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

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
27 December 2018 (27.12.2018)

WIPO | PCT

(10) International Publication Number
WO 2018/237249 A1

(51) International Patent Classification:
A61K 31/409 (2006.01) *C07D 487/22* (2006.01)
A61K 31/555 (2006.01)

(21) International Application Number:
PCT/US2018/038964

(22) International Filing Date:
22 June 2018 (22.06.2018)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
62/523,552 22 June 2017 (22.06.2017) US

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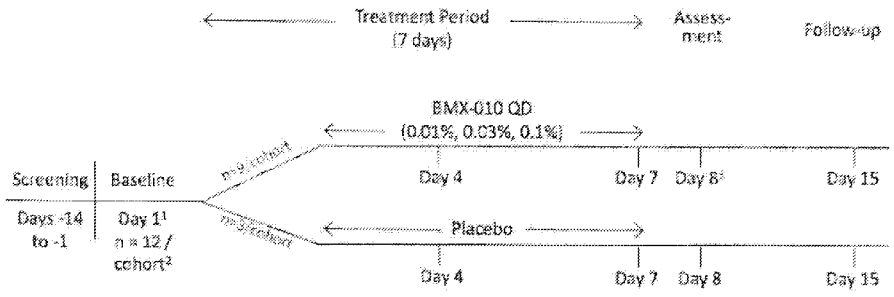
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(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BN, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DJ, DK, DM, DO, DZ, EC, EE, EG, ES, FI,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

(54) Title: METHODS, COMPOSITIONS, AND KITS FOR TREATING INFLAMMATORY SKIN CONDITIONS

Fig. 1



[1] Randomization will occur after completion of all screening assessments. The first dose will be administered at the clinic on Day 1.

[2] N = 12 evaluable subjects with AD or PS per cohort (9 on active drug; 3 on placebo). Subjects are treated in dose escalating cohorts of 0.01%, 0.03% and 0.1%.

[3] The 3 subjects receiving BMX-010 of each dosing cohort who participate in the PK portion of the study will have visits on Days 2 and 9 in addition to clinical visits on Days 4, 8 and 15; the remaining subjects randomized to BMX-010 or Placebo will not.

(57) Abstract: Described herein are methods, compositions, and kits for treating inflammatory skin conditions. In some embodiments, methods, compositions, and kits for topically administering MnTE-2-PyP^{5+} to treat inflammatory skin conditions such as, e.g., atopic dermatitis, rosacea, acne, and/or plaque psoriasis. A composition of the present invention can include a meso-substituted metalloporphyrin, wherein the meso-substituted metalloporphyrin is Ames negative and optionally is present in the composition at a concentration of about 0.005% to about 1% by weight of the composition; water or an aqueous buffer solution; a hydrophobic base; a fatty alcohol; a polyhydric alcohol; a fatty acid ester; a surfactant; optionally a buffer and/or buffering agent; and optionally a preservative.

WO 2018/237249 A1

[Continued on next page]

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

Published:

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

METHODS, COMPOSITIONS, AND KITS FOR TREATING INFLAMMATORY SKIN CONDITIONS

Related Application Information

This application claims the benefit of U.S. Provisional Patent Application Serial No. 62/523,552, filed June 22, 2017, the disclosure of which is incorporated herein by reference in its entirety.

Field

The present invention concerns methods, compositions, and kits for treating inflammatory skin conditions. In some embodiments, the present invention concerns methods, compositions, and kits for topically administering MnTE-2-PyP^{5+} to treat inflammatory skin conditions such as atopic dermatitis, rosacea, acne, and/or plaque psoriasis.

Background

Atopic dermatitis and plaque psoriasis are chronic inflammatory skin diseases that cause patients to suffer from stigmatizing eczematous skin lesions, persistent itching, and sleep disorders. Atopic dermatitis pathogenesis is dominated by the Th2 axis in most subjects, particularly in allergic (extrinsic) and acute lesions. Over time in many patients, contributions of the Th1 and Th2 subsets increase. Topical corticosteroids are the mainstay of the treatment for moderate to severe atopic dermatitis; however, use is limited by their side effect profile (cutaneous atrophy, telangiectasias, and/or hypothalamic-pituitary axis suppression), and they cannot be used on the face. Topical calcineurin inhibitors may be used for the treatment of acute flares and maintenance therapy of atopic dermatitis; however, efficacy is limited, and an association between topical calcineurin inhibitor use and malignancy has not been ruled out. Photo/UV therapies and systemic immunosuppressant treatments are used after first-line topical treatments. Systemic biological therapies such as an antibody directed against IL-4 and IL-13 receptors are currently under clinical development with eligibility likely to be limited to a minor portion of the patients and an unknown long-term safety profile.

Rosacea is an inflammatory skin disease affecting approximately 12 million subjects in the USA. It is characterized by redness, flushing, visible blood vessels, acne-like breakouts, and thickening skin with a bumpy texture. Trigger factors for rosacea flares

include UV irradiation, heat, spicy food, alcohol, stress, microbes, and Dermodex mites. In response to these triggers, immunological mediators are activated, including cytokines (such as TNF-α, IL-1, IL-17, IL-22, and VEGF), chemokines and receptors (such as CCL5, CCL2, CCL20, CXCL1, and CXCL8), and reactive oxygen species (such as O_2^-). Current therapy includes antimicrobials such as metronidazole and doxycycline and bleaching methods.

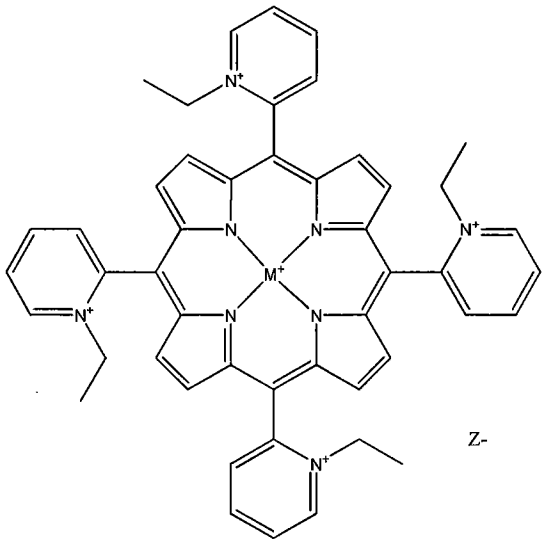
Plaque psoriasis is an immune-mediated disorder, and the characteristic red patches of thickened skin (plaques) covered in silver scales are a result of epidermal hyperproliferation, abnormal keratinocyte differentiation, and the presence of a lymphocyte inflammatory infiltrate. The current understanding is that the disease is driven by proinflammatory CD4-positive T helper cells producing interferon-gamma (Th1) and interleukin (IL)-17 (Th17). These Th1 and Th17 cells interact with dermal dendritic cells, macrophages, mast cells, and neutrophils, leading to further cell activation and release of the cytokines interferon-gamma, tumor necrosis factor (TNF), IL-8, IL-12, IL-17, IL-19, and IL-23. Topical corticosteroids are the cornerstone of treatment for the majority of patients with plaque psoriasis; however use is limited by side effects, as noted above. Secondline therapy includes photo/UV therapies and non-biological systemic agents (e.g., cyclosporin, methotrexate), and third-line therapy refers to systemic biological therapies such as TNF antagonists (e.g., adalimumab, etanercept) and anti-IL12-23 monoclonal antibody (ustekinumab). All of these interventions can be associated with long-term toxicity and in some cases life-threatening infections.

Summary

A first aspect of the present invention is directed to a method of treating a dermatological condition in a subject, comprising: topically administering to the skin of a subject a composition comprising a meso-substituted metalloporphyrin, wherein the meso-substituted metalloporphyrin is Ames negative and is present in the composition at a concentration of about 0.005% to about 1% by weight of the composition. In some embodiments, the meso-substituted metalloporphyrin is present in the composition at a concentration of about 0.01%, 0.03%, or 0.05% to about 0.1%, 0.3%, or 0.5% by weight of the composition, optionally times the activity equivalent of BMX-010. In some embodiments, the dermatological condition is atopic dermatitis, rosacea, acne, and/or plaque psoriasis.

Another aspect of the present invention is a method of treating atopic dermatitis in a subject, comprising: topically administering to the skin of a subject a composition comprising

a meso-substituted metalloporphyrin, wherein the meso-substituted metalloporphyrin is present in the composition at a concentration of about 0.005% to about 1% by weight of the composition and has the structure:



wherein Z^- is a counterion (e.g., a halogen) and M^+ is manganese. In some embodiments, the meso-substituted metalloporphyrin is present in the composition at a concentration of about 0.01%, 0.03%, or 0.05% to about 0.1%, 0.3%, or 0.5% by weight of the composition, optionally times the activity equivalent of BMX-010.

Another aspect of the present invention is directed to a composition comprising: a meso-substituted metalloporphyrin, optionally wherein the meso-substituted metalloporphyrin is Ames negative and optionally is present in the composition at a concentration of about 0.005% to about 1% by weight of the composition; water or an aqueous buffer solution, optionally in an amount of about 40% to about 60% by weight of the composition; a hydrophobic base (e.g., mineral oil and/or petrolatum), optionally in an amount of about 5% to about 35% by weight of the composition; a fatty alcohol, optionally in an amount of about 1% to about 20% by weight of the composition; a polyhydric alcohol, optionally in an amount of about 1% to about 15% by weight of the composition; a fatty acid ester, optionally in an amount of about 0.01% to about 2%; a surfactant (e.g., a non-ionic surfactant), optionally in an amount of about 0.1% to about 5%; optionally a buffer and/or buffering agent (e.g., at a concentration of about 5, 10, 15, or 20 mM to about 25, 30, 35, 40, 45, or 50 mM); and optionally a preservative (e.g., in an amount of about 0.01% to about 2%). In some embodiments, the composition has a pH of about 4, 4.5, or 5 to about 5.5, 6, 6.5, or 7. In some embodiments, the meso-substituted metalloporphyrin is present in the composition at a concentration of about 0.01%, 0.03%, or 0.05% to about 0.1%, 0.3%, or

0.5% by weight of the composition, optionally times the activity equivalent of BMX-010. In some embodiments, the meso-substituted metalloporphyrin is a compound having a structure represented by **Formula I** as described herein. In some embodiments, the meso-substituted metalloporphyrin is a compound having a structure represented by **Formula A1**, **A2**, **B1**, **B2**, **V**, **C1**, **C2**, or **VI** as described herein. In some embodiments, the meso-substituted metalloporphyrin is Ames negative.

It is noted that aspects of the invention described with respect to one embodiment, may be incorporated in a different embodiment although not specifically described relative thereto. That is, all embodiments and/or features of any embodiment can be combined in any way and/or combination. Applicant reserves the right to change any originally filed claim and/or file any new claim accordingly, including the right to be able to amend any originally filed claim to depend from and/or incorporate any feature of any other claim or claims although not originally claimed in that manner. These and other objects and/or aspects of the present invention are explained in detail in the specification set forth below. Further features, advantages and details of the present invention will be appreciated by those of ordinary skill in the art from a reading of the figures and the detailed description of the preferred embodiments that follow, such description being merely illustrative of the present invention.

Brief Description of the Drawings

Fig. 1 shows a schematic of the study design for the dose escalation.

Fig. 2 shows a graph of TCS-AD_{total} mean change from baseline plotted as mean ± SEM. * $p < 0.05$, ** $p < 0.01$ versus baseline; + $p < 0.05$ versus corresponding placebo.

Fig. 3 shows graphs for each cohort and the placebo group in regard to itching data.

Fig. 4 shows images of before and after treatment of a 20 year old female with a small area of atopic dermatitis that had been present for about 1 month. It was treated with a 0.03% BMX-010 cream composition.

Fig. 5 shows an image of an atopic dermatitis lesion before treatment and 4 days after once daily treatment with a 0.03% BMX-010 gel composition.

Fig. 6 shows images of before and after treatment with a 0.1% BMX-010 gel composition.

Fig. 7 is an illustration showing a graph of BMX-010 efficacy data with a 0.1% BMX-010 gel composition compared to published Eucrisa™ data.

Fig. 8 is a schematic of a study design for twice daily dosing.

Detailed Description of Example Embodiments

The present invention is now described more fully hereinafter with reference to the accompanying drawings, in which embodiments of the invention are shown. This invention may, however, be embodied in many different forms and should not be construed as limited to the embodiments set forth herein; rather these embodiments are provided so that this disclosure will be thorough and complete and will fully convey the scope of the invention to those skilled in the art.

The terminology used in the description of the invention herein is for the purpose of describing particular embodiments only and is not intended to be limiting of the invention. As used in the description of the invention and the appended claims, the singular forms "a," "an" and "the" are intended to include the plural forms as well, unless the context clearly indicates otherwise.

Unless otherwise defined, all terms (including technical and scientific terms) used herein have the same meaning as commonly understood by one of ordinary skill in the art to which this invention belongs. It will be further understood that terms, such as those defined in commonly used dictionaries, should be interpreted as having a meaning that is consistent with their meaning in the context of the present application and relevant art and should not be interpreted in an idealized or overly formal sense unless expressly so defined herein. The terminology used in the description of the invention herein is for the purpose of describing particular embodiments only and is not intended to be limiting of the invention. All publications, patent applications, patents and other references mentioned herein are incorporated by reference in their entirety. In case of a conflict in terminology, the present specification is controlling.

Also as used herein, "and/or" refers to and encompasses any and all possible combinations of one or more of the associated listed items, as well as the lack of combinations when interpreted in the alternative ("or").

Unless the context indicates otherwise, it is specifically intended that the various features of the invention described herein can be used in any combination. Moreover, the present invention also contemplates that in some embodiments of the invention, any feature or combination of features set forth herein can be excluded or omitted. To illustrate, if the specification states that a complex comprises components A, B and C, it is specifically intended that any of A, B or C, or a combination thereof, can be omitted and disclaimed.

As used herein, the transitional phrase "consisting essentially of" (and grammatical variants) is to be interpreted as encompassing the recited materials or steps "and those that do

not materially affect the basic and novel characteristic(s)" of the claimed invention. *See, In re Herz*, 537 F.2d 549, 551-52, 190 U.S.P.Q. 461, 463 (CCPA 1976) (emphasis in the original); see also MPEP § 2111.03. Thus, the term "consisting essentially of" as used herein should not be interpreted as equivalent to "comprising."

The term "about," as used herein when referring to a measurable value such as an amount or concentration and the like, is meant to encompass variations of ± 10%, ± 5%, ± 1%, ± 0.5%, or even ± 0.1% of the specified value as well as the specified value. For example, "about X" where X is the measurable value, is meant to include X as well as variations of ± 10%, ± 5%, ± 1%, ± 0.5%, or even ± 0.1% of X. A range provided herein for a measureable value may include any other range and/or individual value therein.

"Alkyl" as used herein alone or as part of another group, refers to a straight or branched chain hydrocarbon containing from 1 to 10 carbon atoms. Representative examples of alkyl include, but are not limited to, methyl, ethyl, n-propyl, iso-propyl, n-butyl, sec-butyl, iso-butyl, tert-butyl, n-pentyl, isopentyl, neopentyl, n-hexyl, 3-methylhexyl, 2,2-dimethylpentyl, 2,3-dimethylpentyl, n-heptyl, n-octyl, n-nonyl, n-decyl, and the like. "Lower alkyl" as used herein, is a subset of alkyl and refers to a straight or branched chain hydrocarbon group containing from 1 to 4 carbon atoms. Representative examples of lower alkyl include, but are not limited to, methyl, ethyl, n-propyl, iso-propyl, n-butyl, iso-butyl, tert-butyl, and the like. The term "akyl" or "lower alkyl" is intended to include both substituted and unsubstituted alkyl or lower alkyl unless otherwise indicated and these groups may be substituted with groups selected from halo (*e.g.,* haloalkyl), alkyl, haloalkyl, alkenyl, alkynyl, cycloalkyl, cycloalkylalkyl, aryl, arylalkyl, heterocyclo, heterocycloalkyl, hydroxyl, alkoxy (thereby creating a polyalkoxy such as polyethylene glycol), alkenyloxy, alkynyloxy, haloalkoxy, cycloalkoxy, cycloalkylalkyloxy, aryloxy, arylalkyloxy, heterocyclooxy, heterocyclolalkyloxy, mercapto, alkyl-$S(O)_m$, haloalkyl-$S(O)_m$, alkenyl-$S(O)_m$, alkynyl-$S(O)_m$, cycloalkyl-$S(O)_m$, cycloalkylalkyl-$S(O)_m$, aryl-$S(O)_m$, arylalkyl-$S(O)_m$, heterocyclo-$S(O)_m$, heterocycloalkyl-$S(O)_m$, amino, carboxy, alkylamino, alkenylamino, alkynylamino, haloalkylamino, cycloalkylamino, cycloalkylalkylamino, arylamino, arylalkylamino, heterocycloamino, heterocycloalkylamino, disubstituted-amino, acylamino, acyloxy, ester, amide, sulfonamide, urea, alkoxyacylamino, aminoacyloxy, nitro or cyano where m= 0, 1, 2 or 3.

