immune cascade underlying the development of dry eye disease and allergic conjunctivitis. In dry eye disease, mast cell-driven lacrimal unit dysfunction with desiccating stress leads to reduced tear film production, cytokine-mediated inflammation, and ocular damage. In allergic conjunctivitis, allergen exposure triggers mast cell degranulation and the release of pro-inflammatory mediators causing ocular signs or symptoms. Bruton's tyrosine kinase (BTK) plays an important role in mast cell activation, cytokine production, and the immune response and was targeted in an approach for treating dry eye disease and allergic conjunctivitis using a topical formulation of an irreversible, BTK inhibitor. The BTK inhibitor's effects in vitro and in vivo were assessed.

[0295] Primary human mast cells derived from bone marrow CD34+ cells were used to evaluate the effects of Compound 128 on antigen-stimulated BTK phosphorylation, activation, calcium flux, histamine release, and cytokine production via multi parameter flow cytometry. Exposure and target BTK occupancy were studied in ocular dog tissue with an ELISA based assay after repeat dosing of 50µL of the Compound 128 topical formulation bilaterally twice daily for 15 days.

[0296] In primary mast cells stimulated with antigen, Compound 128 prevented BTK phosphorylation (average EC_{90} =129nM; Figure 1) and inhibited surface expression of CD63, a marker of mast cell activation and degranulation (EC_{90} =105nM; Figure 2). Compound 128 also inhibited antigen-triggered calcium flux in mast cells from three donors (100nM; Figure 3), histamine release (average EC_{90} =84nM; Figure 4), and the production of cytokines that recruit and activate inflammatory immune cells (e.g. IL-8; MCP-1; Figure 5).

[0297] In dogs, Compound 128 exposure in various ocular tissues was measured after a dosing 1 drop, twice daily for 15 days. Optimal drug exposure ($\geq EC_{90}$) of Compound 128 as a topical formulation was observed in the relevant ocular target tissue (Figure 6) with median BTK occupancy >95% established in the palpebral and bulbar conjunctiva (Figure 7). PK was collected one hour post dose. Optimal drug exposure was 60nM.

[0298] The results demonstrated that Compound 128 inhibits mast cell-driven immune and cytokine responses in dry eye disease and allergic conjunctivitis. In vitro, Compound 128 prevented mast cell activation, degranulation, and cytokine production, indicating modulation of the innate and adaptive immune response. In vivo, ocular administration of Compound 128 topical formulation resulted in inhibition of BTK to target tissue.

[0299] Compound 128 as a topical formulation inhibits IgE-triggered signaling (Figure 8). Mast cell from five healthy donors were stimulated with antigen (NP-BSA) for 15 minutes in the presence and absence of Compound 128. Sensitization and Stimulation: NP-IgE (100ng/mL) 18 hours, Compound 128 incubation 2 hours, NP-BSA (0.5ng/mL) 15 minute stimulation time. Stem cell factor (100 ng/mL) is maintained continuously in media. Significance determined using a paired, parametric t-test: **** $p \leq 0.0001$, *** $p \leq 0.001$, ** $p \leq 0.01$, * $p \leq 0.05$, ns = not significant. Ava is 1 μ M avapritinib (KIT inhibitor).

[0300] Compound 128 as a topical formulation inhibits antigen-induced chemoattractant activity (Figure 9). BTK inhibition is shown to inhibit chemokine production (Figure 5) from antigen-stimulated mast cells, which inhibits trafficking of cells (including other mast cells) to sites of inflammation. This experiment was designed to assess if BTK inhibitor-treated mast cell conditioned media impairs the migration of non-activated mast cells. First, conditioned media (CM) from antigen-stimulated mast cells in the presence and absence of Compound 128 was prepared. Second, this conditioned media was moved to the bottom of a Boyden chamber and non-activated mast cells added to the top of chamber. Third, the number of migrated cells was measured in the presence and absence of Compound 128. Mast

cell activation was achieved with NP-IgE (0.1µg/mL) sensitization in SCF media for 18 hours, BTK inhibitor pre-incubation was for 2 hours, NP-IgE washout was conducted prior to stimulation, NP-BSA (Antigen Stimulation, 0.5ng/mL) 4 hours.

[0301] Fold change = (Sample luminescence) / (unstimulated no drug control luminescence)

[0302] In summary, Compound 128 inhibited the production of chemokines in mast cell cultures, which resulted in decreased chemoattractant activity. This result indicates that mast cell migration towards sites of allergic inflammation is suppressed by BTK inhibition.

