composition is specifically formulated for peri-ocular delivery. In some examples, the lipophilic compound is not delivered systemically to the subject. In some examples, the lipophilic compound is not delivered to a tear or tear duct of the subject. In some examples, the lipophilic compound is not delivered by direct application to an ocular surface of the subject. In some examples, the pharmaceutical composition is not a liquid topical ocular suspension, emulsion, or solution. In some examples, the one or more peri-orbital glands are selected from the group consisting of a meibomian gland, a lacrimal gland, an accessory lacrimal gland, and any combinations thereof. In some examples, the lipophilic compound is delivered to an ocular surface of the subject via the meibomian gland and meibum. In some examples, the lipophilic compound is selected from the group consisting of steroids, antibiotics, immunomodulatory drugs, integrin antagonists, anti-inflammatory agents, and anti-glaucoma or ocular anti-hypertension agents.

[0011a] In one example, the present disclosure refers to a pharmaceutical composition comprising: a) a therapeutically effective amount of a lipophilic compound; and b) a pharmaceutically acceptable carrier adapted for peri-ocular transdermal delivery of the lipophilic compound to one or more peri-orbital glands of a subject; wherein the pharmaceutical composition is specifically formulated for peri-ocular delivery.

[0012] In one example, provided herein are pharmaceutical compositions comprising a therapeutically effective amount of a steroid, and a pharmaceutically acceptable carrier adapted for per-ocular transdermal delivery of the steroid to one or more peri-orbital (*e.g.,* oil-secreting peri-orbital) glands of a subject. In some examples, the pharmaceutical composition is specifically formulated for peri-ocular delivery. In some examples, the steroid is not delivered systemically to the subject. In some examples, the steroid is not delivered to a tear or tear duct of the subject. In some examples, the steroid is not delivered by direct application to an ocular surface of the subject. In some examples, the pharmaceutical composition is not a liquid topical ocular suspension, emulsion, or solution. In some examples, the one or more peri-orbital glands are selected from the group consisting of a meibomian gland, a lacrimal gland, an accessory lacrimal gland, and any combinations thereof. In some examples, the steroid is delivered to an ocular surface of the subject via the meibomian gland and meibum.

[0013] The steroid can be any steroid. In some examples that may be combined with any of the preceding examples, the steroid is selected from the compound of Formula I, fluocinolone, difluprednate, fluticasone, fluorometholone, loteprednol, dexamethasone, prednisolone, triamcinolone acetonide, rimexolone, cortisol, cortisone, hydrocortisone, testosterone, and ester derivatives thereof. In some examples, the steroid is selected from the compound of Formula I, difluprednate, loteprednol, dexamethasone, prednisolone, triamcinolone acetonide, and ester derivatives thereof. In some examples, the steroid is

sensory abnormalities, meibomian gland dysfunction, exacerbated inflammatory ocular surface disease, phlyctenular keratitis, chalazion, anterior blepharitis, posterior blepharitis, bacterial infection, glaucoma, ocular hypertension, and any combinations thereof.

[0036a] In another aspect, the present disclosure refers to use of a pharmaceutical composition comprising (a) a therapeutically effective amount of a compound of Formula I; and (b) a pharmaceutically acceptable carrier adapted for peri-ocular transdermal delivery of the compound of Formula I to one or more peri-orbital glands of a subject, in the manufacture of a medicament for providing prophylactic, palliative, or therapeutic relief of dry eye disease or blepharitis in a subject,

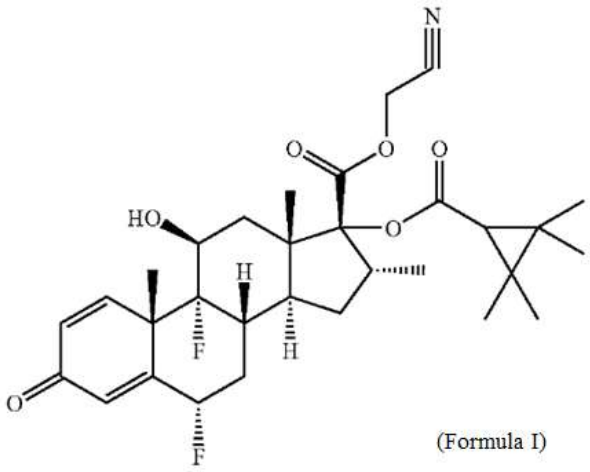
wherein the pharmaceutically acceptable carrier is an ointment or a cream;

wherein the medicament is specifically formulated for peri-ocular delivery;

wherein the medicament is to be topically administered to the external portion of the upper and/or lower eyelid of the subject;

wherein the medicament is to be administered one time each day that it is administered; and

wherein the compound of Formula I comprises the structure:



(Formula I)

.