"Alkenyl" as used herein alone or as part of another group, refers to a straight or branched chain hydrocarbon containing from 1 to 10 carbon atoms (or in lower alkenyl 1 to 4 carbon atoms) which include 1 to 9 double bonds in the chain. Representative examples of

alkenyl include, but are not limited to, vinyl, 2-propenyl, 3-butenyl, 2-butenyl, 4-pentenyl, 3-pentenyl, 2-hexenyl, 3-hexenyl, 2,4-heptadiene, and the like. The term "alkenyl" or "lower alkenyl" is intended to include both substituted and unsubstituted alkenyl or lower alkenyl unless otherwise indicated and these groups may be substituted with groups as described in connection with alkyl and lower alkyl above.

"Alkynyl" as used herein alone or as part of another group, refers to a straight or branched chain hydrocarbon containing from 1 to 10 carbon atoms (or in lower alkynyl 1 to 4 carbon atoms) which include at least 1 triple bond in the chain. Representative examples of alkynyl include, but are not limited to, 2-propynyl, 3-butynyl, 2- butynyl, 4-pentynyl, 3-pentynyl, and the like. The term "alkynyl" or "lower alkynyl" is intended to include both substituted and unsubstituted alkynyl or lower alknynyl unless otherwise indicated and these groups may be substituted with the same groups as set forth in connection with alkyl and lower alkyl above.

"Cycloalkyl" as used herein alone or as part of another group, refers to a saturated or partially unsaturated cyclic hydrocarbon group containing from 3, 4 or 5 to 6, 7 or 8 carbons (which carbons may be replaced in a heterocyclic group as discussed below). Representative examples of cycloalkyl include, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, and cyclooctyl. These rings may be optionally substituted with additional substituents as described herein such as halo or lower alkyl.

"Heterocyclic group" or “heterocyclo” as used herein alone or as part of another group, refers to an aliphatic (e.g., fully or partially saturated heterocyclo) or aromatic (*e.g.,* heteroaryl) monocyclic- or a bicyclic-ring system having as ring members atoms of at least two different elements. Monocyclic ring systems are exemplified by any 5 or 6 membered ring containing 1, 2, 3, or 4 heteroatoms independently selected from oxygen, nitrogen and sulfur. The 5 membered ring has from 0-2 double bonds and the 6 membered ring has from 0-3 double bonds. Representative examples of monocyclic ring systems include, but are not limited to, azetidine, azepine, aziridine, diazepine, 1,3-dioxolane, dioxane, dithiane, furan, imidazole, imidazoline, imidazolidine, isothiazole, isothiazoline, isothiazolidine, isoxazole, isoxazoline, isoxazolidine, morpholine, oxadiazole, oxadiazoline, oxadiazolidine, oxazole, oxazoline, oxazolidine, piperazine, piperidine, pyran, pyrazine, pyrazole, pyrazoline, pyrazolidine, pyridine, pyrimidine, pyridazine, pyrrole, pyrroline, pyrrolidine, tetrahydrofuran, tetrahydrothiophene, tetrazine, tetrazole, thiadiazole, thiadiazoline, thiadiazolidine, thiazole, thiazoline, thiazolidine, thiophene, thiomorpholine, thiomorpholine sulfone, thiopyran, triazine, triazole, trithiane, and the like. Bicyclic ring systems are

exemplified by any of the above monocyclic ring systems fused to an aryl group as defined herein, a cycloalkyl group as defined herein, or another monocyclic ring system as defined herein. Representative examples of bicyclic ring systems include but are not limited to, for example, benzimidazole, benzothiazole, benzothiadiazole, benzothiophene, benzoxadiazole, benzoxazole, benzofuran, benzopyran, benzothiopyran, benzodioxine, 1,3-benzodioxole, cinnoline, indazole, indole, indoline, indolizine, naphthyridine, isobenzofuran, isobenzothiophene, isoindole, isoindoline, isoquinoline, phthalazine, purine, pyranopyridine, quinoline, quinolizine, quinoxaline, quinazoline, tetrahydroisoquinoline, tetrahydroquinoline, thiopyranopyridine, and the like. These rings include quaternized derivatives thereof and may be optionally substituted with groups selected from halo, alkyl, haloalkyl, alkenyl, alkynyl, cycloalkyl, cycloalkylalkyl, aryl, arylalkyl, heterocyclo, heterocycloalkyl, hydroxyl, alkoxy, alkenyloxy, alkynyloxy, haloalkoxy, cycloalkoxy, cycloalkylalkyloxy, aryloxy, arylalkyloxy, heterocyclooxy, heterocyclolalkyloxy, mercapto, alkyl-$S(O)_m$, haloalkyl-$S(O)_m$, alkenyl-$S(O)_m$, alkynyl-$S(O)_m$, cycloalkyl-$S(O)_m$, cycloalkylalkyl-$S(O)_m$, aryl-$S(O)_m$, arylalkyl-$S(O)_m$, heterocyclo-$S(O)_m$, heterocycloalkyl-$S(O)_m$, amino, alkylamino, alkenylamino, alkynylamino, haloalkylamino, cycloalkylamino, cycloalkylalkylamino, arylamino, arylalkylamino, heterocycloamino, heterocycloalkylamino, disubstituted-amino, acylamino, acyloxy, ester, amide, sulfonamide, urea, alkoxyacylamino, aminoacyloxy, nitro or cyano where m = 0, 1, 2 or 3.

"Aryl" as used herein alone or as part of another group, refers to a monocyclic carbocyclic ring system or a bicyclic carbocyclic fused ring system having one or more aromatic rings. Representative examples of aryl include, azulenyl, indanyl, indenyl, naphthyl, phenyl, tetrahydronaphthyl, and the like. The term "aryl" is intended to include both substituted and unsubstituted aryl unless otherwise indicated and these groups may be substituted with the same groups as set forth in connection with alkyl and lower alkyl above.

"Arylalkyl" as used herein alone or as part of another group, refers to an aryl group, as defined herein, appended to the parent molecular moiety through an alkyl group, as defined herein. Representative examples of arylalkyl include, but are not limited to, benzyl, 2-phenylethyl, 3-phenylpropyl, 2-naphth-2-ylethyl, and the like.

"Heteroaryl" as used herein is as described in connection with heterocyclo above.

"Alkoxy" as used herein alone or as part of another group, refers to an alkyl or lower alkyl group, as defined herein (and thus including substituted versions such as polyalkoxy), appended to the parent molecular moiety through an oxy group, -O-. Representative examples

of alkoxy include, but are not limited to, methoxy, ethoxy, propoxy, 2-propoxy, butoxy, tert-butoxy, pentyloxy, hexyloxy and the like.

"Halo" as used herein refers to any suitable halogen, including –F, -Cl, -Br, and –I.

"Mercapto" as used herein refers to an -SH group.

"Azido" as used herein refers to an $-N_3$ group.

"Cyano" as used herein refers to a -CN group.

"Formyl" as used herein refers to a -C(O)H group.

"Carboxylic acid" as used herein refers to a –C(O)OH group.

"Hydroxyl" as used herein refers to an –OH group.

"Nitro" as used herein refers to an $-NO_2$ group.

"Acyl" as used herein alone or as part of another group refers to a -C(O)R radical, where R is any suitable substituent such as aryl, alkyl, alkenyl, alkynyl, cycloalkyl or other suitable substituent as described herein.

"Alkylthio" as used herein alone or as part of another group, refers to an alkyl group, as defined herein, appended to the parent molecular moiety through a thio moiety, as defined herein. Representative examples of alkylthio include, but are not limited, methylthio, ethylthio, tert-butylthio, hexylthio, and the like.

"Amino" as used herein means the radical $-NH_2$.

"Alkylamino" as used herein alone or as part of another group means the radical –NHR, where R is an alkyl group.

"Arylalkylamino" as used herein alone or as part of another group means the radical –NHR, where R is an arylalkyl group.

"Disubstituted-amino" as used herein alone or as part of another group means the radical $-NR_aR_b$, where R_a and R_b are independently selected from the groups alkyl, haloalkyl, alkenyl, alkynyl, cycloalkyl, cycloalkylalkyl, aryl, arylalkyl, heterocyclo, heterocycloalkyl.

"Acylamino" as used herein alone or as part of another group means the radical $-NR_aR_b$, where R_a is an acyl group as defined herein and R_b is selected from the groups hydrogen, alkyl, haloalkyl, alkenyl, alkynyl, cycloalkyl, cycloalkylalkyl, aryl, arylalkyl, heterocyclo, heterocycloalkyl.

"Acyloxy" as used herein alone or as part of another group means the radical –OR, where R is an acyl group as defined herein.

"Ester" as used herein alone or as part of another group refers to a -C(O)OR radical, where R is any suitable substituent such as alkyl, cycloalkyl, alkenyl, alkynyl or aryl.

"Amide" as used herein alone or as part of another group refers to a $-C(O)NR_aR_b$ radical, where R_a and R_b are any suitable substituent such as alkyl, cycloalkyl, alkenyl, alkynyl or aryl.

"Sulfoxyl" as used herein refers to a compound of the formula –S(O)R, where R is any suitable substituent such as alkyl, cycloalkyl, alkenyl, alkynyl or aryl.

"Sulfonyl" as used herein refers to a compound of the formula –S(O)(O)R, where R is any suitable substituent such as alkyl, cycloalkyl, alkenyl, alkynyl or aryl.

"Sulfonate" as used herein refers to a compounnd of the formula –S(O)(O)OR, where R is any suitable substituent such as alkyl, cycloalkyl, alkenyl, alkynyl or aryl.

"Sulfonic acid" as used herein refers to a compound of the formula –S(O)(O)OH.

"Sulfonamide" as used herein alone or as part of another group refers to a $-S(O)_2NR_aR_b$ radical, where R_a and R_b are any suitable substituent such as H, alkyl, cycloalkyl, alkenyl, alkynyl or aryl.

"Urea" as used herein alone or as part of another group refers to an $-N(R_c)C(O)NR_aR_b$ radical, where R_a, R_b and R_c are any suitable substituent such as H, alkyl, cycloalkyl, alkenyl, alkynyl or aryl.

"Alkoxyacylamino" as used herein alone or as part of another group refers to an $-N(R_a)C(O)OR_b$ radical, where R_a, R_b are any suitable substituent such as H, alkyl, cycloalkyl, alkenyl, alkynyl or aryl.

"Aminoacyloxy" as used herein alone or as part of another group refers to an $-OC(O)NR_aR_b$ radical, where R_a and R_b are any suitable substituent such as H, alkyl, cycloalkyl, alkenyl, alkynyl or aryl.

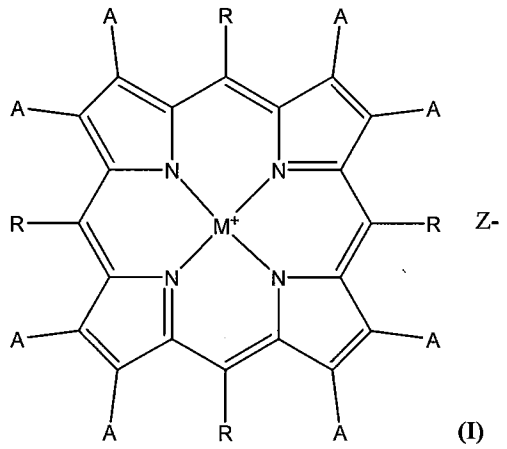
“Pharmaceutically acceptable” as used herein means that the compound, anion, or composition is suitable for administration to a subject to achieve the treatments described herein, without unduly deleterious side effects in light of the severity of the disease and necessity of the treatment.

As used herein, the terms “increase,” “increases,” “increased,” “increasing,” “improve,” “enhance,” and similar terms indicate an elevation in the specified parameter of at least about 5%, 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, 100%, 150%, 200%, 300%, 400%, 500% or more.

As used herein, the terms “reduce,” “reduces,” “reduced,” “reduction,” “inhibit,” and similar terms refer to a decrease in the specified parameter of at least about 5%, 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, 97%, or 100%.

Provided according to embodiments of the present invention are topical compositions comprising a meso-substituted metalloporphyrin. Compositions of the present invention may be used for the treatment of inflammatory skins conditions such as, e.g., atopic dermatitis, rosacea, acne, and/or plaque psoriasis. In some embodiments, a composition of the present invention is in the form of a gel, cream, ointment, solution, lotion, or foam. In some embodiments, the composition is in the form of a cream. The composition may be pharmaceutically acceptable.

A composition of the present invention may comprise a meso-substituted metalloporphyrin that is Ames negative. Multiple meso-substituted metalloporphyrins have been found to be Ames positive. Example meso-substituted metalloporphyrins include, but are not limited to, those having a structure represented by **Formula I**:



(I)

wherein:

each R is independently substituted or unsubstituted aryl, heteroaryl, cycloalkyl, or heterocycloalkyl;

each A is an independently selected hydrogen, or an electron-withdrawing or electron donating group (*e.g.,* is halogen, $-NO_2$ or -CHO),

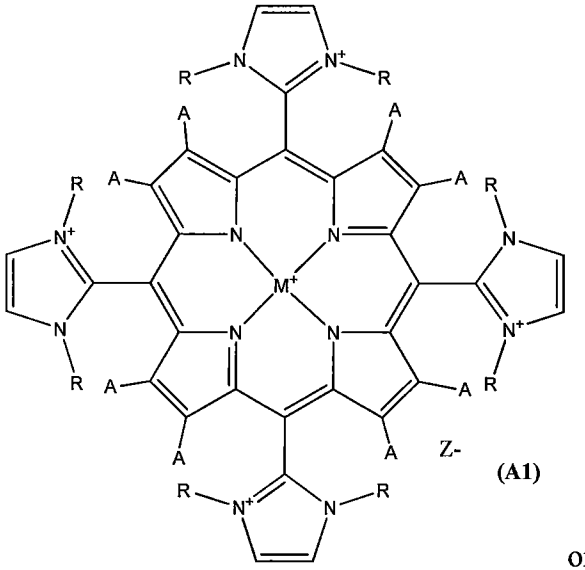
M is a metal (*e.g.,* selected from the group consisting of manganese, iron, copper, cobalt, nickel and zinc) or is absent (in which case a hydrogen is added to each of the two nitrogens required to correct valency), and

Z^- is a counterion (e.g., a halogen such as chlorine, fluorine, bromine, and/or iodine).