Example 3: Safety and Efficacy of a BTK Inhibitor for the Treatment of Allergic Conjunctivitis

[0303] Subjects with allergic conjunctivitis using the Ora-CAC® allergen model are randomized 1:1 to receive either Compound 128 as a 0.1% ophthalmic microemulsion or vehicle. On day 1 and 2, each dose consists of a loading dose of 1-2 drops in each eye (if first drop did not instill properly, an additional drop is administered) followed by a 5 minute (±1 minute) wait before instillation of an additional 1-2 drops (if first drop did not instill properly, an additional drop is administered), twice daily. On day 3 to 14 a dose of 1-2 drops in each eye is administered. Optionally, on day 15 and 22, two loading doses are administered of 1-2 drops in each eye.

[0304] The primary endpoints are conjunctival redness score and ocular itching score. The secondary endpoints are ciliary redness scores, episcleral redness scores, chemosis redness scores, tearing scores, eyelid swelling scores, rhinorrhea scores, nasal pruritus scores, ear or palate pruritus scores, and nasal congestion scores.

Example 4: Microemulsion Formulation Library

[0305] Microemulsions are thermodynamically stable and isotropic formulations composed of a polar phase (e.g., water), a non-polar phase (e.g., oil), surfactant, and co-surfactant. Unlike nanoemulsions, microemulsions form spontaneously without the need for input energy. Traditional (kinetically stable) microemulsions require surfactants for stability, however, at any given time in the microemulsion, surfactants may be freely dispersed in the aqueous phase, and will break down at the tear film layer as the surfactants stabilizing them are diluted. Ocular tissues are then exposed to these dispersed surfactants which can cause irritation. The oil-in-water microemulsion described herein, although consisting of up to 40% surfactant, does not cause irritation as the surfactant molecules are ordered in the microemulsion droplets in such a way that ocular tissues are only exposed to the hydrophilic

component of the surfactant. Further, microemulsions do not break down when exposed to the corneal tear film interface.

[0306] With over 1000 unique oil-in-water microemulsion formulations, a high throughput screening process is used to identify the best candidate formulations with Compound 128. The screen is based on visual examination to detect possible phase separation after two weeks, viscosity measurements, osmolality measurements, and measurement of droplet size. The critical quality attributes are listed below.

Quality Attributes of the Drug Product		Target	Justification
Physical Attributes	Appearance (emulsion)	non-opaque, transparent solution visibly free of foreign material	Appearance indicates consistent product free of visible particulate
Particle Diameter by Dynamic Light Scattering (DLS)		<50 nm	Possibly critical for achieving clinically effective dose, process may impact the globule size diameter of product
Viscosity		20 – 400 cP	Critical to achieve desired residence time in the eye, process and formulation may impact the viscosity of product
Osmolality		Specified range is determined from initial measurements	Microemulsions osmolality parameters are not a critical parameter with regards to ocular tolerability. It does allow for another impresses test for quality control
pH		5.0 – 8.0	Critical to prevent irritation, formulation may impact the pH of product

[0307] To screen individual formulations, 2 mg of Compound 128 was weighed out and added to a glass vial. The appropriate oil and surfactant ratio volume was then added to the vial, and briefly sonicated until the drug was dispersed. Water was then added to bring the final volume to 2 ml, and the vial was briefly vortexed and sonicated, followed by mixing on a roller overnight at room temperature. The following day, the formulations were screened based on visual appearance, viscosity, and particle size. Formulations that met inclusion criteria were kept at room temperature and re-evaluated at 1 week and 2 weeks. Formulations that met inclusion criteria at 2 weeks underwent osmolality measurements.

[0308] Formulations with Compound 128 at a concentration of 0.1% (1.0 mg/ml) were screened. Formulations were first screened at 40% (v/v) total surfactants (Surfactant 1 + Surfactant 2), and then screened in decreasing 5%(v/v) total surfactant levels based on success at the previous higher level. Of 276 unique formulations screened, 124 formulations successfully formed microemulsions at total surfactant percentages ranging from 15% to 40%. Representative successful candidates are listed below. Surfactant 1 = Tween 80; Surfactant 2 = Tween 20; Oil = Isopropyl Myristate.

Formulation ID	Compound 128 (mg)	Viscosity (cP)	Particle Size (nm)	Water (%v/v)	Surfactant 1 (%v/v)	Surfactant 2 (%v/v)	Oil (%v/v)
1	2	2.8	7.226	84%	8%	8%	2%
2	2	0	6.726	84%	12%	3%	1%
3	2	3.1	7.617	78%	10%	10%	2%
4	2	3.7	2.354	78%	18%	2%	2%
5	2	0	1.92	73%	13%	13%	3%
6	2	27.8	2.22	73%	17%	8%	2%
7	2	0	2.246	73%	5%	20%	2%
8	2	61.3	2.284	67%	15%	15%	3%
9	2	154.5	1.978	67%	24%	6%	3%
10	2	33.8	2.274	68%	6%	24%	2%
11	2	329.7	2.076	62%	18%	18%	4%
12	2	164.6	2.394	62%	28%	7%	3%
13	2	99.5	2.272	63%	7%	28%	3%
14	2	162	2.524	57%	36%	4%	3%
15	2	140.6	1.715	57%	4%	36%	3%