[0037] In some examples that may be combined with any of the preceding examples, the pharmaceutical composition is topically administered to an external portion of an eyelid of the subject, including the upper lateral region of an orbit of the subject. In some examples, the pharmaceutical composition is topically administered to the external portion of the upper and/or lower eyelid of the subject. In some examples, the lipophilic compound is delivered to an ocular surface of the subject via the meibomian gland. In some examples, the pharmaceutical composition is administered one, two, three, four, five, six or more times per

day. In some examples, the pharmaceutical composition is administered for one day, two days, three days, four days, five days, six days, one week, two weeks, three weeks, four weeks, five weeks, six weeks, seven weeks, eight weeks, nine weeks, 10 weeks, 11 weeks, 12 weeks or more, 24 weeks, 36 weeks, 48 weeks or more. In some examples, prolonged administration of the pharmaceutical composition does not result in an adverse ocular event in the subject. In some examples, the adverse ocular event is selected from elevated intraocular pressure, cataracts, ocular infection, and any combinations thereof. In some examples, the lipophilic compound is not delivered systemically to the subject by the administration of the pharmaceutical composition. In some examples, the lipophilic compound is not delivered to a tear or tear duct of the subject by the administration of the pharmaceutical composition. In some examples, the lipophilic compound is not delivered directly to an ocular surface of the subject by the administration of the pharmaceutical composition.

[0038] In another example, provided herein are articles of manufacture or kits comprising any of the pharmaceutical compositions described herein. In some examples, the article of manufacture or kit further comprises a package insert comprising instructions for administering the pharmaceutical composition.

[0038a] In another example, the present disclosure refers to a kit comprising: a) the pharmaceutical composition as disclosed herein; and b) a package insert comprising instructions for administering the pharmaceutical composition.

[0039] It is to be understood that one, some, or all of the properties of the various examples described above and herein may be combined to form other examples of the present disclosure. These and other examples of the present disclosure will become apparent to one of skill in the art. These and other examples of the present disclosure are further described by the detailed description that follows.

CLAIMS

What is claimed is:

1. Use of a pharmaceutical composition comprising (a) a therapeutically effective amount of a compound of Formula I; and (b) a pharmaceutically acceptable carrier adapted for peri-ocular transdermal delivery of the compound of Formula I to one or more peri-orbital glands of a subject, in the manufacture of a medicament for providing prophylactic, palliative, or therapeutic relief of dry eye disease or blepharitis in a subject,

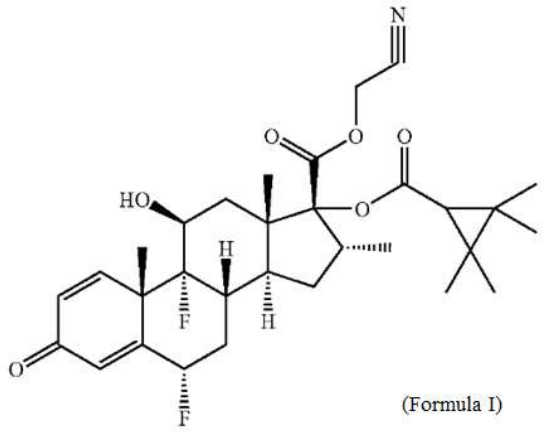
wherein the pharmaceutically acceptable carrier is an ointment or a cream;

wherein the medicament is specifically formulated for peri-ocular delivery;

wherein the medicament is to be topically administered to the external portion of the upper and/or lower eyelid of the subject;

wherein the medicament is to be administered one time each day that it is administered; and

wherein the compound of Formula I comprises the structure:



(Formula I)

2. The use of claim 1, wherein the subject is a human or a non-human animal.

3. The use of claim 1 or claim 2, wherein the compound of Formula I of the medicament is to be delivered to an ocular surface of the subject via the Meibomian gland.