In some embodiments of **Formula I** above, each R is a heteroaryl or heterocycloalkyl, particularly those containing at least one or two nitrogen atoms in the heterocyclic ring (*e.g.,* pyrrolyl, imidazolyl, triazolyl, pyridyl, pyrimidyl, triazinyl, oxazolyl, thiazolyl, oxazinyl, thiazinyl, oxathiazinyl, etc.). In some embodiments, in a compound of **Formula I**, each R is

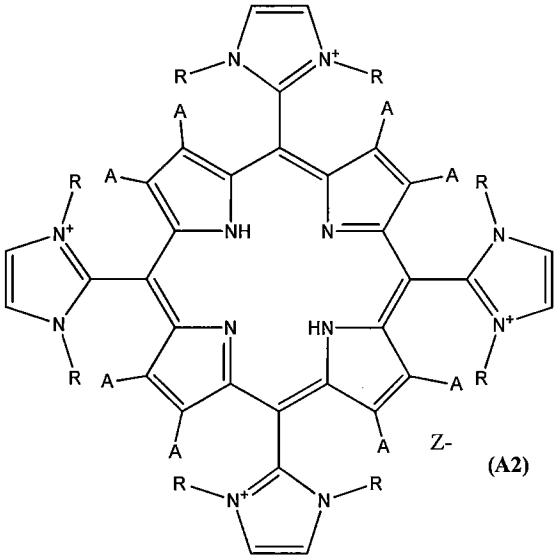
a heteroaryl or heterocycloalkyl that includes at least one nitrogen atom (or in some embodiments at least two nitrogen atoms) that is substituted (*e.g.*, quaternized) with a substituent such as described in connection with heterocyclic groups above (*e.g.*, substituted with alkyl, alkoxyalkyl, etc.).

In some embodiments, the meso-substituted metalloporphyrin is an alkyl substituted imidazole porphyrin, which may have a structure represented by **Formula A1** or **A2**:



(A1)

or



(A2)

wherein:

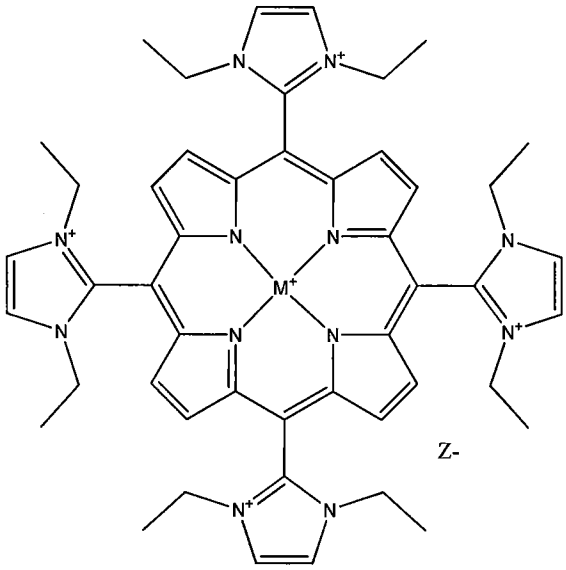
each R is $C_{1\text{-}12}$ alkyl (straight chain or branched), more preferably $C_{2\text{-}6}$ alkyl, and most preferably ethyl, propyl, butyl, or pentyl (straight chain or branched);

each A is, independently, hydrogen or an electron withdrawing group (*e.g.*, halogen, -NO_2 or -CHO),

M is metal selected from the group consisting of manganese, iron, copper, cobalt, nickel and zinc, and

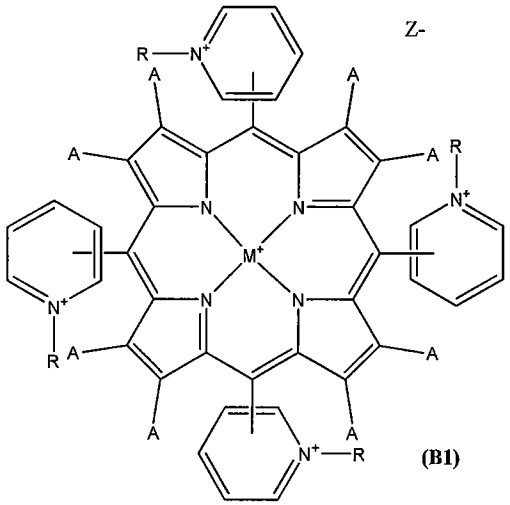
Z^- is a counterion.

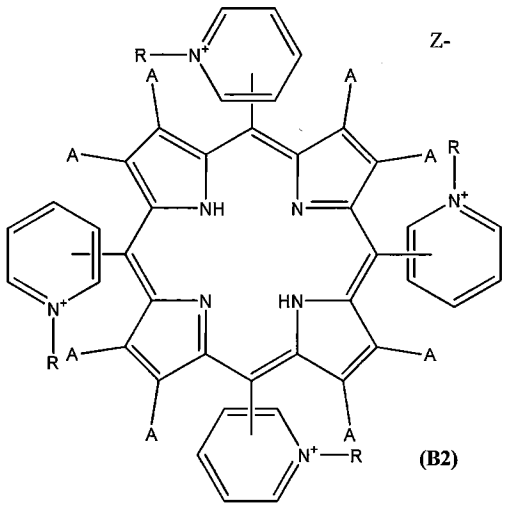
In some embodiments, the meso-substituted metalloporphyrin has the structure:



wherein Z- is a counterion.

In some embodiments, the meso-substituted metalloporphyrin is an alkyl substituted pyridyl porphyrin, which may have a structure represented by **Formula B1** or **B2**:





or

or

wherein:

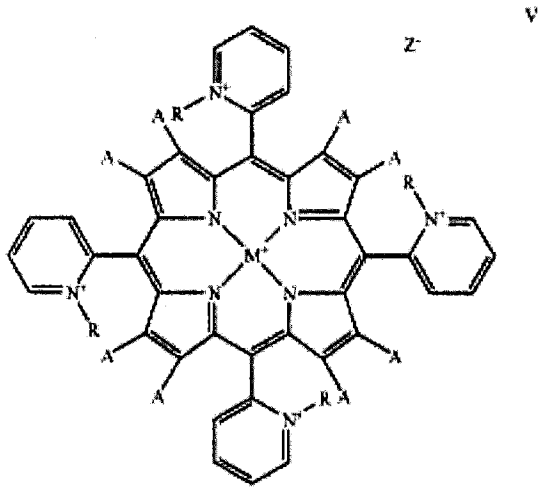
each R is C_{1-12} alkyl (straight chain or branched), more preferably C_{2-6} alkyl, and most preferably ethyl, propyl, butyl, or pentyl (straight chain or branched);

each A is, independently, hydrogen or an electron withdrawing group (*e.g.,* halogen, -NO_2 or -CHO),

M is metal selected from the group consisting of manganese, iron, copper, cobalt, nickel and zinc, and

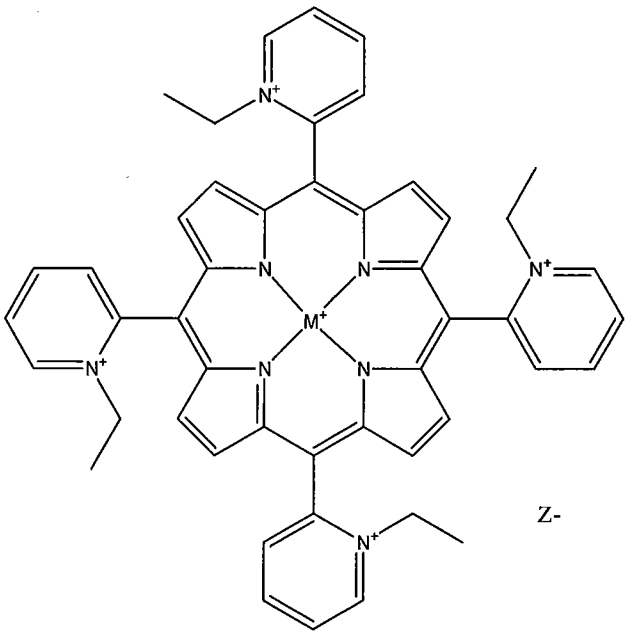
Z^- is a counterion.

In some embodiments, the meso-substituted metalloporphyrin has a structure represented by **Formula V:**



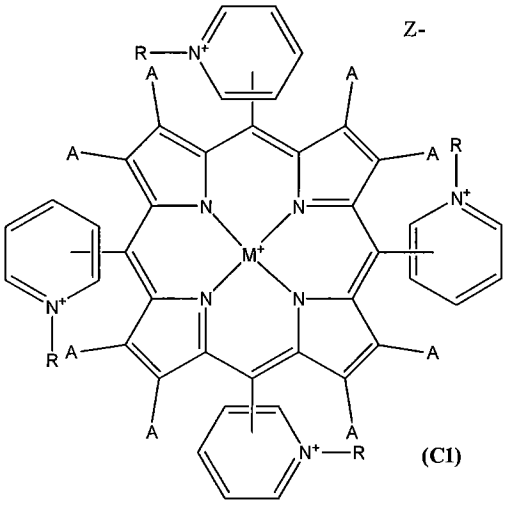
wherein each R , A, M, and Z is as given in connection with **Formula B1** and **B2** above.

In some embodiments, the meso-substituted metalloporphyrin has the structure:

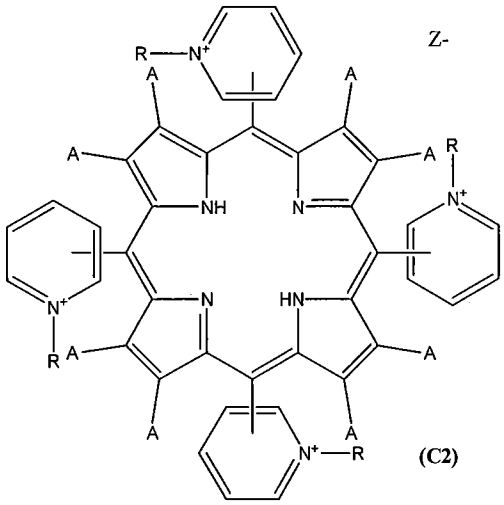


wherein Z^- is a counterion.

In some embodiments, the meso-substituted metalloporphyrin is an alkoxyalkyl substituted pyridyl porphyrin, which may have a structure represented by **Formula C1** or **C2**:



(C1)



(C2)

or

wherein:

each R is $—(CH_2)_mCH_2OX$;

m is 1 or 2, preferably 1;

each X is C_{1-12} alkyl (straight chain or branched), more preferably C_{2-6} alkyl, and most preferably ethyl, propyl, butyl, or pentyl (straight chain or branched).

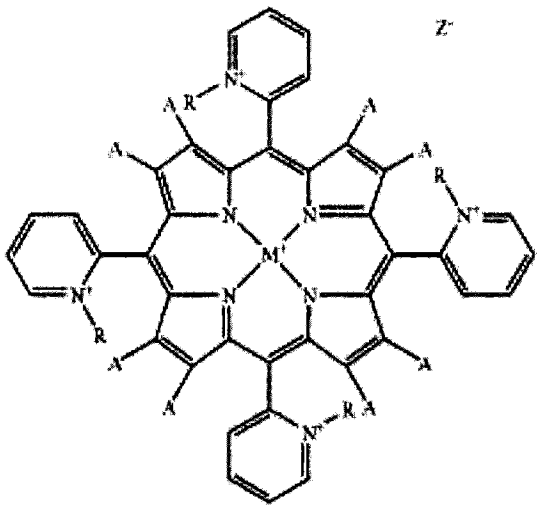
each A is, independently, hydrogen or an electron withdrawing group (*e.g.*, halogen, NO_2 or CHO),

M is metal selected from the group consisting of manganese, iron, copper, cobalt, nickel and zinc, and

Z^- is a counterion.

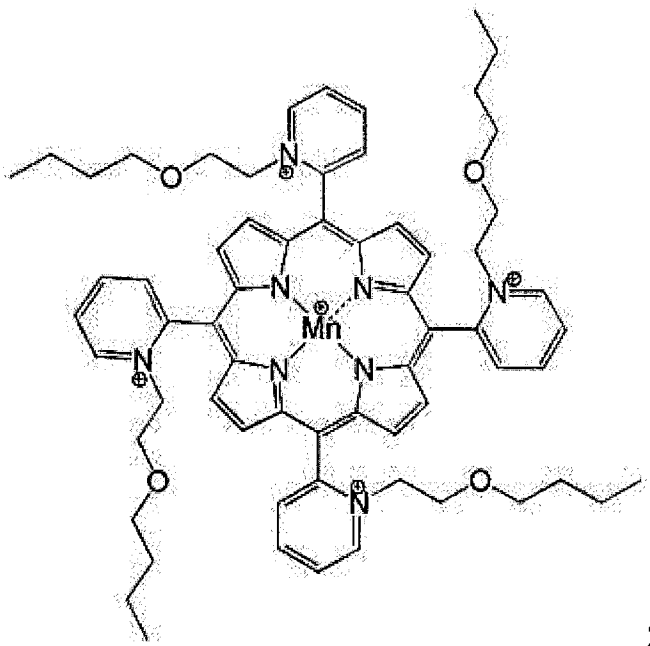
In some embodiments, the meso-substituted metalloporphyrin has a structure represented by **FormulaV:**

V



wherein each R , A, M, and Z is as given in connection with **Formula C1** and **C2** above.

In some embodiments, the meso-substituted metalloporphyrin has the structure:

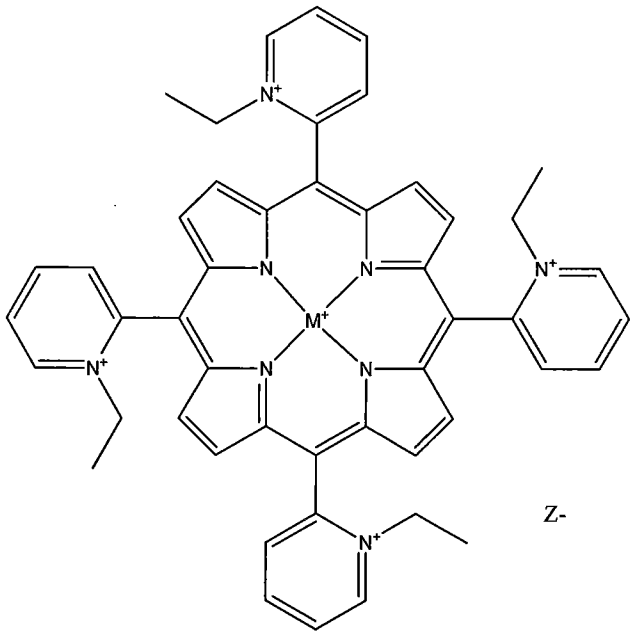


Z^- ,

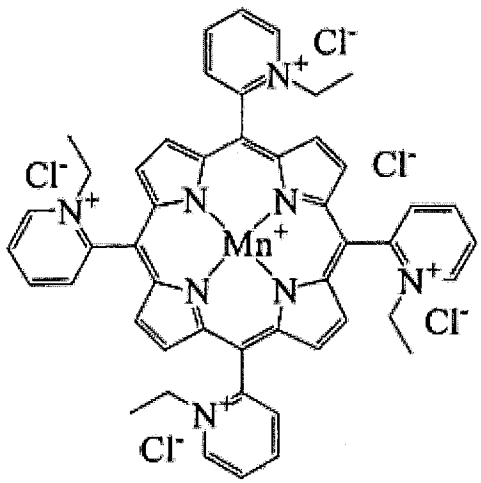
wherein Z^- is a counterion.

The meso-substituted metalloporphyrins disclosed herein can, as noted above, be prepared in the form of their salts or pharmaceutically acceptable salts, *e.g.,* to provide a compound or composition including a counterion as noted above. Pharmaceutically acceptable salts are salts that retain the desired biological activity of the parent compound and do not impart undesired toxicological effects. Examples of such salts are (a) acid addition salts formed with inorganic acids, for example hydrochloric acid, hydrobromic acid, sulfuric acid, phosphoric acid, nitric acid and the like; and salts formed with organic acids such as, for example, acetic acid, oxalic acid, tartaric acid, succinic acid, maleic acid, fumaric acid, gluconic acid, citric acid, malic acid, ascorbic acid, benzoic acid, tannic acid, palmitic acid, alginic acid, polyglutamic acid, naphthalenesulfonic acid, methanesulfonic acid, p-toluenesulfonic acid, naphthalenedisulfonic acid, polygalacturonic acid, and the like; (b) salts formed from elemental anions such as chlorine, bromine, and iodine, and (c) salts derived from bases, such as ammonium salts, alkali metal salts such as those of sodium and potassium, alkaline earth metal salts such as those of calcium and magnesium, and salts with organic bases such as dicyclohexylamine and N-methyl-D-glucamine.