16	2	157	2.373	57%	4%	36%	3%
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Example 5: Microemulsion Formulation of Compound 128

[0309] Exemplary formulation with Compound 128 at a concentration of 0.1% (w/v, 1.0 mg/ml) was made and contains the following ingredients. Briefly, phosphate-buffered saline was charged to a first container. Then isopropyl myristate is charged to the first container, and the mixing is continued to form a uniform, white and opaque mixture. Then, polysorbate 80 is charged to the first container and stirring is continued to form a uniform, yellow and opaque mixture. Polysorbate 20 and Compound 128 are charged to a second container, and mixing is continued until Compound 128 dissolves to form a solution. The contents of the second container were added to the first container. The resulting mixture was homogenized using a mixer to form an oil-in-water microemulsion with Compound 128 at a concentration of 0.1% (1.0 mg/ml).

Component	mg per vial (0.3 ml)	% w/w	Function
Active Ingredient			
Compound 128	0.30	0.09	Active
Excipients			
Phosphate-Buffered Saline	240.51	73.52	Buffer
Isopropyl Myristate	5.78	1.77	Oil Phase
Tween 80	52.95	16.19	Surfactant
Tween 20	27.56	8.43	Surfactant
Total Unit Dose	327.10	100	

Example 6: Safety and Efficacy of Compound 128 for the Treatment of Allergic Conjunctivitis

[0310] A randomized, double-masked, vehicle-controlled, phase 2 study evaluating the safety and efficacy of Compound 128 as a 0.1% ophthalmic microemulsion (Example 5) compared to vehicle for the treatment of allergic conjunctivitis in the Ora-CAC® allergen model was conducted. The study comprises a screening period (Visits 1 to 3) and a treatment period (Visits 4a to 6c), and the study employed a conventional CAC protocol. The purpose of the screening period is to determine the specific allergen and

dose required to elicit a response in the CAC (Visit 2), to ensure that the response is repeatable (Visit 3), and to establish a baseline for response (Visit 3). The purpose of the treatment period is to evaluate the efficacy of Compound 128 as a 0.1% ophthalmic microemulsion (Example 5) compared to vehicle for the treatment of the signs and symptoms of acute allergic conjunctivitis. The Ora-CAC® Allergen Model is a proprietary, controlled method used in clinical research to study ocular allergies. In this model, a known allergen is carefully administered to the eyes of study participants to trigger allergic conjunctivitis symptoms (such as redness, itching, and tearing) in a reproducible and measurable way. This controlled induction of symptoms allows researchers to objectively evaluate how effective a treatment—typically an eye drop—is at alleviating those symptoms during a clinical trial.

[0311] At Visit 4a (Day 1), eligible subjects were randomized to receive either Compound 128 as a 0.1% ophthalmic microemulsion (Example 5) or vehicle bilaterally in a double-masked fashion. Each dose consists of 1-2 drops in each eye OU (if first drop did not instill properly, administer an additional drop) followed by a 5 ($\pm$ 1) minute wait before instillation of an additional 1-2 drops OU (if first drop did not instill properly, administer an additional drop).

[0312] During the 24 hours before the CAC protocol begins, subjects received 2 loading doses of study drug administered 12 ($\pm$ 1.5) hours apart at Visit 4a (Day 1 - pm), Visit 4b (Day 2 - am), Visit 5a (Day 15 - am), Visit 5b (Day 15 - pm), Visit 6a (Day 22 - am), and Visit 6b (Day 22 - pm). The CAC protocol began after completion of 2 loading doses with instillation of the third dose of study drug at Visit 4c (Day 2 - pm), Visit 5c (Day 16 - am), and Visit 6c (Day 23 - am). Subjects underwent a CAC at 16 hours (Visits 4d), 8 hours (Visit 5d), and at 30 minutes (Visit 6c) after instillation of the third dose of study drug.

[0313] 76 subjects with allergic conjunctivitis using the Ora-CAC® allergen model were randomized 1:1 to receive either Compound 128 as a 0.1% ophthalmic microemulsion (Example 5) or vehicle.

[0314] The primary endpoints are conjunctival redness score and ocular itching score. This study has demonstrated statistically significant and clinically meaningful efficacy in both redness and ocular itching as shown in the table below.

Timepoint	Arms	% of patients with $\geq$ 1 unit improvement from baseline on itching and redness		
		TP1	TP2	TP3
16-hr Duration	CP-128	28.9	31.6	39.5
	Vehicle	18.4	21.1	15.8
8-hr Duration	CP-128	44.7	55.3	57.9
	Vehicle	5.3	2.6	7.9

30-min Onset	CP-128	52.6	63.2	60.5
	Vehicle	0	0	2.6

TP1, 3-minute ocular itching and 7-minute conjunctival redness Post-CAC; TP2, 5-minute ocular itching and 15-minute conjunctival redness Post-CAC; TP3, 7-minute ocular itching and 20-minute conjunctival redness Post-CAC.