4. The use of any one of claims 1-3, wherein the medicament is to be administered for one day, two days, three days, four days, five days, six days, one week, two weeks, three weeks, four weeks, five weeks, six weeks, seven weeks, eight weeks, nine weeks, 10 weeks, 11 weeks, 12 weeks or more, 24 weeks, 36 weeks, 48 weeks or more.

5. The use of any one of claims 1-3, wherein the medicament is to be administered for two weeks or more.

6. The use of any one of claims 1-5, wherein prolonged administration of the medicament does not result in an adverse ocular event in the subject.

7. The use of claim 6, wherein the adverse ocular event is selected from the group consisting of elevated intraocular pressure, cataracts, ocular infection, and any combinations thereof.

8. The use of claim 6, wherein the adverse ocular event is elevated intraocular pressure.

9. The use of any one of claims 1-8, wherein the compound of Formula I of the medicament is not to be delivered systemically to the subject.

10. The use of any one of claims 1-9, wherein the compound of Formula I of the medicament is not to be delivered to a tear or tear duct of the subject.

11. The use of any one of claims 1-10, wherein the compound of Formula I of the medicament is not to be delivered directly to an ocular surface of the subject.

12. The use of any one of claims 1-11, wherein the one or more peri-orbital glands are selected from the group consisting of a Meibomian gland, a lacrimal gland, an accessory lacrimal gland, and any combinations thereof.

13. The use of any one of claims 1-12, wherein the medicament comprises the compound of Formula I at a concentration between 0.001% and 10% weight per weight (w/w), between 0.0001% and 10% weight per weight (w/w), or between 0.0001% and 5% weight per weight (w/w).

14. The use of any one of claims 1-13, wherein the medicament comprises the compound of Formula I at a concentration between 0.01% and 2% w/w.

15. The use of any one of claims 1-14, wherein the medicament further comprises a therapeutically effective amount of an additional steroid.

16. The use of claim 15, wherein the additional steroid is selected from the group consisting of fluocinolone, difluprednate, fluticasone, fluorometholone, loteprednol,

dexamethasone, prednisolone, triamcinolone acetonide, rimexolone, cortisol, cortisone, hydrocortisone, testosterone, and ester derivatives thereof.

17. The use of any one of claims 1-16, wherein the medicament further comprises a therapeutically effective amount of one or more antibiotics.

18. The use of claim 17, wherein the one or more antibiotics are selected from the group consisting of sulfonamides, macrolides, chloramphenicol, aminoglycosides, fluoroquinolones, vancomycin, tetracyclines, and any combinations thereof.

19. The use of claim 17 or claim 18, wherein the one or more antibiotics are selected from the group consisting of azithromycin, erythromycin, gentamicin, natamycin, neomycin, tobramycin, vancomycin, bacitracin, besifloxacin, ciprofloxacin, gatifloxacin, levofloxacin, moxifloxacin, oxifloxacin, chloramphenicol, doxycycline, tetracyclin, gramicidin, mupirocin, polymyxin B, sulfacetamide, and any combinations thereof.

20. The use of any one of claims 1-19, wherein the medicament further comprises a therapeutically effective amount of one or more immunomodulatory drugs.

21. The use of claim 20, wherein the one or more immunomodulatory drugs are selected from the group consisting of calcineurin inhibitors, thalidomide analogues, and any combinations thereof.

22. The use of claim 20 or claim 21, wherein the one or more immunomodulatory drugs are selected from the group consisting of cyclosporine A, voclosporine, tacrolimus, pimecrolimus, thalidomide, lenalidomide, pomalidomide, and any combinations thereof.

23. The use of any one of claims 1-22, wherein the medicament further comprises a therapeutically effective amount of one or more integrin antagonists.

24. The use of claim 23, wherein the one or more integrin antagonists are selected from the group consisting of lifitegrast, GW559090, ester derivatives thereof, and any combinations thereof.

25. The use of any of claims 1-24, wherein the medicament further comprises a therapeutically effective amount of one or more anti-inflammatory agents.