In some embodiments, the meso-substituted metalloporphyrin is MnTE-2-PyP^{5+} and has the structure:



wherein M^+ is manganese and Z^- is a counterion (e.g., a halogen such as chlorine, fluorine, bromine, and/or iodine). In some embodiments, the meso-substituted metalloporphyrin is BMX-010, which has a structure represented by **Formula VI**:



(VI)

The meso-substituted metalloporphyrin may be present in a composition of the present invention at a concentration in a range of about 0.005% to about 1% by weight of the composition times the activity equivalent of BMX-010. Thus, when the meso-substituted metalloporphyrin is BMX-010, the meso-substituted metalloporphyrin may be present in the composition at a concentration in a range of about 0.005% to about 1% by weight of the composition. When referring to the activity equivalent of BMX-010, activity equivalent is determined according to methods known to those of skill, such as, but not limited to,

determined using a cytochrome c assay and/or pulse radiolysis (Spasojevic, Ivan, et al., *Inorganic Chemistry*, Vol. 40, No. 4, 2001, 726-739). For BMX-010, the calculated activity is 7676 units/mg by the cytochrome C assay. Accordingly, a dose of a meso-substituted metalloporphyrin (e.g., an Ames negative meso-substituted metalloporphyrin) that is equivalent to 0.01 – 0.1% of BMX-010 will consist of 767.6 to 7676 activity units per ml of the composition. When the meso-substituted metalloporphyrin is BMX-010, the composition may be administered to the subject with the meso-substituted metalloporphyrin present in an amount of about 0.005% to about 1% by weight of the composition. Accordingly, the activity equivalent of BMX-010 is 1 when the meso-substituted metalloporphyrin is BMX-010. Alternatively, when a meso-substituted metalloporphyrin is 20% less active than BMX-010, the activity equivalent of BMX-010 is 1.25, so the dosage may be determined by taking 0.005 times 1.25 and 1 mg times 1.25 to get the loading dose range (e.g., about 0.00625% to about 1.25% by weight of the composition). In some embodiments, the composition provides the meso-substituted metalloporphyrin in an amount that minimizes discoloration of the skin (e.g., yellow and/or brown discoloration of the skin).

The inventors of the present invention surprisingly discovered that a low dose of a meso-substituted metalloporphyrin (e.g., BMX-010) may treat and/or prevent an inflammatory skin condition, such as, but not limited to, atopic dermatitis, in a subject quickly and/or with improved results (e.g., improved efficacy and/or response rate) compared to a current commercial treatment. In some embodiments, a method and/or composition of the present invention may administer a low dose of a meso-substituted metalloporphyrin (e.g., BMX-010) and may treat and/or prevent an inflammatory skin condition, such as, but not limited to, atopic dermatitis, in a subject quickly and/or with improved results (e.g., improved efficacy and/or response rate) compared to a current commercial treatment, which was unexpected. For example, a method and/or composition of the present invention may alleviate one or more symptoms of the inflammatory skin condition within seconds, minutes, or days and/or provide an improved response to treatment (e.g., decreased lesion size and/or itching) compared to a current commercial treatment.

A composition of the present invention may comprise a meso-substituted metalloporphyrin (e.g., BMX-010), water, a hydrophobic base, a fatty alcohol, a polyhydric alcohol, a fatty acid ester, a surfactant, a preservative, and/or a colorant.

A composition of the present invention may comprise a meso-substituted metalloporphyrin at a concentration in a range of about 0.005% to about 1% by weight of the composition times the activity equivalent of BMX-010. In some embodiments, the meso-

substituted metalloporphyrin is present in the composition at a concentration of about 0.01%, 0.03%, or 0.05% to about 0.1%, 0.3%, or 0.5% by weight of the composition times the activity equivalent of BMX-010. In some embodiments, a composition of the present invention comprises a meso-substituted metalloporphyrin in a concentration of about 0.01%, 0.02%, 0.03%, 0.04%, 0.05%, 0.06%, 0.07%, 0.08%, 0.09%, 0.1%, 0.2%, 0.3%, 0.4%, 0.5%, 0.6%, 0.7%, 0.8%, 0.9%, or 1% by weight of the composition times the activity equivalent of BMX-010.

In some embodiments, water is present in the composition. Water may be present in the composition in an amount of about 40% to about 65% by weight of the composition. In some embodiments, water is present in an amount of about 40%, 41%, 42%, 43%, 44%, 45%, 46%, 47%, 48%, 49%, 50%, 51%, 52%, 53%, 54%, 55%, 56%, 57%, 58%, 59%, 60%, 61%, 62%, 63%, 64%, or 65% by weight of the composition. In some embodiments, the water makes up the balance of the composition to total 100% by weight of the composition.

A buffer may be present in a composition of the present invention. Thus, in some embodiments, a composition of the present invention is buffered. In some embodiments, an aqueous buffer solution is present in the composition in an amount of about 40%, 41%, 42%, 43%, 44%, 45%, 46%, 47%, 48%, 49%, 50%, 51%, 52%, 53%, 54%, 55%, 56%, 57%, 58%, 59%, 60%, 61%, 62%, 63%, 64%, or 65% by weight of the composition. In some embodiments, an aqueous buffer solution makes up the balance of the composition to total 100% by weight of the composition. In some embodiments, an aqueous buffer solution may be used rather than water alone (e.g., to make up the balance of the composition to total 100% by weight of the composition). One or more (e.g., 1, 2, 3, 4, or more) buffering agent(s) (e.g., an acetate, acetic acid, citric acid, etc.) may be present in a composition of the present invention. Example buffer solutions include, but are not limited to, acetate buffer solutions (e.g., sodium acetate buffer solutions), phosphate buffer solutions, and citrate buffer solution. An aqueous buffer solution may have a concentration of about 5, 10, 15, or 20 mM to about 25, 50, 75, or 100 mM. In some embodiments, the composition comprises an acetate buffer, optionally wherein the acetate is present in the composition at a concentration of about 5, 10, 15, or 20 mM to about 25, 50, 75, or 100 mM.

One or more (e.g., 1, 2, 3, 4, or more) hydrophobic base(s) may be present in a composition of the present invention. Example hydrophobic bases include, but are not limited to, mineral oil, petrolatum, and any combination thereof. In some embodiments, a hydrophobic base may be present in the composition in an amount of about 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%, 32%, 33%, 34%, or 35% by weight of the composition. In some embodiments, a hydrophobic base may be present in the composition in an amount of about 1%, 2%, 3%, 4%, or 5% to about 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%, 32%, 33%, 34%, or 35% by weight of the composition. In some embodiments, the total amount of the one or more hydrophobic base(s) in the composition is about 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%, 32%, 33%, 34%, or 35% by weight of the composition. In some embodiments, the total amount of the one or more hydrophobic base(s) in the composition is about 1%, 2%, 3%, 4%, 5%, 6%, 7%, 8%, 9%, 10%, 11%, 12%, 13%, 14%, 15%, 16%, 17%, 18%, 19%, or 20% to about 21%, 22%, 23%, 24%, 25%, 26%, 27%, 28%, 29%, 30%, 31%, 32%, 33%, 34%, or 35% by weight of the composition.

One or more (e.g., 1, 2, 3, 4, or more) fatty alcohol(s) may be present in a composition of the present invention. Example fatty alcohols include, but are not limited to, cetostearyl alcohol. In some embodiments, a fatty alcohol may be present in the composition in an amount of about 1%, 2%, 3%, 4%, 5%, 6%, 7%, 8%, 9%, 10%, 11%, 12%, 13%, 14%, 15%, 16%, 17%, 18%, 19%, or 20% by weight of the composition. In some embodiments, a fatty alcohol may be present in the composition in an amount of about 1%, 2%, 3%, 4%, 5%, 6%, 7%, 8%, 9%, or 10% to about 11%, 12%, 13%, 14%, 15%, 16%, 17%, 18%, 19%, or 20% by weight of the composition. In some embodiments, the total amount of the one or more fatty alcohol(s) in the composition is about 1%, 2%, 3%, 4%, 5%, 6%, 7%, 8%, 9%, 10%, 11%, 12%, 13%, 14%, 15%, 16%, 17%, 18%, 19%, or 20% by weight of the composition. In some embodiments, the total amount of the one or more fatty alcohol(s) in the composition is about 1%, 2%, 3%, 4%, 5%, 6%, 7%, 8%, 9%, or 10% to about 11%, 12%, 13%, 14%, 15%, 16%, 17%, 18%, 19%, or 20% by weight of the composition.

One or more (e.g., 1, 2, 3, 4, or more) polyhydric alcohol(s) may be present in a composition of the present invention. Example polyhydric alcohols include, but are not limited to, glycols such as, e.g., propylene glycol. In some embodiments, a polyhydric alcohol may be present in the composition in an amount of about 1%, 2%, 3%, 4%, 5%, 6%, 7%, 8%, 9%, 10%, 11%, 12%, 13%, 14%, or 15% by weight of the composition. In some embodiments, a polyhydric alcohol may be present in the composition in an amount of about 1%, 2%, 3%, 4%, or 5% to about 6%, 7%, 8%, 9%, 10%, 11%, 12%, 13%, 14%, or 15% by weight of the composition. In some embodiments, the total amount of the one or more

polyhydric alcohol(s) in the composition is about 1%, 2%, 3%, 4%, 5%, 6%, 7%, 8%, 9%, 10%, 11%, 12%, 13%, 14%, or 15% by weight of the composition. In some embodiments, the total amount of the one or more polyhydric alcohol(s) in the composition is about 1%, 2%, 3%, 4%, or 5% to about 6%, 7%, 8%, 9%, 10%, 11%, 12%, 13%, 14%, or 15% by weight of the composition.

One or more (e.g., 1, 2, 3, 4, or more) fatty acid ester(s) may be present in a composition of the present invention. Example fatty acid esters include, but are not limited to, isopropyl palmitate. In some embodiments, a fatty acid ester may be present in the composition in an amount of about 0.01%, 0.02%, 0.03%, 0.04%, 0.05%, 0.06%, 0.07%, 0.08%, 0.09%, 0.1%, 0.2%, 0.3%, 0.4%, 0.5%, 0.6%, 0.7%, 0.8%, 0.9%, 1%, 1.5%, 2%, 2.5%, 3%, 3.5%, 4%, 4.5%, or 5% by weight of the composition. In some embodiments, a fatty acid ester may be present in the composition in an amount of about 0.01%, 0.02%, 0.03%, 0.04%, 0.05%, 0.06%, 0.07%, 0.08%, 0.09%, 0.1%, 0.2%, 0.3%, 0.4%, or 0.5% to about 0.6%, 0.7%, 0.8%, 0.9%, 1%, 1.5%, 2%, 2.5%, 3%, 3.5%, 4%, 4.5%, or 5% by weight of the composition. In some embodiments, the total amount of the one or more fatty acid ester(s) in the composition is about 0.01%, 0.02%, 0.03%, 0.04%, 0.05%, 0.06%, 0.07%, 0.08%, 0.09%, 0.1%, 0.2%, 0.3%, 0.4%, 0.5%, 0.6%, 0.7%, 0.8%, 0.9%, 1%, 1.5%, or 2%, 2.5%, 3%, 3.5%, 4%, 4.5%, or 5% by weight of the composition. In some embodiments, the total amount of the one or more fatty acid ester(s) in the composition is about 0.01%, 0.02%, 0.03%, 0.04%, 0.05%, 0.06%, 0.07%, 0.08%, 0.09%, 0.1%, 0.2%, 0.3%, 0.4%, or 0.5% to about 0.6%, 0.7%, 0.8%, 0.9%, 1%, 1.5%, or 2%, 2.5%, 3%, 3.5%, 4%, 4.5%, or 5% by weight of the composition.

One or more (e.g., 1, 2, 3, 4, or more) surfactant(s) may be present in a composition of the present invention. Example surfactants include, but are not limited to, non-ionic surfactants such as, e.g., Tween-20 (polysorbate-20), Tween-80 (polysorbate-80), and any combination thereof. In some embodiments, a surfactant may be present in the composition in an amount of about 0.01%, 0.02%, 0.03%, 0.04%, 0.05%, 0.06%, 0.07%, 0.08%, 0.09%, 0.1%, 0.2%, 0.3%, 0.4%, 0.5%, 0.6%, 0.7%, 0.8%, 0.9%, 1%, 1.5%, 2%, 2.5%, 3%, 3.5%, 4%, 4.5%, 5%, 5.5%, 6%, 6.5%, 7%, 7.5%, 8%, 8.5%, 9%, 9.5%, or 10% by weight of the composition. In some embodiments, a surfactant may be present in the composition in an amount of about 0.01%, 0.02%, 0.03%, 0.04%, 0.05%, 0.06%, 0.07%, 0.08%, 0.09%, 0.1%, 0.2%, 0.3%, 0.4%, or 0.5% to about 0.6%, 0.7%, 0.8%, 0.9%, 1%, 1.5%, 2%, 2.5%, 3%, 3.5%, 4%, 4.5%, 5%, 5.5%, 6%, 6.5%, 7%, 7.5%, 8%, 8.5%, 9%, 9.5%, or 10% by weight of the composition. In some embodiments, the total amount of the one or more surfactants(s) in

the composition is about 0.01%, 0.02%, 0.03%, 0.04%, 0.05%, 0.06%, 0.07%, 0.08%, 0.09%, 0.1%, 0.2%, 0.3%, 0.4%, 0.5%, 0.6%, 0.7%, 0.8%, 0.9%, 1%, 1.5%, 2%, 2.5%, 3%, 3.5%, 4%, 4.5%, 5%, 5.5%, 6%, 6.5%, 7%, 7.5%, 8%, 8.5%, 9%, 9.5%, or 10% by weight of the composition. In some embodiments, the total amount of the one or more surfactants(s) in the composition is about 0.01%, 0.02%, 0.03%, 0.04%, 0.05%, 0.06%, 0.07%, 0.08%, 0.09%, 0.1%, 0.2%, 0.3%, 0.4%, or 0.5% to about 0.6%, 0.7%, 0.8%, 0.9%, 1%, 1.5%, 2%, 2.5%, 3%, 3.5%, 4%, 4.5%, 5%, 5.5%, 6%, 6.5%, 7%, 7.5%, 8%, 8.5%, 9%, 9.5%, or 10% by weight of the composition. In some embodiments, a surfactant is not present in the composition.

One or more (e.g., 1, 2, 3, 4, or more) preservatives(s) may be present in a composition of the present invention. Example preservatives include, but are not limited to, imidazolidinyl urea, methylparaben, propylparaben, and any combination thereof. In some embodiments, a preservative may be present in the composition in an amount of about 0.01%, 0.02%, 0.03%, 0.04%, 0.05%, 0.06%, 0.07%, 0.08%, 0.09%, 0.1%, 0.2%, 0.3%, 0.4%, 0.5%, 0.6%, 0.7%, 0.8%, 0.9%, 1%, 1.5%, or 2% by weight of the composition. In some embodiments, a preservative may be present in the composition in an amount of about 0.01%, 0.02%, 0.03%, 0.04%, or 0.05% to about 0.06%, 0.07%, 0.08%, 0.09%, 0.1%, 0.2%, 0.3%, 0.4%, 0.5%, 0.6%, 0.7%, 0.8%, 0.9%, 1%, 1.5%, or 2% by weight of the composition. In some embodiments, the total amount of the one or more preservative(s) in the composition is about 0.01%, 0.02%, 0.03%, 0.04%, 0.05%, 0.06%, 0.07%, 0.08%, 0.09%, 0.1%, 0.2%, 0.3%, 0.4%, 0.5%, 0.6%, 0.7%, 0.8%, 0.9%, 1%, 1.5%, or 2% by weight of the composition. In some embodiments, the total amount of the one or more preservative(s) in the composition is about 0.01%, 0.02%, 0.03%, 0.04%, 0.05%, 0.06%, 0.07%, 0.08%, 0.09%, or 0.1% to about 0.2%, 0.3%, 0.4%, 0.5%, 0.6%, 0.7%, 0.8%, 0.9%, 1%, 1.5%, or 2% by weight of the composition.