Example 7: A Single-Center, Randomized, Double-masked, Vehicle-controlled Phase 2 Study Evaluating the Safety and Efficacy of Compound 128 Formulated as Ophthalmic Microemulsion 0.1% Compared to Vehicle for the Treatment of Allergic Conjunctivitis in the Allergen Biocube® (ABC®) Model

[0315] In this study, approximately 60 eligible subjects will be randomized 1:1 to receive either Compound 128 formulated as ophthalmic microemulsion 0.1% (Example 5) or vehicle as topical ophthalmic eye drops administered bilaterally (OU). The Allergen BioCube® Model is a controlled, enclosed environment designed for clinical research that simulates real-world allergen exposure. In this model, participants are placed in a chamber where a specific concentration of allergens (such as pollen or dust mites) is uniformly dispersed. This controlled exposure induces allergic symptoms (like itching, redness, or nasal congestion) in a consistent and reproducible way, allowing researchers to accurately assess the efficacy and safety of anti-allergy treatments under standardized conditions.

[0316] The study comprises a screening period (Visits 1 to 3) and a treatment period (Visits 4 to 5b), and the study will employ an ABC protocol in subjects allergic to Timothy grass pollen. The study design evaluates the prophylactic and relief efficacy of Compound 128 formulated as ophthalmic microemulsion 0.1% compared to vehicle. The purpose of the screening period is to establish that the subject has sufficient ocular allergic response at 90 minutes of exposure of Timothy grass pollen in the ABC (Visit 2), to which ensures that the response is repeatable (Visit 3), and to establish a baseline for response (Visit 3) for both the prophylactic and relief phases of the trial. To screen out placebo responders, all subjects will receive vehicle 1-2 drops OU (if first drop did not instill properly, administer an additional drop) followed by a 5 (± 1) minute wait before instillation of an additional 1-2 drops OU (if first drop did not instill properly, administer an additional drop). Vehicle will be administered by staff at the study site.

[0317] At the end of Visit 3, eligible subjects will be randomized 1:1 to receive either Compound 128 formulated as ophthalmic microemulsion 0.1% or vehicle in a double-masked fashion. Kits and dosing diaries will be dispensed to the subjects along with instructions to dose twice at home on the day prior to Visit 4. Dosing will be 1-2 drops OU (if first drop did not instill properly, administer an additional drop)

followed by a 5 (± 1) minute wait before instillation of an additional 1-2 drops OU (if first drop did not instill properly, administer an additional drop). Each dose of study drug will be administered 12 (± 1.5) hours apart. The subject will be instructed not to dose on the morning of Visit 4.

[0318] At Visit 4 (Day 2), subjects will be dosed with their assigned treatment per the description above. If a drop is not instilled properly then a replacement drop may be administered. Study drug will be administered by staff at the study site.

[0319] The ABC protocol will begin with instillation of the pre-ABC dose of study drug at Visit 4 (Day 2) and Visit 5 (Day 15). Subjects will begin ABC exposure at approximately 5 minutes (Visit 4b) and 4 hours (Visit 5b) after instillation of the pre-ABC exposure dose of study drug. The relief dose will be administered after the 90-minute exposure assessment is completed at Visit 4 and Visit 5b.

[0320] Efficacy evaluations will be conducted at Visit 4 and Visit 5b.

CLAIMS

1. A method of treating or preventing dry eye disease (DED) in a human subject in need thereof comprising topically administering to an eye of the human subject an ophthalmic composition comprising a Bruton's Tyrosine Kinase (BTK) inhibitor, wherein the BTK inhibitor is 1-(4-(((6-amino-5-(4-phenoxyphenyl)pyrimidin-4-yl)amino)methyl)-4-fluoropiperidin-1-yl)prop-2-en-1-one or a pharmaceutically acceptable salt thereof.
2. A method of treating or preventing allergic conjunctivitis (AC) in a human subject in need thereof comprising topically administering to an eye of the human subject an ophthalmic composition comprising a Bruton's Tyrosine Kinase (BTK) inhibitor, wherein the BTK inhibitor is 1-(4-(((6-amino-5-(4-phenoxyphenyl)pyrimidin-4-yl)amino)methyl)-4-fluoropiperidin-1-yl)prop-2-en-1-one or a pharmaceutically acceptable salt thereof.
3. The method of any one of claims 1-2, wherein the ophthalmic composition is an oil-in-water microemulsion.
4. The method of claim 3, wherein the oil-in-water microemulsion further comprises:
 - (i) an oil selected from the group consisting of isopropyl myristate, isopropyl palmitate, and medium chain triglycerides;
 - (ii) a pair of surfactants selected from the group consisting of two polysorbates, a polysorbate and propylene glycol, a polysorbate and glycerol, a polysorbate and 1,2,3- triacetoxyp propane, polyethoxylated castor oil and 1,2,3-triacetoxyp propane, and polyethoxylated castor oil and propylene glycol; and (iii) water,wherein: the water represents about 50% to about 95% (v/v) of the oil-in-water microemulsion; and the ratio of percent (v/v) total surfactant to percent (v/v) oil is at least about 10: 1.
5. The method of claim 4, wherein the pair of surfactants represent about 10% to about 50% (v/v) of the oil-in-water microemulsion.
6. The method of claim 4, wherein the pair of surfactants represent about 15% to about 40% (v/v) of the oil-in-water microemulsion.