26. The use of claim 25, wherein the one or more anti-inflammatory agents are selected from the group consisting of omega 3 fatty acids, non-steroidal anti-inflammatory drugs (NSAIDs), and any combinations thereof.

27. The use of claim 26, wherein the omega 3 fatty acids are selected from the group consisting of eicosapentaenoic acid (EPA), docosahexaenoic acid (DHA), alpha-linolenic acid (ALA), and any combinations thereof.

28. The use of claim 27, wherein the NSAIDs are selected from the group consisting of bromfenac, diclofenac, indomethacin, flurbiprofen, ketorolac, nepafenac, and any combinations thereof.

29. The use of any of claims 1-28, wherein the medicament further comprises a therapeutically effective amount of one or more anti-glaucoma or ocular anti-hypertension agents.

30. The use of claim 29, wherein the one or more anti-glaucoma or ocular anti-hypertension agents are selected from the group consisting of bimatoprost, latanoprost, travoprost, tafluprost, latanoprostene-bunod, timolol, betaxolol, levobunolol, metipranolol, brimonidine, clonidine, apraclonidine, dorzolamide, brinzolamide, acetazolamide, methazolamide, netarsudil, and any combinations thereof.

31. The use of any one of claims 1-30, wherein the pharmaceutically acceptable carrier is an ointment.

32. The use of claim 31, wherein the ointment comprises a paraffinic or a water-miscible ointment base.

33. The use of claim 31 or claim 32, wherein the ointment comprises 61.5% w/w white soft paraffin, 8% w/w mineral oil, 8% w/w propylene glycol, 5% w/w of St. cyclomethicone-5NF, 5% w/w of labrasol, 5% w/w of propylene carbonate, 2.5% w/w of steareth 2, 2.5% w/w of St. emulsifier 10, and 2.5% w/w of St. elastomer-10.

34. The use of any one of claims 1-30, wherein the pharmaceutically acceptable carrier is a cream.

35. The use of claim 34, wherein the cream comprises an oil-in-water base or a water-in-oil base.

36. The use of claim 34 or claim 35, wherein the cream comprises 48% w/w white soft paraffin, 8% w/w mineral oil, 8% w/w propylene glycol, 6.6% w/w ST-cyclomethicone-5NF, 3.3% w/w ST-emulsifier, 2% w/w ST-elastomer-10, 0.08% w/w methylparaben, 0.06% w/w dibasic sodium phosphate, 0.05% w/w citric acid, 0.02% w/w propylparaben, and purified water.

37. The use of claim 34 or claim 35, wherein the cream comprises 48% w/w white soft paraffin, 8% w/w mineral oil, 8% w/w propylene glycol, 6.6% w/w cyclomethicone, 3.3% w/w emulsifier 10, 2% w/w ST-elastomer-10, 0.08% w/w methylparaben, 0.06% w/w sodium phosphate dibasic anhydrous, 0.046% w/w citric acid anhydrous, 0.02% w/w propylparaben, and purified water.

38. The use of any one of claims 34-37, wherein the cream comprises benzalkonium chloride (BAK).

39. The use of any one of claims 34-38, wherein the cream comprises 48% w/w white petrolatum, 8% w/w mineral oil, 8% w/w propylene glycol, 6.6% w/w ST-cyclomethicone-5NF, 3.3% w/w emulsifier 10, 2% w/w ST-elastomer-10, 0.06% w/w sodium phosphate dibasic anhydrous, 0.05% w/w citric acid anhydrous, 0.02% w/w benzalkonium chloride, and purified water.

40. The use of any one of claims 34-37, wherein the cream is preservative-free.

41. The use of claim 40, wherein the cream that is preservative-free comprises white soft paraffin/petrolatum, mineral oil, propylene glycol, ST-cyclomethicone-5NF, emulsifier-10, ST-elastomer-10, dibasic sodium phosphate, citric acid, and purified water.

42. The use of claim 40 or claim 41, wherein the cream that is preservative-free comprises 48% w/w white petrolatum, 8% w/w mineral oil, 8% w/w propylene glycol, 6.6% w/w ST-cyclomethicone-5NF, 3.3% w/w emulsifier 10, 2% w/w ST-elastomer-10, 0.06% w/w sodium phosphate dibasic anhydrous, 0.05% w/w citric acid anhydrous, and purified water.