One or more (e.g., 1, 2, 3, 4, or more) colorant(s) and/or pigment(s) may be present in a composition of the present invention. Example colorants and/or pigments include, but are not limited to, titanium dioxide and/or iron oxide. In some embodiments, a colorant and/or pigment may be present in the composition in an amount of about 0.5%, 1%, 2%, 3%, 4%, 5%, 6%, 7%, 8%, 9%, or 10% by weight of the composition. In some embodiments, a colorant and/or pigment may be present in the composition in an amount of about 0.5%, 1%, 2%, 3%, 4%, or 5% to about 6%, 7%, 8%, 9%, or 10% by weight of the composition. In some embodiments, the total amount of the one or more colorant(s) and/or pigment(s) in the composition is about 0.5%, 1%, 2%, 3%, 4%, 5%, 6%, 7%, 8%, 9%, or 10% by weight of the

composition. In some embodiments, the total amount of the one or more colorant(s) and/or pigment(s) in the composition is about 0.5%, 1%, 2%, 3%, 4%, or 5% to about 6%, 7%, 8%, 9%, or 10% by weight of the composition.

A composition of the present invention may have a pH of about 3, 3.5, 4, 4.5, or 5 to about 5.5, 6, 6.5, or 7. In some embodiments, the composition has a pH of about 3, 3.5, 4, 4.5, 5, 5.5, 6, 6.5, or 7. In some embodiments, a composition of the present invention comprises a meso-substituted metalloporphyrin (e.g., MnTE-2-PyP^{5+}), mineral oil, petrolatum, cetostearyl alcohol, propylene glycol, Tween-20, Tween-80, isopropyl palmitate, imidazolidinyl urea, methylparaben, and/or propylparaben. In some embodiments, the meso-substituted metalloporphyrin is BMX-010. In some embodiments, a composition of the present invention comprises a meso-substituted metalloporphyrin (e.g., MnTE-2-PyP^{5+}), an acetate (e.g., sodium acetate and/or potassium acetate), mineral oil, petrolatum, cetostearyl alcohol, propylene glycol, Tween-20, isopropyl palmitate, imidazolidinyl urea, methylparaben, and/or propylparaben. In some embodiments, the composition has a pH of about 5.

A composition of the present invention may be in the form of a cream. In some embodiments, a cream of the present invention may maintain its physical integrity (e.g., does not separate) and/or its viscosity over a period of time. In some embodiments, the cream may remain as one phase and may not separate (e.g., into at least two phases) after a period of time when the cream is present in an unopened and/or opened container and stored at ambient conditions. In some embodiments, the cream does not separate into at least two distinct phases after about 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, or 30 days, weeks, and/or months from initial formation of the cream when stored at ambient temperature, ambient pressure, and 75% room humidity. In some embodiments, the cream does not separate into at least two distinct phases after about 1, 2, 3, 4, 5, or 6 days, weeks, and/or months to about 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, or 30 days, weeks, and/or months from initial formation of the cream when stored at ambient temperature, ambient pressure, and 75% room humidity. In some embodiments, a composition of the present invention does not separate into a liquid layer and a solid or semi-solid layer and/or into a water layer and an oil layer after about 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, or 30 days, weeks, and/or months from initial formation of the composition when stored at ambient temperature , ambient pressure, and 75% room humidity.

In some embodiments, a composition of the present invention has a viscosity of about 2,000, 5,000, 10,000, 15,000, 20,000, 25,000, 30,000, 35,000, 40,000, 45,000, 50,000, 55,000, 60,000, 65,000, or 70,000 cP, optionally when the composition is in the form of a cream and/or after about 1, 2, 3, 4, 5, or 6 days, weeks, and/or months from initial formation of the composition when stored at ambient temperature, ambient pressure, and 75% room humidity. In some embodiments, a composition of the present invention has a viscosity of about 2,000, 3,000, 4,000, or 5,000 cP to about 6,000, 7,000, 8,000, 9,000, 10,000, 11,000, 12,000, 13,000, 14,000, 15,000, 16,000, 17,000, 18,000, 19,000, or 20,000 cP, optionally when the composition is in the form of a cream and/or after about 1, 2, 3, 4, 5, or 6 days, weeks, and/or months from initial formation of the composition when stored at ambient temperature, ambient pressure, and 75% room humidity. In some embodiments, a composition of the present invention has a viscosity of about 20,000, 25,000, 30,000, or 35,000 cP to about 40,000, 45,000, 50,000, 55,000, 60,000, 65,000, or 70,000 cP, optionally when the composition is in the form of a cream and/or after about 1, 2, 3, 4, 5, or 6 days, weeks, and/or months from initial formation of the composition when stored at ambient temperature, ambient pressure, and 75% room humidity. Viscosity can be measured using methods known to those of skill in the art such as, for example, using a Brookfield viscometer (e.g., using a Brookfield LVDV-E viscosity, small sample chamber, spindle 25), optionally at 3 rpm, 2 minutes, and ambient temperature.

In some embodiments, the viscosity of a composition of the present invention at two different points in time changes by less than about 75% (e.g., less than about 70%, 65%, 60%, 55%, 50%, 45%, 40%, 35%, 30%, 25%, 20%, 15%, 10%, 5%, or 1%). In some embodiments, the two different points in time are a first time at initial formulation or at 1, 2, 3, or 4 days after initial formulation and a second time at 5, 6, 7, 8, 9, 10, 11, 12, or more days after initial formulation.

MnTE-2-PyP^{5+} is a manganese (Mn) porphyrin drug. MnTE-2-PyP^{5+} may be useful as an anti-inflammatory agent and/or may catalytically inactivate a range of reactive oxygen species (ROS), including peroxynitrite and superoxide anion. MnTE-2-PyP may exhibit extremely high enzymatic redox activity for a broad range of oxidant species including O_2^-, H_2O_2, and $ONOO^-$ (ROS). MnTE-2-PyP^{5+} may have catalytic antioxidant activity capable of scavenging ROS as well as the mimicking of superoxide dismutase. Unlike other antioxidants, this class of agents can be catalytic and may repetitively eliminate ROS. MnTE-2-PyP^{5+} may act as a scavenger in the cell cytoplasm, as in the context of reduced TACE oxidation and yet may function as an oxidizer in the nucleus, inhibiting the reduction

of the p50 subunit of NF-κB and effectively blocking DNA binding. MnTE-2-PyP^{5+} and other metalloporphyrin compounds may exhibit an unexpected potency in inflammatory injury models at doses 100 to 1000 times less than would be expected if they were acting primarily as stochiometric antioxidants.

T cells may become hypo-responsive after MnTE-2-PyP^{5+} treatment. MnTE-2-PyP^{5+} treatment with a composition of the present invention may promote metabolic quiescence, impede diabetogenic autoimmune responses by restricting the metabolic pathways for energy production and/or affect anabolic processes necessary for cell proliferation. This metabolic reduction may decrease T cell differentiation, returning T cells to stasis or quiescence, all while retaining viability.

In some embodiments, a meso-substituted metalloporphyrin (e.g., MnTE-2-PyP^{5+}) may modulate Th1 cells and/or effector cytokine production and/or protect islets during isolation for transplantation. "Modulate," "modulating," and grammatical variations thereof as used herein refer to an increase or reduction in the amount and/or activity of a component (e.g., cytokine, mediator, etc. and/or a component involved in inflammation) in a subject compared to the amount and/or activity of the component in the absence of a method of the present invention (e.g., the amount and/or activity of the component prior to a method of the present invention, such as, e.g., prior to administering a composition of the present invention to the subject).

In some embodiments, a composition and/or method of the present invention may modulate inflammatory cells such as, but not limited to, lymphocytes, monocytes, macrophages, neutrophils, eosinophils, and/or basophils. In some embodiments, a composition and/or method of the present invention may reduce infiltration of one or more different inflammatory cells to a skin lesion.

In some embodiments, a composition and/or method of the present invention may modulate one or more cytokines (e.g., pro-inflammatory cytokines) and/or pharmacologic mediators such as, but not limited to, TNF, IL-5, IL-13, IL-18, IL-22, IL-23, IL-36, and/or those associated with diseases of the skin. In some embodiments, a composition and/or method of the present invention may reduce the expression of and/or down regulate one or more pro-inflammatory cytokines and/or pharmacologic mediators.

In some embodiments, a composition and/or method of the present invention may modulate the expression of one or more genes such as, but not limited to, pro-inflammatory genes (e.g., NF-κB axis) and/or genes associated with an inflammatory skin disease. In some embodiments, a composition and/or method of the present invention may reduce the

expression of one or more genes such as, but not limited to, pro-inflammatory genes (e.g., NF-κB axis) and/or genes associated with an inflammatory skin disease.

In some embodiments, a composition (e.g., a composition comprising MnTE-2-PyP^{5+}) and/or method of the present invention may reduce NF-κB activation and//or CD8 T cell effector function.

According to some embodiments of the present invention provided are methods of treating a dermatological condition in a subject comprising topically administering to the skin of a subject a composition of the present invention. In some embodiments, a method of the present invention comprises topically administering to the skin of a subject a composition comprising a meso-substituted metalloporphyrin, wherein the meso-substituted metalloporphyrin is Ames negative and is present in the composition at a concentration of about 0.005% to about 1% by weight of the composition. In some embodiments, the meso-substituted metalloporphyrin is MnTE-2-PyP^{5+}.

The dermatological condition may be an inflammatory skin condition. Example dermatological conditions include, but are not limited to, eczema (e.g., atopic dermatitis), psoriasis, rosacea, acne, and/or arthropod bites or stings.

In some embodiments, a method of treating atopic dermatitis is provided, the method comprising topically administering to the skin of a subject a composition comprising a meso-substituted metalloporphyrin, wherein the meso-substituted metalloporphyrin is present in the composition at a concentration of about 0.005% to about 1% by weight of the composition and is MnTE-2-PyP^{5+}.

A method of the present invention may locally deliver the meso-substituted metalloporphyrin to the skin of the subject. In some embodiments, the meso-substituted metalloporphyrin is not systemically absorbed and/or has low distribution to the brain and/or other organs. In some embodiments, no more than about 2% or 1% of the amount of the meso-substituted metalloporphyrin administered to the subject is systemically absorbed. In some embodiments, a meso-substituted metalloporphyrin and/or a metabolite and/or derivative thereof may be systemically absorbed in an amount that is below the level of detection for the meso-substituted metalloporphyrin and/or a metabolite and/or derivative thereof using an assay, such as, but not limited to, a high-performance liquid chromatography (HPLC) assay. In some embodiments, a meso-substituted metalloporphyrin and/or a metabolite and/or derivative thereof may be systemically absorbed in an amount that results in a plasma level that is less than 1 nM of the meso-substituted metalloporphyrin and/or a metabolite and/or derivative thereof, optionally as determined using an assay, such as, but not

limited to, a high-performance liquid chromatography (HPLC) assay or undetectable using such an assay.

A method of the present invention may comprise topically applying a composition of the present invention to the skin (e.g., skin affected by a dermatological condition) of a subject 1, 2, 3, 4, 5, 6, 7, or more times a day for a period of time (e.g., 1, 2, 3, 7, 14, 21, 28, or 30 consecutive or non-consecutive day(s)). In some embodiments, a method of the present invention comprises topically applying a composition of the present invention to the skin of a subject 1, 2, 3, 4, 5, 6, 7, or more times a day until the dermatological condition is alleviated and/or as needed and/or desired. In some embodiments, a method of the present invention comprises topically applying a composition of the present invention to the skin of a subject one or two times a day and/or when necessary (e.g., when itching occurs), optionally up to 3, 4, 5, or 6 times a day. In some embodiments, a thin layer of the composition and/or an amount sufficient to cover a lesion on the skin may be applied onto the skin of the subject.

A composition and/or method of the present invention may reduce the severity of a dermatological condition in a subject by at least about 25% (e.g., about 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, or 100%) in about 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, or 30 days. The severity of the dermatological condition may be determined in accordance with the EASI (Eczema Area and Severity Index), ADSI (Atopic Dermatology Severity Index), SCORAD (SCORing Atopic Dermatitis), PASI (Psoriasis Area Severity Index), and/or by Investigator's Static Global Assessment Scale (ISGA) of a physician and/or the subject. In some embodiments, a composition and/or method of the present invention may reduce the severity of a dermatological condition in a subject by at least about 25% compared to the severity of a dermatological condition in a subject (e.g., a control subject or the subject receiving the composition) in the absence of a method and/or composition of the present invention and/or compared to a current commercial treatment.

In some embodiments, a composition and/or method of the present invention may reduce inflammation and/or one or more symptoms associated with inflammation in the skin of a subject by at least about 25% (e.g., about 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, or 100%) in about 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, or 30 days. In some embodiments, a composition and/or method of the present invention may reduce inflammation and/or one or more symptoms associated with inflammation in the skin of a subject by at least about 25% compared to the inflammation and/or one or more symptoms

associated with inflammation in the skin of a subject in the absence of a method and/or composition of the present invention and/or compared to a current commercial treatment.

In some embodiments, a composition and/or method of the present invention may reduce the number and/or size of lesions present on the subject by at least about 25% (e.g., about 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, or 100%) in about 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, or 30 days. In some embodiments, a composition and/or method of the present invention may reduce the number and/or size of lesions present on the subject by at least about 25% compared to the number and/or size of lesions present on a subject in the absence of a method and/or composition of the present invention and/or compared to a current commercial treatment.

In some embodiments, a composition and/or method of the present invention may improve the esthetic appearance of the skin (e.g., reduce redness, dryness, scaling, and/or bloching) compared to the esthetic appearance of the skin in the absence of a method and/or composition of the present invention and/or compared to a current commercial treatment. In some embodiments, a composition and/or method of the present invention may reduce wrinkles and/or other signs of ageing on the skin of a subject compared to the amount of wrinkles and/or other signs of ageing on the skin of a subject in the absence of a method and/or composition of the present invention and/or compared to a current commercial treatment. In some embodiments, a composition and/or method of the present invention may protect against and/or reduce the effects of UV radiation on the skin of a subject.

In some embodiments, a composition and/or method of the present invention may be useful for treating keloids and/or preventing regrowth of keloids (e.g., following surgical removal).

In some embodiments, a composition and/or method of the present invention may reduce the rate of reoccurrence of the dermatological condition in the subject compared to the rate of recurrence of the same type of dermatological condition in the absence of administering a composition of the present invention. The rate of recurrence may be determined using methods known to those of skill in the art. For example, after treatment of skin affected by the dermatological condition, the number of lesions may be visually determined after a given period of time to determine the rate of recurrence. In some embodiments, a composition and/or method of the present invention may provide a remission period for a specific skin lesion and/or skin condition of about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 12, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, or 24 days, weeks, and/ or months.

In some embodiments a composition of the present invention may further comprise at least one additional therapeutic agent and/or a method of the present invention may further comprise administering at least one additional therapeutic agent. Example additional therapeutic agents include, but are not limited to, a moisturizer, UV protecting agent (e.g., titanium dioxide), anti-itch agent, anti-inflammation agent (e.g., a steroid), calcineurin inhibitor (e.g., pimecrolimus), and/or sodium channel blocker), a topical antibiotic (e.g., clindamcin, retinoids, and/or benzoyl peroxide), and/or an anti-acne agent (e.g., salicylic acid). In some embodiments, a composition of the present invention and an additional therapeutic agent are separately administered to a subject sequentially or concurrently.

A composition and/or method of the present invention may reduce and/or stop itching (e.g., pruritus) of the skin to which the composition is applied within about 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, or 30 seconds or minutes. In some embodiments, a composition and/or method of the present invention may reduce and/or stop itching (e.g., pruritus) of the skin to which the composition is applied within about 1, 5, 10, 15, or 20 seconds to about 30 or 45 seconds or about 1, 2, 5, 10, 15, 20, 25, or 30 minutes. In some embodiments, the composition and/or method reduces and/or stops itching of the skin to which the composition is applied for at least about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, or 24 hours and/or days, or optionally permanently. In some embodiments, the composition and/or method may reduce and/or stop itching of the skin to which the composition is applied for about 1, 2, or 4 to about 5, 6, 8, 10, 12, 16, or 24 hours. In some embodiments, a skin lesion (e.g. an atopic dermatitis lesion and/or psoriatic plaque) may be present on the skin and the composition and/or method may be applied to the lesion and may reduce and/or stop itching in less than about 30 seconds or minutes and/or may reduce and/or stop itching of the skin to which the composition is applied for about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, or 24 hours, or optionally permanently.