7. The method of claim 4, wherein the pair of surfactants represent about 20% to about 40% (v/v) of the oil-in-water microemulsion.
8. The method of claim 4, wherein the pair of surfactants represent about 15%, about 20%, about 25%, about 30%, about 35%, about 40%, or about 45% percent (v/v) of the oil-in-water microemulsion.
9. The method of claim 4, wherein the oil represents about 1% to about 5% (v/v) of the oil-in-water microemulsion.
10. The method of claim 4, where the oil represents about 1%, about 2%, about 3%, about 4%, or about 5% (v/v) of the oil-in-water microemulsion.
11. The method of claim 4, wherein the ratio of the pair of surfactants (v/v) is in a range of about 1:10 to 10:1.
12. The method of claim 4, wherein the ratio of the pair of surfactants (v/v) is in a range of about 1:4 to 4:1.
13. The method of claim 4, wherein the ratio of the pair of surfactants (v/v) is in a range of about 1:2 to 2:1.
14. The method of claim 4, wherein the ratio of the pair of surfactants (v/v) is about 1:1.
15. The method of claim 4, wherein one of the surfactants is polysorbate 20.
16. The method of claim 4, wherein one of the surfactants is polysorbate 80.
17. The method of claim 4, wherein the appearance of the oil-in-water microemulsion is clear.
18. The method of claim 4, wherein the particle size of the oil-in-water microemulsion is between about 1 nm and 10 nm.
19. The method of claim 4, wherein the particle size of the oil-in-water microemulsion is between about 1 nm and 8 nm.
20. The method of claim 4, wherein the particle size of the oil-in-water microemulsion is between about 1 nm and 5 nm.
21. The method of claim 4, wherein the particle size of the oil-in-water microemulsion is between about 2 nm and 5 nm.
22. The method of claim 4, wherein the particle size of the oil-in-water microemulsion is between about 2 nm and 3 nm.

23. The method of claim 4, wherein the particle size of the oil-in-water microemulsion is between about 2 nm and 8 nm.
24. The method of claim 4, wherein viscosity of the oil-in-water microemulsion is between about 0 to about 500 centipoise.
25. The method of claim 4, wherein viscosity of the oil-in-water microemulsion is between about 0 to about 400 centipoise.
26. The method of claim 4, wherein osmolality of the oil-in-water microemulsion is between about 5 to about 100 mOsm/kg at 1:3 dilution.
27. The method of claim 4, wherein osmolality of the oil-in-water microemulsion is between about 5 to about 50 mOsm/kg at 1:3 dilution.
28. The method of claim 4, wherein osmolality of the oil-in-water microemulsion is between about 15 to about 40 mOsm/kg at 1:3 dilution.
29. The method of claim 4, wherein osmolality of the oil-in-water microemulsion is between about 20 to about 30 mOsm/kg at 1:3 dilution.
30. An ophthalmic composition comprising a Bruton's Tyrosine Kinase (BTK) inhibitor, and a pharmaceutical carrier, wherein the BTK inhibitor is 1-(4-(((6-amino-5-(4-phenoxyphenyl)pyrimidin-4-yl)amino)methyl)-4-fluoropiperidin-1-yl)prop-2-en-1-one or a pharmaceutically acceptable salt thereof, wherein the ophthalmic composition is an oil-in-water microemulsion.
31. The ophthalmic composition of claim 30, wherein the oil-in-water microemulsion further comprises:
- (i) an oil selected from the group consisting of isopropyl myristate, isopropyl palmitate, and medium chain triglycerides;
 - (ii) a pair of surfactants selected from the group consisting of two polysorbates, a polysorbate and propylene glycol, a polysorbate and glycerol, a polysorbate and 1,2,3- triacetoxyp propane, polyethoxylated castor oil and 1,2,3-triacetoxyp propane, and polyethoxylated castor oil and propylene glycol; and (iii) water,

wherein: the water represents about 50 to about 95 percent (v/v) of the oil-in-water microemulsion; and the ratio of percent (v/v) total surfactant to percent (v/v) oil is at least about 10: 1.

32. The ophthalmic composition of claim 31, wherein the pair of surfactants represent about 10% to about 50% (v/v) of the oil-in-water microemulsion.
33. The ophthalmic composition of claim 31, wherein the pair of surfactants represent about 15% to about 40% (v/v) of the oil-in-water microemulsion.
34. The ophthalmic composition of claim 31, wherein the pair of surfactants represent about 20% to about 40% (v/v) of the oil-in-water microemulsion.
35. The ophthalmic composition of claim 31, wherein the pair of surfactants represent about 15%, about 20%, about 25%, about 30%, about 35%, about 40%, or about 45% (v/v) of the oil-in-water microemulsion.
36. The ophthalmic composition of claim 31, wherein the oil represents about 1% to about 5% (v/v) of the oil-in-water microemulsion.
37. The ophthalmic composition of claim 31, where the oil represents about 1%, about 2%, about 3%, about 4%, or about 5% (v/v) of the oil-in-water microemulsion.
38. The ophthalmic composition of claim 31, wherein the ratio of the pair of surfactants (v/v) is in a range of about 1:10 to 10:1.
39. The ophthalmic composition of claim 31, wherein the ratio of the pair of surfactants (v/v) is in a range of about 1:4 to 4:1.
40. The ophthalmic composition of claim 31, wherein the ratio of the pair of surfactants (v/v) is in a range of about 1:2 to 2:1.
41. The ophthalmic composition of claim 31, wherein the ratio of the pair of surfactants (v/v) is about 1:1.
42. The ophthalmic composition of claim 31, wherein one of the surfactants is polysorbate 20.
43. The ophthalmic composition of claim 31, wherein one of the surfactants is polysorbate 80.
44. The ophthalmic composition of claim 31, wherein the appearance of the oil-in-water microemulsion is clear.

45. The ophthalmic composition of claim 31, wherein the particle size of the oil-in-water microemulsion is between about 1 nm and 10 nm.
46. The ophthalmic composition of claim 31, wherein the particle size of the oil-in-water microemulsion is between about 1 nm and 8 nm.
47. The ophthalmic composition of claim 31, wherein the particle size of the oil-in-water microemulsion is between about 1 nm and 5 nm.
48. The ophthalmic composition of claim 31, wherein the particle size of the oil-in-water microemulsion is between about 2 nm and 5 nm.
49. The ophthalmic composition of claim 31, wherein the particle size of the oil-in-water microemulsion is between about 2 nm and 3 nm.
50. The ophthalmic composition of claim 31, wherein the particle size of the oil-in-water microemulsion is between about 2 nm and 8 nm.
51. The ophthalmic composition of claim 31, wherein viscosity of the oil-in-water microemulsion is between about 0 to about 500 centipoise.
52. The ophthalmic composition of claim 31, wherein viscosity of the oil-in-water microemulsion is between about 0 to about 400 centipoise.
53. The ophthalmic composition of claim 31, wherein osmolality of the oil-in-water microemulsion is between about 5 to about 100 mOsm/kg at 1:3 dilution.
54. The ophthalmic composition of claim 31, wherein osmolality of the oil-in-water microemulsion is between about 5 to about 50 mOsm/kg at 1:3 dilution.
55. The ophthalmic composition of claim 31, wherein osmolality of the oil-in-water microemulsion is between about 15 to about 40 mOsm/kg at 1:3 dilution.
56. The ophthalmic composition of claim 31, wherein osmolality of the oil-in-water microemulsion is between about 20 to about 30 mOsm/kg at 1:3 dilution.
57. A method of reducing ocular mast cell degranulation and/or ocular mast cell cytokine production in a human subject in need thereof comprising topically administering to an eye of the human subject an amount of a Bruton's Tyrosine Kinase (BTK) inhibitor compound effective to reduce the ocular mast cell degranulation and/or ocular mast cell cytokine production in the human subject,

wherein the BTK inhibitor compound is 1-(4-(((6-amino-5-(4-phenoxyphenyl)pyrimidin-4-yl)amino)methyl)-4-fluoropiperidin-1-yl)prop-2-en-1-one or a pharmaceutically acceptable salt thereof.

58. A method of inhibiting ocular mast cell activation in a lacrimal functional unit of a human subject in need thereof comprising topically administering to an eye of the human subject an amount of a Bruton's Tyrosine Kinase (BTK) inhibitor compound effective to inhibit ocular mast cell activation in the lacrimal functional unit of the human subject, wherein the BTK inhibitor compound is 1-(4-(((6-amino-5-(4-phenoxyphenyl)pyrimidin-4-yl)amino)methyl)-4-fluoropiperidin-1-yl)prop-2-en-1-one or a pharmaceutically acceptable salt thereof.