In some embodiments, a method of the present invention comprises administering a therapeutically effective amount of a composition of the present invention and/or meso-substituted metalloporphyrin to a subject. As used herein, the term "therapeutically effective amount" refers to an amount of a meso-substituted metalloporphyrin and/or composition of the present invention that elicits a therapeutically useful response in a subject. Those skilled in the art will appreciate that the therapeutic effects need not be complete or curative, as long as some benefit is provided to the subject.

"Treat," "treating" or "treatment of" (and grammatical variations thereof) as used herein refer to any type of treatment that imparts a benefit to a subject and may mean that the severity of the subject's condition is reduced, at least partially improved or ameliorated and/or that some alleviation, mitigation or decrease in at least one clinical symptom associated with an inflammatory skin condition is achieved and/or there is a delay in the progression of the symptom. In some embodiments, the severity of a symptom associated with an inflammatory skin condition may be reduced in a subject compared to the severity of the symptom in the absence of a method of the present invention.

In some embodiments, a composition of the present invention and/or meso-substituted metalloporphyrin may be administered in a treatment effective amount. A "treatment effective" amount as used herein is an amount that is sufficient to treat (as defined herein) a subject. Those skilled in the art will appreciate that the therapeutic effects need not be complete or curative, as long as some benefit is provided to the subject. In some embodiments, a treatment effective amount may be achieved by administering a composition of the present invention.

The terms "prevent," "preventing" and "prevention" (and grammatical variations thereof) refer to avoidance, reduction and/or delay of the onset of a symptom associated with an inflammatory skin condition and/or a reduction in the severity of the onset of symptom associated with an inflammatory skin condition relative to what would occur in the absence of a method of the present invention. The prevention can be complete, e.g., the total absence of the symptom. The prevention can also be partial, such that the occurrence of the symptom in the subject and/or the severity of onset is less than what would occur in the absence of a method of the present invention.

In some embodiments, a meso-substituted metalloporphyrin may be administered in a prevention effective amount. A "prevention effective" amount as used herein is an amount that is sufficient to prevent (as defined herein) a symptom associated with an inflammatory skin condition in a subject. Those skilled in the art will appreciate that the level of prevention need not be complete, as long as some benefit is provided to the subject. In some embodiments, a prevention effective amount may be achieved by administering a composition of the present invention.

The present invention finds use in both veterinary and medical applications. Subjects suitable to be treated with a method of the present invention include, but are not limited to, mammalian subjects. Mammals of the present invention include, but are not limited to, canines, felines, bovines, caprines, equines, ovines, porcines, rodents (*e.g.* rats and mice),

lagomorphs, primates (*e.g.*, simians and humans), non-human primates (*e.g.*, monkeys, baboons, chimpanzees, gorillas), and the like, and mammals *in utero*. Any mammalian subject in need of being treated according to the present invention is suitable. Human subjects of both genders and at any stage of development (*i.e.*, neonate, infant, juvenile, adolescent, adult) may be treated according to the present invention. In some embodiments of the present invention, the subject is a mammal and in certain embodiments the subject is a human. Human subjects include both males and females of all ages including fetal, neonatal, infant, juvenile, adolescent, adult, and geriatric subjects as well as pregnant subjects. In particular embodiments of the present invention, the subject is a human adolescent and/or adult.

A method of the present invention may also be carried out on animal subjects, particularly mammalian subjects such as mice, rats, dogs, cats, livestock and horses for veterinary purposes, and/or for drug screening and drug development purposes.

In some embodiments, the subject is "in need of" or "in need thereof" a method of the present invention, for example, the subject has findings typically associated with an inflammatory skin condition, is suspected to have an inflammatory skin condition, and/or the subject has an inflammatory skin condition.

The present invention is explained in greater detail in the following non-limiting examples.

EXAMPLES

Example 1

A single-blind (subject blind) dose-escalation study designed to determine the maximum tolerated dose (MTD) of planned BMX-010 doses and the PK profile in each dose cohort in subjects with AD or PS when applied once daily was performed. The study is a randomized, single-blind, placebo-controlled, parallel-group, ascending-dose study in adult men and women with atopic dermatitis (AD) or plaque psoriasis (PS). **Fig. 1** shows a schematic of the study design for the dose escalation.

A total of 36 evaluable subjects with AD or PS were dosed once daily (QD) in 3 dose escalating cohorts. In each cohort, 9 subjects received BMX-010 and 3 subjects received Placebo (in accordance with the randomization schedule) QD for 7 days. The dose levels of study drug were only escalated following a review and approval by the Clinical Safety Committee (CSC) of the available 7-day safety data for all subjects in the previous cohort. The BMX-010 0.01%, 0.03%, and 0.1% gel formulations are provided in **Table 1**.

Table 1: BMX-010 0.01%, 0.03%, and 0.1% formulations.

	Quantity per batch, g *(wt%)*			
Component, Quality *(Function)*	**Placebo**	**0.01% BMX-010**	**0.03% BMX-010**	**0.1% BMX-010**
BMX-010, AMRI *(API)*	—	1 *(0.01%)*	3 *(0.03%)*	10 *(0.10%)*
Natrosol™ 250 Hydroxyethylcellulose HX, Pharm, NF *(gelling agent)*	300 *(3.00%)*	300 *(3.00%)*	300 *(3.00%)*	300 *(3.00%)*
Propylene Glycol, USP *(gelling agent)*	500 *(5.00%)*	500 *(5.00%)*	500 *(5.00%)*	500 *(5.00%)*
Potassium Sorbate Powder, NF *(preservative)*	15 *(0.15%)*	15 *(0.15%)*	15 *(0.15%)*	15 *(0.15%)*
Sodium Benzoate, NF *(preservative)*	30 *(0.30%)*	30 *(0.30%)*	30 *(0.30%)*	30 *(0.30%)*
Titanium Dioxide, USP *(colorant)*	200 *(2.00%)*	200 *(2.00%)*	200 *(2.00%)*	200 *(2.00%)*
Glacial Acetic Acid, USP *(buffer)*	15.2 *(0.15%)*	15.2 *(0.15%)*	15.2 *(0.15%)*	15.2 *(0.15%)*
Sodium Hydroxide 1*N* solution, USP *(buffer)*	164.4 *(1.64%)*	164.4 *(1.64%)*	164.4 *(1.64%)*	164.4 *(1.64%)*
Sterile Purified Water, USP *(solvent)*	8775.4 *(87.75%)*	8774.4 *(87.74%)*	8772.4 *(87.72%)*	8765.4 *(87.65%)*
Medical Air, USP *(blowing agent)*	0	0	0	0
Total batch weight	10000	10000	10000	10000

The planned dose levels for BMX-010 (QD dosing) were 0.01%, 0.03%, and 0.1%. The planned treatment duration is 7 days (8 days for subjects participating in the PK portion) with a Follow-Up Visit approximately 1 week following the last dose of study drug. Placebo (vehicle) consisted of a formulation containing the same excipients as the active drug product.

Study drug was applied topically as demonstrated to subjects at the baseline clinic visit to the target lesions (up to 100 cm^2 of body surface area) at approximately the same time of day for 7 days (8 days for subjects participating in the PK portion).

A "target lesion" was selected for treatment and thus a Targeted Clinical Score (TCS) system was used to score the lesion at each weekly visit. The EASI/PASI were done at

screening and the Day 15 visit. In this part, subjects were issued subject diaries on which they were to record dosing and the presence and severity of pruritus on non-clinic days, and the duration of the effect on pruritus on all study days.

Scoring Atopic Dermatitis lesions was done using a Total Clinical Score (TCS-AD) evaluating erythema, induration, excoriation and lichenification on a 0-3 scale (maximum score is 12). All AD subjects were to have a full EASI score to evaluate both severity and extent of AD on the screening visit and the Day 15 follow-up visit. All AD subjects were to report itch on a visual analogue 0-10 scale (pruritus VAS). All AD subjects were to report sleeplessness on a visual analogue 0-10 scale (sleeplessness VAS). Scoring Psoriasis lesions was done using a total clinical score (TCS-PS) evaluating erythema, induration and desquamation on a 0-4 scale (maximum score is 12). All psoriasis subjects were to have a full Psoriasis Area Severity Index (PASI) to evaluate both severity and extent of psoriasis on the screening visit and the Day 15 follow-up visit. At Screening, subjects were to have a diagnosis of mild to moderate chronic plaque-type psoriasis. All psoriasis subjects were to report itch on a visual analogue 0-10 scale (pruritus VAS) Prior to dosing on Day 1, subjects were issued subject diaries to record dosing times and self-reported pruritus assessments for non-clinic days/times throughout the study.

Pruritus was to be assessed daily and include a severity score using a 0-10 VAS (0 = no pruritus $\rightarrow$ 10 = worst imaginable pruritus) at predose and 30 minutes postdose, and the duration of the effect on pruritus will be recorded. Severity assessments was to be recorded on case report forms (CRFs) on clinic-visit days (except for Days 2 and 9, which are PK assessment days only) and in the subject diary on non-clinic days, and duration data will be captured in the subject diary on all treatment days. On Days 1, 4, 8, and 15, the investigator was to review pruritus history with each subject. Clinical safety laboratory assessments were to include CBC with differential and CMP.

The results from this study demonstrated efficacy in atopic dermatitis, no adverse events, and no detectable systemic absorption of the drug. A graph of the TCS-AD_{total} Mean Change from Baseline is provided in **Fig. 2**. **Fig. 3** shows graphs for each cohort and the placebo group in regard to itching data. For comparison purposes, separate from the present study, **Fig. 4** shows images of before and after treatment with a 0.03% BMX-010 cream composition. **Fig. 5** shows an image of an atopic dermatitis lesion before treatment and 4 days after once daily treatment with a 0.03% BMX-010 composition according to the present study. **Fig. 6** shows images over a period of time with the first image being before treatment and the remaining images after treatment with a 0.1% BMX-010 composition according to

the present study. **Fig. 7** is an illustration showing a graph of a 0.1% BMX-010 composition efficacy results according to the present study compared to published Eucrisa™ data. BMX-010 full scoring range (clear → severe) is 12 points (modified EASI), whereas Eucrisa™ full range is 5 points. In many cases, patients and clinical staff observed reduction of itch and erythema within 30 minutes in subjects treated with BMX-010 topically.

Example 2

In this study, there will be two cohorts, one with AD and one with PS. A total of up to 100 evaluable subjects with AD and a total of up to 100 subjects with PS will be dosed with BMX-010 (0.03% or 0.1%) twice daily (BID) and up to 50 evaluable subjects will be dosed with Placebo in 2 parallel arms in each cohort. Both cohorts and both arms in each cohort will run concurrently. Subjects will receive either BMX-010 (0.03% or 0.1%) or placebo (in accordance with the randomization schedule) BID for 7 days followed by prn (i.e., as needed) treatment BID until lesions fully clear or for a maximum of 28 days. A schematic of the study design is provided in **Fig. 8**.

The cream base that will be used in this study to provide the 0.03% or 0.1% BMX-010 cream is provided in **Table 2**. The cream base of **Table 2** will include either 0.03% or 0.1% BMX-010 by weight of the composition to provide the 0.03% or 0.1% BMX-010 cream, respectively.

Table 2: Cream base formulation.

Ingredient	Amount
25 mM Acetate pH 5.0	56.5%
Mineral Oil	12.0%
Petrolatum	9.0%
Cetostearyl alcohol	12.0%
Propylene glycol	8.0%
Tween 20	1.0%
Isopropyl palmitate	1.0%
Imidazolidinyl urea	0.2%
Methylparaben	0.2%
Propylparaben	0.1%

Three to six subjects will be selected to consent to participate in PK analysis of BMX-010 levels in plasma. These subjects will receive BMX-010 (0.1%) and will not be randomized. These subjects must have active lesions to be treated on at least 5% body surface

area. All active lesions on the body, which can include the head (excluding the eyes and scalp), neck, trunk, and limbs (excluding the axillae, genitals, groin area, backs of hands, palms and soles), will be treated.

Following written informed consent, subjects will undergo screening evaluations within 14 days prior to the first application of study drug. The maximum disease extent must involve no more than 25% of body surface area. The screening evaluations will include medical history, physical examination (including vital signs, weight, and height), clinical laboratory evaluations, urine pregnancy test for females of child-bearing potential (a negative pregnancy test is required within 48 hours prior to the start of drug treatment), concurrent medical conditions, and concomitant medication assessments.

Subjects with atopic dermatitis will be scored for EASI and ISGA for AD, pruritus VAS and sleeplessness VAS. The EASI will be done prior to the start of treatment, at days 15, 29 and when the treated area is deemed to have cleared. The ISGA for AD subjects will be used for assessment at each weekly visit. Subjects with psoriasis will be scored for PASI and ISGA for PS, pruritus VAS and sleeplessness VAS. The PASI will be done prior to the start of treatment, at days 15, 29 and when the treated area is deemed to have cleared. The ISGA for PS subjects will be used for assessment at each weekly visit. Subjects enrolled will treat all active lesions on the body, which can include the head (excluding the eyes and scalp), neck, trunk, and limbs (excluding the axillae, genitals, groin area, backs of hands, palms and soles). The subjects will answer questions during in-clinic study visit days about itching, scratching, and clearing of the lesions.

Example 3

Subject 1 is a 67 year-old white male with a history of rosacea triggered by sunlight exposure with a duration of over 5 years. Over a period of 6 months, the subject experienced rosacea flares, characterized by redness, a sensation of heat, and appearance of pustules once or twice a month. The flares were treated with BMX-010 in the cream base formulation shown in **Table 2** including either 0.03% or 0.1% BMX-010 by weight of the composition. It was observed that a single treatment reduced symptom severity by approximately 80% within 12 hours and completely within 2 days. After treatment, the subject's skin remained essentially clear for at least one week.

Subject 2 is a 55 year old while female with a history of chronic facial rosacea characterized as erythema with papules. She experienced a significant flare that had lasted several weeks. This was treated for a week with daily 0.03% BMX-010 by weight in the

cream base formulation shown in **Table 2**. Marked clearing occurred within 24 hours with virtual clearing of both erythema and papules by 48 hours.

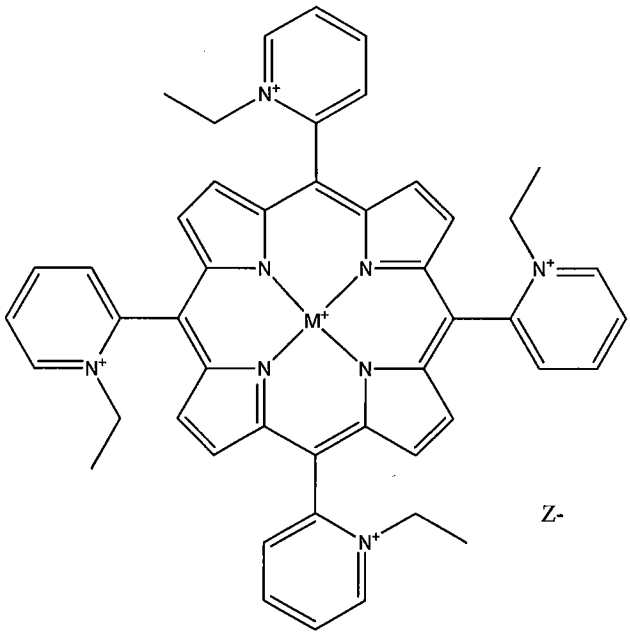
The foregoing is illustrative of the present invention, and is not to be construed as limiting thereof. The invention is defined by the following claims, with equivalents of the claims to be included therein. All publications, patent applications, patents, patent publications, and other references cited herein are incorporated by reference in their entireties for the teachings relevant to the sentence and/or paragraph in which the reference is presented.

THAT WHICH IS CLAIMED IS:

1. A method of treating a dermatological condition in a subject, comprising:

topically administering to the skin of a subject a composition comprising a meso-substituted metalloporphyrin, wherein the meso-substituted metalloporphyrin is Ames negative and is present in the composition at a concentration of about 0.005% to about 1% by weight of the composition.