59. The method of claim 57 or 58, wherein the lacrimal functional unit of a human subject is a lacrimal gland.

60. The method of claim 57 or 58, wherein the inhibition of ocular mast cell activation occurs in the surface and glandular epithelia of the cornea.

61. The method of claim 57 or 58, wherein the inhibition of ocular mast cell activation occurs in the conjunctiva.

62. The method of claim 57 or 58, wherein the inhibition of ocular mast cell activation occurs in the lacrimal gland or accessory lacrimal glands.

63. The method of claim 57, wherein the reduction occurs in the meibomian gland.

64. A method of treating meibomian gland dysfunction (MGD) in a human subject in need thereof comprising topically administering to an eye of the human subject an amount of a Bruton's Tyrosine Kinase (BTK) inhibitor compound effective to reduce the meibomian gland dysfunction in the human subject, wherein the BTK inhibitor compound is 1-(4-(((6-amino-5-(4-phenoxyphenyl)pyrimidin-4-yl)amino)methyl)-4-fluoropiperidin-1-yl)prop-2-en-1-one or a pharmaceutically acceptable salt thereof.

65. A method of inhibiting mast cell activation in a human subject in need thereof comprising topically administering to an eye of the human subject an amount of a Bruton's Tyrosine Kinase (BTK) inhibitor compound effective to reduce a meibomian gland dysfunction in the human subject, wherein the BTK inhibitor compound is 1-(4-(((6-amino-5-(4-phenoxyphenyl)pyrimidin-4-yl)amino)methyl)-4-fluoropiperidin-1-yl)prop-2-en-1-one or a pharmaceutically acceptable salt thereof.

66. The method of any one of claims 57 to 65, wherein the human subject has dry eye disease.

67. The method of any one of claims 57 to 65, wherein the human subject has allergic conjunctivitis.
68. The method of any one of claims 57 to 65, wherein the amount of BTK inhibitor compound administered is effective to reduce inflammation in the eye of the human subject compared to pre-treatment.
69. The method of any one of claims 57 to 65, wherein the amount of BTK inhibitor compound administered is effective to reduce ocular redness in the eye of the human subject compared to pre-treatment.
70. The method of any one of claims 57 to 65, wherein the amount of BTK inhibitor compound administered is effective to increase tear volume in the eye of the human subject compared to pre-treatment.
71. A method of reducing or alleviating a sign or symptom of dry eye disease, the method comprising administering to a human subject with dry eye disease an amount of a Bruton's Tyrosine Kinase (BTK) inhibitor compound effective to reduce at least one sign or symptom of dry eye disease wherein the reducing or alleviating of a sign or symptom of dry eye disease accompanies at least one of reduced total corneal fluorescein staining score, reduced central corneal fluorescein staining score, reduced inferior corneal fluorescein staining score, reduced superior corneal fluorescein staining score, increased Schirmer's unanesthetized test score, reduced conjunctival lissamine staining score, reduced tear osmolarity, increased tear break-up time, reduced conjunctival redness, reduced ocular discomfort severity (ODS) score, reduced ocular discomfort and four-symptom (OD4S) score, reduced ocular surface disease index (OSDI) score, reduced visual analog scale (VAS) ocular discomfort score, reduced inflammation of an eye, reduced ocular redness, reduced ocular itching score, increased tear volume in an eye, or any combination thereof, and the BTK inhibitor compound is 1-(4-(((6-amino-5-(4-phenoxyphenyl)pyrimidin-4-yl)amino)methyl)-4-fluoropiperidin-1-yl)prop-2-en-1-one or a pharmaceutically acceptable salt thereof.
72. The method of claim 66 or 71, wherein the dry eye disease is aqueous-deficient dry eye disease.
73. The method of claim 66 or 71, wherein the dry eye disease is hyper-evaporative dry eye disease.

74. The method of claim 66 or 71, wherein the dry eye disease is mixed aqueous-deficient and hyper-evaporative dry eye disease.
75. The method of claim 66 or 71, wherein the human subject also has allergic conjunctivitis.
76. A method of reducing or alleviating a sign or symptom of allergic conjunctivitis, the method comprising administering to a human subject with allergic conjunctivitis an amount of a Bruton's Tyrosine Kinase (BTK) inhibitor compound effective to reduce at least one sign or symptom of allergic conjunctivitis wherein the reducing or alleviating of a sign or symptom of allergic conjunctivitis comprises reduced conjunctival redness, a reduced ocular itching score, or a combination thereof, and the BTK inhibitor compound is 1-(4-(((6-amino-5-(4-phenoxyphenyl)pyrimidin-4-yl)amino)methyl)-4-fluoropiperidin-1-yl)prop-2-en-1-one or a pharmaceutically acceptable salt thereof.
77. The method of any one of claims 57 to 76, wherein the administering occurs at a frequency of twice daily.
78. The method of any one of claims 57 to 76, wherein the administering occurs at a frequency of once daily.
79. The method of any one of claims 57 to 76, wherein the administering occurs for at least fourteen days.
80. The method of any one of claims 57 to 76, wherein the administering occurs for at least twenty-eight days.
81. The method of claim 76, wherein the human subject also has dry eye disease.
82. The method of claim 76, wherein the administering occurs seasonally.
83. The method of claim 76, wherein the administering occurs perennially.
84. The method of any one of the preceding claims, wherein the BTK inhibitor compound is present in an ophthalmic composition comprising one or more pharmaceutically acceptable excipients formulated for topical administration.
85. The method of claim 84, wherein the ophthalmic composition is administered as an eye drop.
86. The method of claims 1-29, or 85, wherein the ophthalmic composition is formulated as an oil-in-water microemulsion comprising:

0.1% (1.0 mg/ml) of 1-(4-(((6-amino-5-(4-phenoxyphenyl)pyrimidin-4-yl)amino)methyl)-4-fluoropiperidin-1-yl)prop-2-en-1-one or a pharmaceutically acceptable salt thereof;

about 8.43% polysorbate 20 (w/w);

about 16.19% polysorbate 80 (w/w);

about 1.77% isopropyl myristate (w/w); and

phosphate buffered saline.

87. The method of claim 86, wherein the eye drop is administered by instilling a first eye drop in each eye, waiting a period of time, and then instilling a second eye drop in each eye.
88. The method of claim 87, wherein the period of time is 10 minutes $\pm$ 1 minute.
89. The method of claim 87, wherein the period of time is 9 minutes $\pm$ 1 minute.
90. The method of claim 87, wherein the period of time is 8 minutes $\pm$ 1 minute.
91. The method of claim 87, wherein the period of time is 7 minutes $\pm$ 1 minute.
92. The method of claim 87, wherein the period of time is 6 minutes $\pm$ 1 minute.
93. The method of claim 87, wherein the period of time is 5 minutes $\pm$ 1 minute.
94. The method of claim 87, wherein the period of time is 4 minutes $\pm$ 1 minute.
95. The method of claim 87, wherein the period of time is 3 minutes $\pm$ 1 minute.
96. The method of any one of claims 87 to 85, further comprising administering a loading dose via at least one eye drop in each eye.
97. The method of claim 96, wherein the loading dose comprises two doses administered 12 hours $\pm$ 1.5 hours apart.
98. The method of claim 96, wherein the loading dose comprises two doses administered 24 hours $\pm$ 1.5 hours apart.
99. The method of claim 96, wherein the loading dose comprises two doses administered less than 12 hours apart $\pm$ 1.5 hours.

100. The method of claim 96, wherein the loading dose comprises two doses administered more than 24 hours apart $\pm$ 1.5 hours.

101. A method of treating allergic conjunctivitis in a human subject in need thereof comprising administering as an eye drop to an eye of the human subject an amount of a Bruton's Tyrosine Kinase (BTK) inhibitor compound effective to treat the allergic conjunctivitis in the human subject, wherein the eye drop is administered by instilling at least one first eye drop in each eye, waiting at least 5 minutes $\pm$ 1 minute, and then instilling at least one second eye drop in each eye; and the BTK inhibitor compound is 1-(4-(((6-amino-5-(4-phenoxyphenyl)pyrimidin-4-yl)amino)methyl)-4-fluoropiperidin-1-yl)prop-2-en-1-one or a pharmaceutically acceptable salt thereof.

102. The method of claim 101, further comprising administering a loading dose, wherein the loading dose comprises two doses administered 12 hours apart $\pm$ 1.5 hours.

103. The method of claim 101, further comprising administering a loading dose, wherein the loading dose comprises two doses administered 24 hours apart $\pm$ 1.5 hours.

104. The method of claim 101, further comprising administering a loading dose, wherein the loading dose comprises two doses administered less than 12 hours apart $\pm$ 1.5 hours.

105. The method of claim 101, further comprising administering a loading dose, wherein the loading dose comprises two doses administered more than 24 hours apart $\pm$ 1.5 hours.

106. An ophthalmic composition comprising:

0.1% (1.0 mg/ml) of 1-(4-(((6-amino-5-(4-phenoxyphenyl)pyrimidin-4-yl)amino)methyl)-4-fluoropiperidin-1-yl)prop-2-en-1-one or a pharmaceutically acceptable salt thereof;
and an oil-in-water microemulsion comprising:

about 8.43% polysorbate 20 (w/w);

about 16.19% polysorbate 80 (w/w);

about 1.77% isopropyl myristate (w/w); and

phosphate buffered saline.

107. The ophthalmic composition of claim 106, wherein the ophthalmic composition is formulated as an eye drop.

108. The ophthalmic composition of claim 106, wherein the ophthalmic composition does not contain any preservatives.