2. The method of claim 1, wherein the meso-substituted metalloporphyrin is $MnTE\text{-}2\text{-}PyP^{5+}$ and has the structure:



wherein Z^- is a counterion (e.g., a halogen) and M^+ is manganese.

3. The method of any preceding claim, wherein the meso-substituted metalloporphyrin is not systemically absorbed in an amount that is detectable in plasma (e.g., in an amount greater than 1 nM using an assay, e.g., a high-performance liquid chromatography (HPLC) assay) or no more than about 2% of the amount of the meso-substituted metalloporphyrin administered to the subject is systemically absorbed.

4. The method of any preceding claim, wherein the meso-substituted metalloporphyrin is locally delivered to the skin of the subject.

5. The method of any preceding claim, wherein the meso-substituted metalloporphyrin is present in the composition at a concentration of about 0.01% to about 0.2% by weight of the composition.

6. The method of any preceding claim, wherein the composition is in the form of a cream, gel, foam, solution, lotion, or ointment, optionally wherein the composition is in the form of a cream.

7. The method of any preceding claim, wherein the composition comprises:

water or an aqueous buffer solution, optionally in an amount of about 40% to about 65% by weight of the composition;

a hydrophobic base (e.g., mineral oil and/or petrolatum), optionally in an amount of about 5% to about 35% by weight of the composition;

a fatty alcohol, optionally in an amount of about 1% to about 20% by weight of the composition;

a polyhydric alcohol, optionally in an amount of about 1% to about 15% by weight of the composition;

a fatty acid ester, optionally in an amount of about 0.01% to about 2%;

a surfactant (e.g., a non-ionic surfactant), optionally in an amount of about 0.1% to about 5%;

optionally a buffer and/or buffering agent (e.g., at a concentration of about 5, 10, 15, or 20 mM to about 25, 30, 35, 40, 45, or 50 mM); and

optionally a preservative (e.g., in an amount of about 0.01% to about 2%);

optionally wherein the composition has a pH of about 4, 4.5, or 5 to about 5.5, 6, 6.5, or 7.

8. The method of any preceding claim, wherein the composition comprises mineral oil, petrolatum, cetostearyl alcohol, propylene glycol, Tween-20, isopropyl palmitate, imidazolidinyl urea, methylparaben, and/or propylparaben.

9. The method of any preceding claim, wherein the composition further comprises a colorant and/or pigment (e.g., titanium dioxide), optionally in an amount of about 0.1% to about 10% by weight of the composition.

10. The method of any preceding claim, wherein the dermatological condition is an inflammatory skin condition.

11. The method of any preceding claim, wherein the dermatological condition is selected from eczema (e.g., atopic dermatitis), psoriasis, rosacea, acne, and/or arthropod bites or stings.

12. The method of any preceding claim, wherein the composition is topically applied to the subject 1, 2, 3, 4 or more times a day, optionally for 7, 14, 21, 28, or 30 days or until the dermatological condition is alleviated.

13. The method of any preceding claim, wherein the composition is topically applied to the skin of the subject twice a day and optionally wherein the composition is topically applied to the skin of the subject as needed up to a total of 4 times per day.

14. The method of any preceding claim, wherein the composition is topically applied for at least 3, 7, 14, or 30 days.

15. The method of any preceding claim, wherein the method reduces the severity of the dermatological condition in the subject by at least 25% or 50% in about 1, 2, 3, 4, 5, 6, or 7 days, optionally wherein the severity is determined in accordance with the EASI (Eczema Area and Severity Index), ADSI (Atopic Dermatology Severity Index), SCORAD (SCORing Atopic Dermatitis), PASI (Psoriasis Area Severity Index), and/or by Investigator's Static Global Assessment Scale (ISGA) of a physician and/or the subject.

16. The method of any preceding claim, wherein the method reduces the number and/or size of lesions present on the subject by at least 25% or 50% in about 1, 2, 3, 4, 5, 6, or 7 days.

17. The method of any preceding claim, wherein the method reduces the rate of reoccurrence of the dermatological condition in the subject.

18. The method of any preceding claim, further comprising administering at least one additional therapeutic agent (e.g., a moisturizer, UV protecting agent, anti-itch agent,

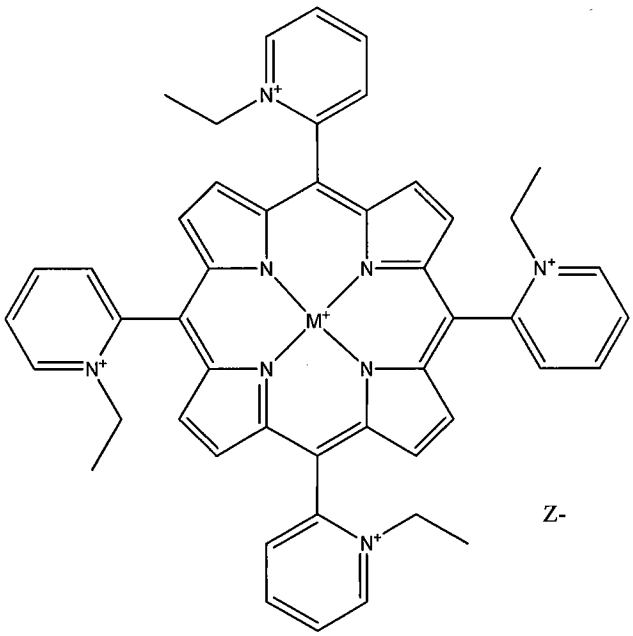
anti-inflammation agent (e.g., a steroid), calcineurin inhibitor (e.g., pimecrolimus), and/or sodium channel blocker).

19. The method of any preceding claim, wherein the composition reduces and/or stops itching of the skin to which it is applied within about 1, 5, 10, 15, or 30 minutes.

20. The method of any preceding claim, wherein the composition reduces and/or stops itching of the skin to which it is applied for at least about 2, 3, 4, 5, 6, 7, or 8 hours.

21. A method of treating atopic dermatitis in a subject, comprising:

topically administering to the skin of a subject a composition comprising a meso-substituted metalloporphyrin, wherein the meso-substituted metalloporphyrin is present in the composition at a concentration of about 0.005% to about 1% by weight of the composition and has the structure:



wherein Z^- is a counterion (e.g., a halogen) and M^+ is manganese.

22. The method of claim 21, wherein the composition reduces and/or stops itching of the skin to which it is applied within about 1, 5, 10, 15, or 30 minutes.

23. The method of claim 21 or 22, wherein the composition reduces and/or stops itching of the skin to which it is applied for at least about 4, 5, 6, 7, or 8 hours.

24. The method of any one of claims 21-23, wherein the meso-substituted metalloporphyrin is not systemically absorbed in an amount that is detectable in plasma (e.g., in an amount greater than 1 nM using an assay, e.g., a high-performance liquid chromatography (HPLC) assay) or no more than about 2% of the amount of the meso-substituted metalloporphyrin administered to the subject is systemically absorbed.

25. The method of any one of claims 21-24, wherein the meso-substituted metalloporphyrin is locally delivered to the skin of the subject.

26. The method of any one of claims 21-25, wherein the meso-substituted metalloporphyrin is present in the composition at a concentration of about 0.01% to about 0.2% by weight of the composition.

27. The method of any one of claims 21-26, wherein the composition is in the form of a cream, gel, foam, solution, lotion, or ointment, optionally wherein the composition is in the form of a cream.

28. The method of any one of claims 21-27, wherein the composition comprises:

water or an aqueous buffer solution, optionally in an amount of about 40% to about 65% by weight of the composition;

a hydrophobic base (e.g., mineral oil and/or petrolatum), optionally in an amount of about 5% to about 35% by weight of the composition;

a fatty alcohol, optionally in an amount of about 1% to about 20% by weight of the composition;

a polyhydric alcohol, optionally in an amount of about 1% to about 15% by weight of the composition;

a fatty acid ester, optionally in an amount of about 0.01% to about 2%;

a surfactant (e.g., a non-ionic surfactant), optionally in an amount of about 0.1% to about 5%;

optionally a buffer and/or buffering agent (e.g., at a concentration of about 5, 10, 15, or 20 mM to about 25, 30, 35, 40, 45, or 50 mM); and

optionally a preservative (e.g., in an amount of about 0.01% to about 2%);

optionally wherein the composition has a pH of about 4, 4.5, or 5 to about 5.5, 6, 6.5, or 7.

29. The method of any one of claims 21-28, wherein the composition comprises mineral oil, petrolatum, cetostearyl alcohol, propylene glycol, Tween-20, isopropyl palmitate, imidazolidinyl urea, methylparaben, and/or propylparaben.

30. The method of any one of claims 21-29, wherein the composition further comprises a colorant and/or pigment (e.g., titanium dioxide), optionally in an amount of about 0.1% to about 10% by weight of the composition.

31. The method of any one of claims 21-30, wherein the composition is topically applied to the skin of the subject 1, 2, 3, 4 or more times a day, optionally for 7, 14, 21, 28, or 30 days or until the dermatological condition is alleviated.

32. The method of any one of claims 21-31, wherein the composition is topically applied to the subject twice a day and optionally wherein the composition is topically applied to the skin of the subject as needed up to a total of 4 times per day.

33. The method of any one of claims 21-32, wherein the composition is topically applied for at least 3, 7, 14, or 30 days.

34. The method of any one of claims 21-33, wherein the method reduces the severity of the dermatological condition in the subject by at least 25% or 50% in about 1, 2, 3, 4, 5, 6, or 7 days, optionally wherein the severity is determined in accordance with the EASI (Eczema Area and Severity Index), ADSI (Atopic Dermatology Severity Index), SCORAD (SCORing Atopic Dermatitis), PASI (Psoriasis Area Severity Index), and/or by Investigator's Static Global Assessment Scale (ISGA) of a physician and/or the subject.

35. The method of any one of claims 21-34, wherein the method reduces the number and/or size of lesions present on the subject by at least 25% or 50% in about 1, 2, 3, 4, 5, 6, or 7 days.

36. The method of any one of claims 21-35, wherein the method reduces the rate of reoccurrence of the dermatological condition in the subject.

37. The method of any one of claims 21-36, further comprising administering at least one additional therapeutic agent (e.g., a moisturizer, UV protecting agent, anti-itch agent, anti-inflammation agent (e.g., a steroid), calcineurin inhibitor (e.g., pimecrolimus), and/or sodium channel blocker).

38. A composition comprising:

a meso-substituted metalloporphyrin, optionally wherein the meso-substituted metalloporphyrin is Ames negative and optionally is present in the composition at a concentration of about 0.005% to about 1% by weight of the composition;

water or an aqueous buffer solution, optionally in an amount of about 40% to about 60% by weight of the composition;

a hydrophobic base (e.g., mineral oil and/or petrolatum), optionally in an amount of about 5% to about 35% by weight of the composition;

a fatty alcohol, optionally in an amount of about 1% to about 20% by weight of the composition;

a polyhydric alcohol, optionally in an amount of about 1% to about 15% by weight of the composition;

a fatty acid ester, optionally in an amount of about 0.01% to about 2%;

a surfactant (e.g., a non-ionic surfactant), optionally in an amount of about 0.1% to about 5%;

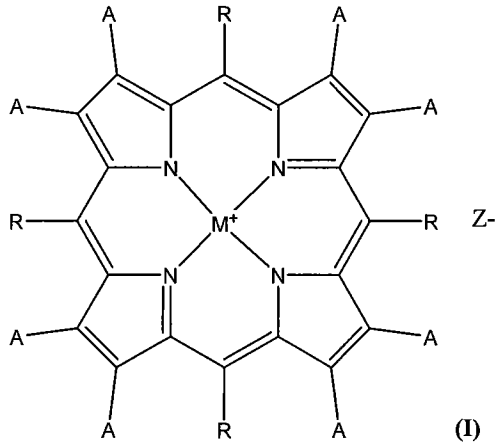
optionally a buffer and/or buffering agent (e.g., at a concentration of about 5, 10, 15, or 20 mM to about 25, 30, 35, 40, 45, or 50 mM); and

optionally a preservative (e.g., in an amount of about 0.01% to about 2%);

optionally wherein the composition has a pH of about 4, 4.5, or 5 to about 5.5, 6, 6.5, or 7.

39. The composition of claim 38, wherein the meso-substituted metalloporphyrin has

a structure represented by **Formula I**:



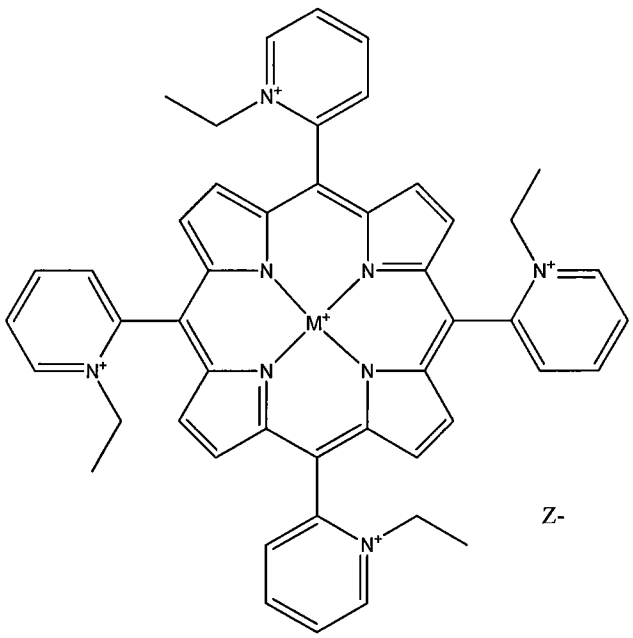
wherein:

each R is independently substituted or unsubstituted aryl, heteroaryl, cycloalkyl, or heterocycloalkyl;

each A is an independently selected hydrogen, or an electron-withdrawing or electron donating group (*e.g.*, is halogen, $-NO_2$ or -CHO),

M is a metal (*e.g.*, selected from the group consisting of manganese, iron, copper, cobalt, nickel and zinc) or is absent (in which case a hydrogen is added to each of the two nitrogens required to correct valency), and

Z^- is a counterion (e.g., a halogen such as chlorine, fluorine, bromine, and/or iodine), optionally wherein the meso-substituted metalloporphyrin is MnTE-2-PyP^{5+} and has the structure:

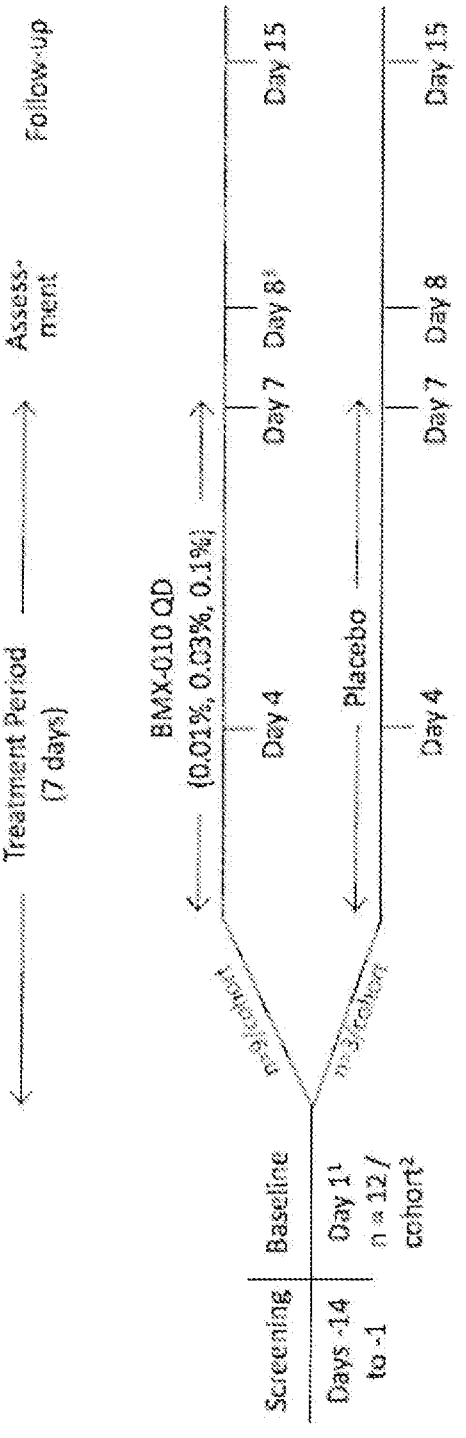


wherein Z^- is a counterion (e.g., a halogen) and M^+ is manganese.

40. The composition of any one of claims 38 or 39, wherein the composition comprises mineral oil, petrolatum, cetostearyl alcohol, propylene glycol, Tween-20, Tween-80, isopropyl palmitate, imidazolidinyl urea, methylparaben, and/or propylparaben.

41. The composition of any one of claims 38-40, further comprising a colorant and/or pigment (e.g., titanium dioxide), optionally in an amount of about 0.1% to about 10% by weight of the composition.

Fig. 1

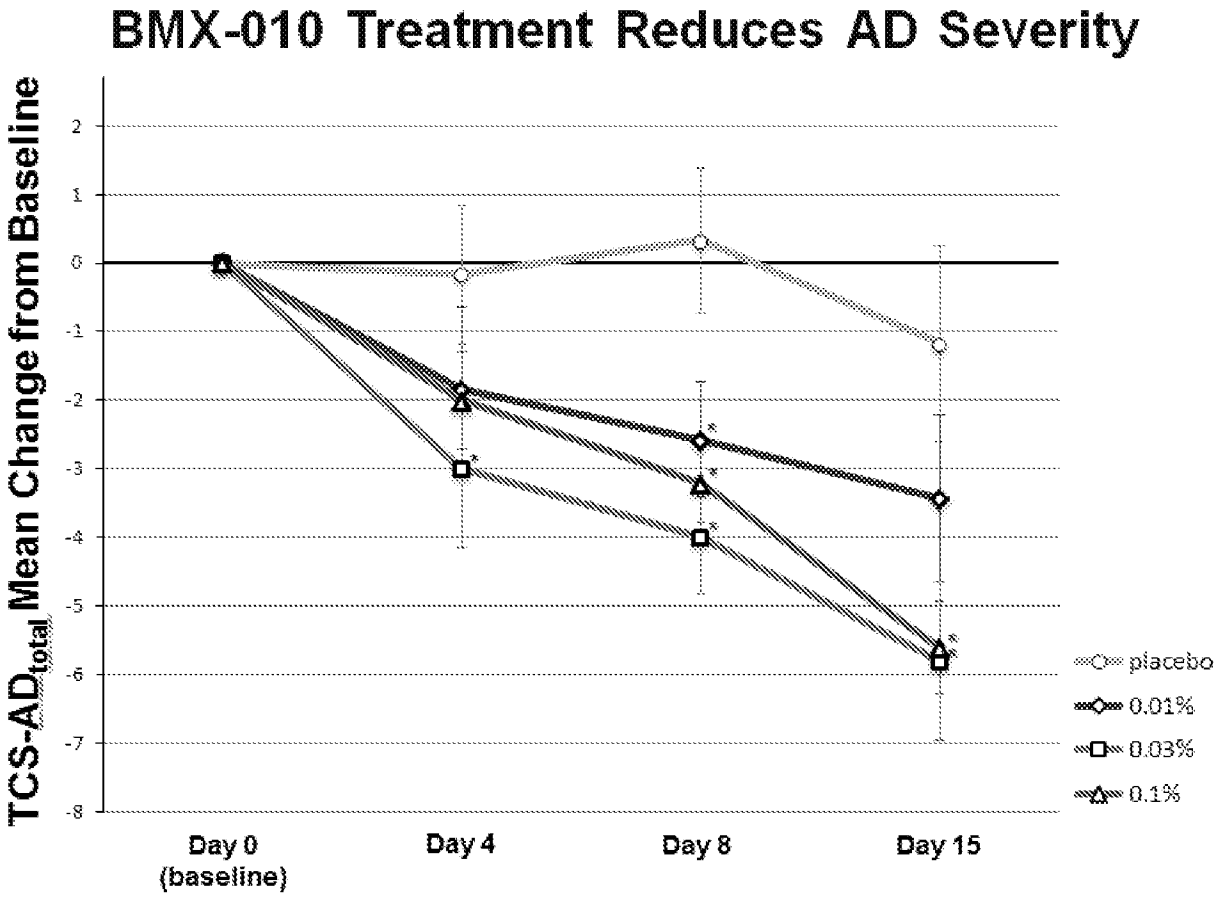


[1] Randomization will occur after completion of all screening assessments. The first dose will be administered at the clinic on Day 1.

[2] N = 12 evaluable subjects with AD or PS per cohort (9 on active drug; 3 on placebo). Subjects are treated in dose escalating cohorts of 0.01%, 0.03% and 0.1%.

[3] The 3 subjects receiving BMX-010 of each dosing cohort who participate in the PK portion of the study will have visits on Days 2 and 9 in addition to clinical visits on Days 4, 8 and 15; the remaining subjects randomized to BMX-010 or Placebo will not.

Fig. 2



TCS-AD$_{total}$ change from baseline plotted as mean ± SEM.
* $p < 0.05$ versus corresponding placebo.

Fig. 3

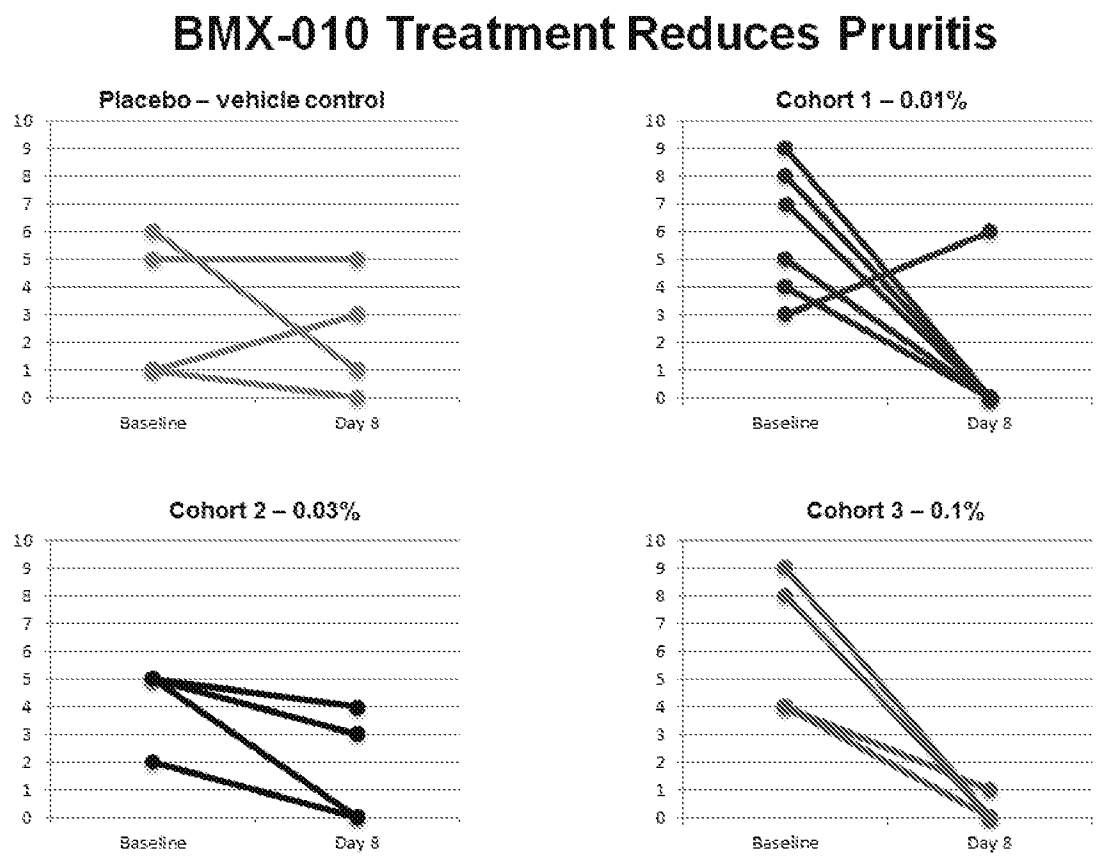

BMX-010 Treatment Reduces Pruritis
Placebo – vehicle control
Cohort 1 – 0.01%
Cohort 2 – 0.03%
Cohort 3 – 0.1%
Baseline
Day 8
0
1
2
3
4
5
6
7
8
9
10

Fig. 4

Mild Atopic Dermatitis -
Rapid Response to
BMX-010
before treatment → after 1 day,
2 applications
after 1 day → after 7 days

Fig. 5

Localized, Severe Atopic Dermatitis

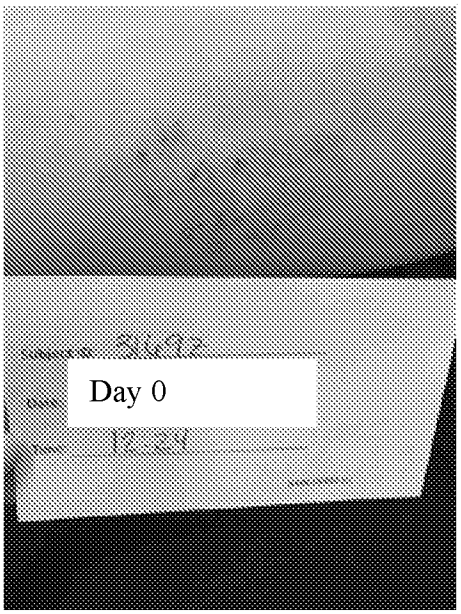


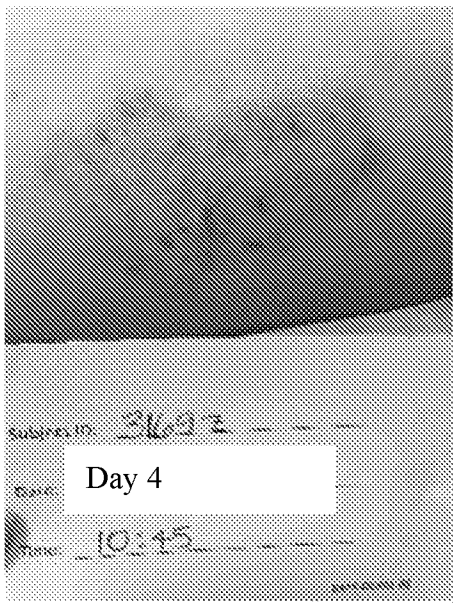
before treatment

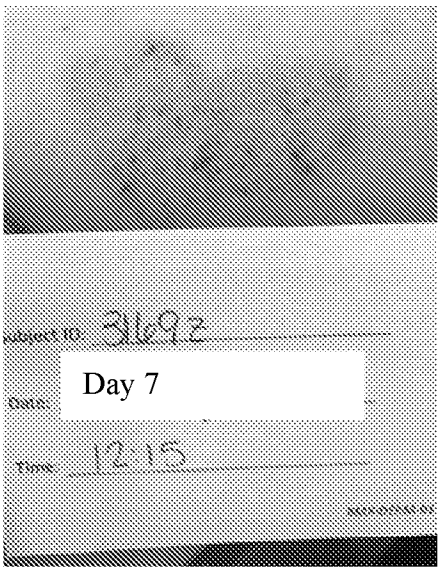


4 days, q.d. 0.03% BMX-010

Fig. 6







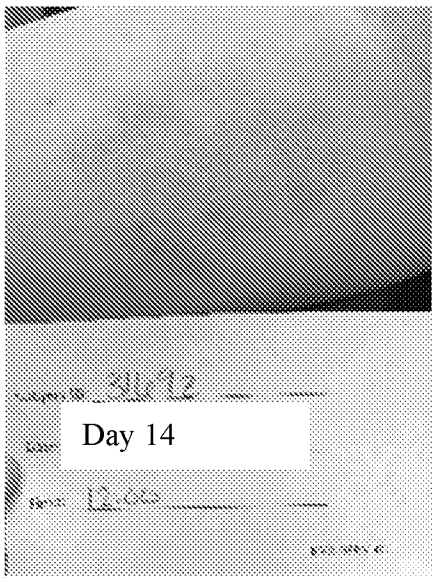


Fig. 7

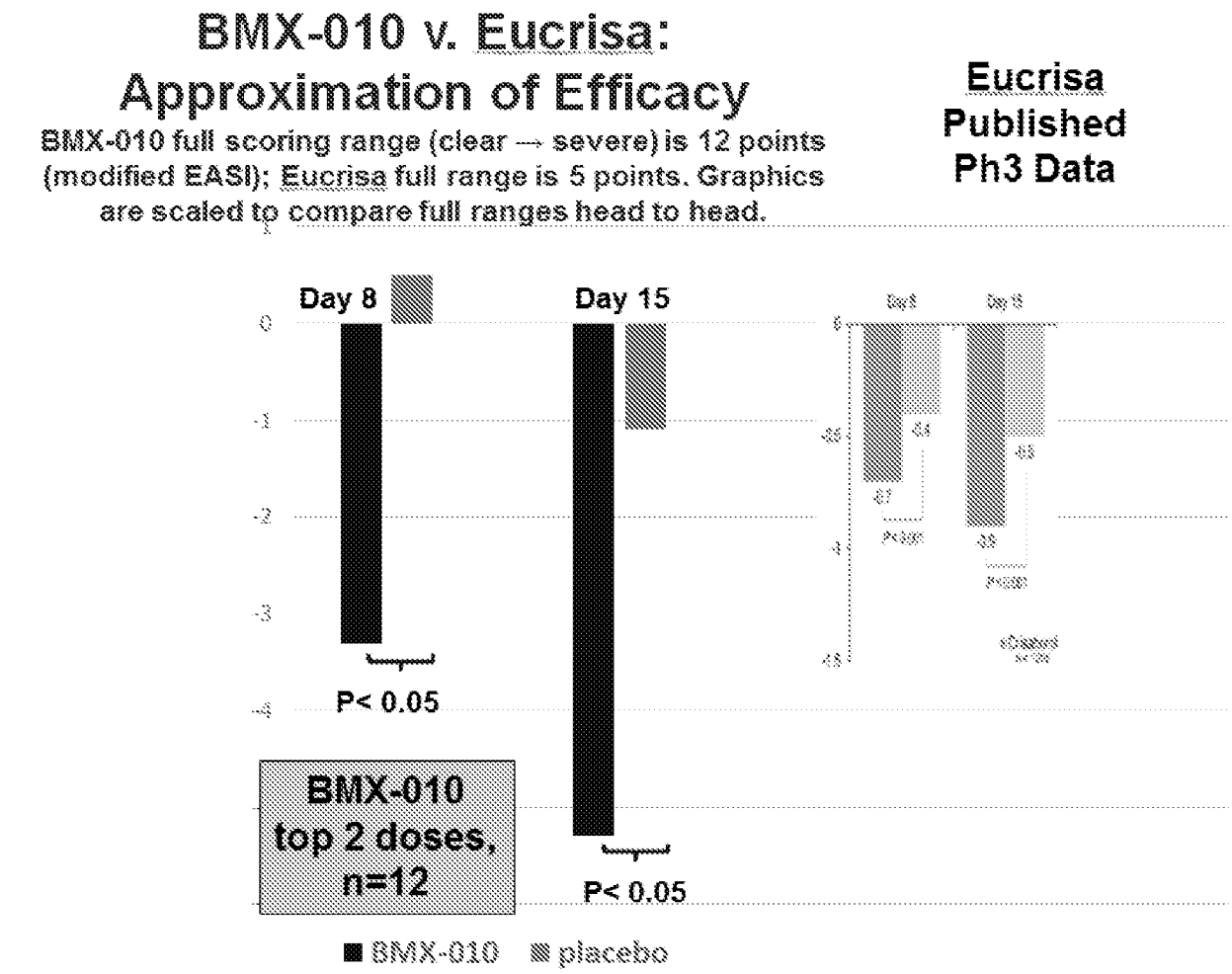
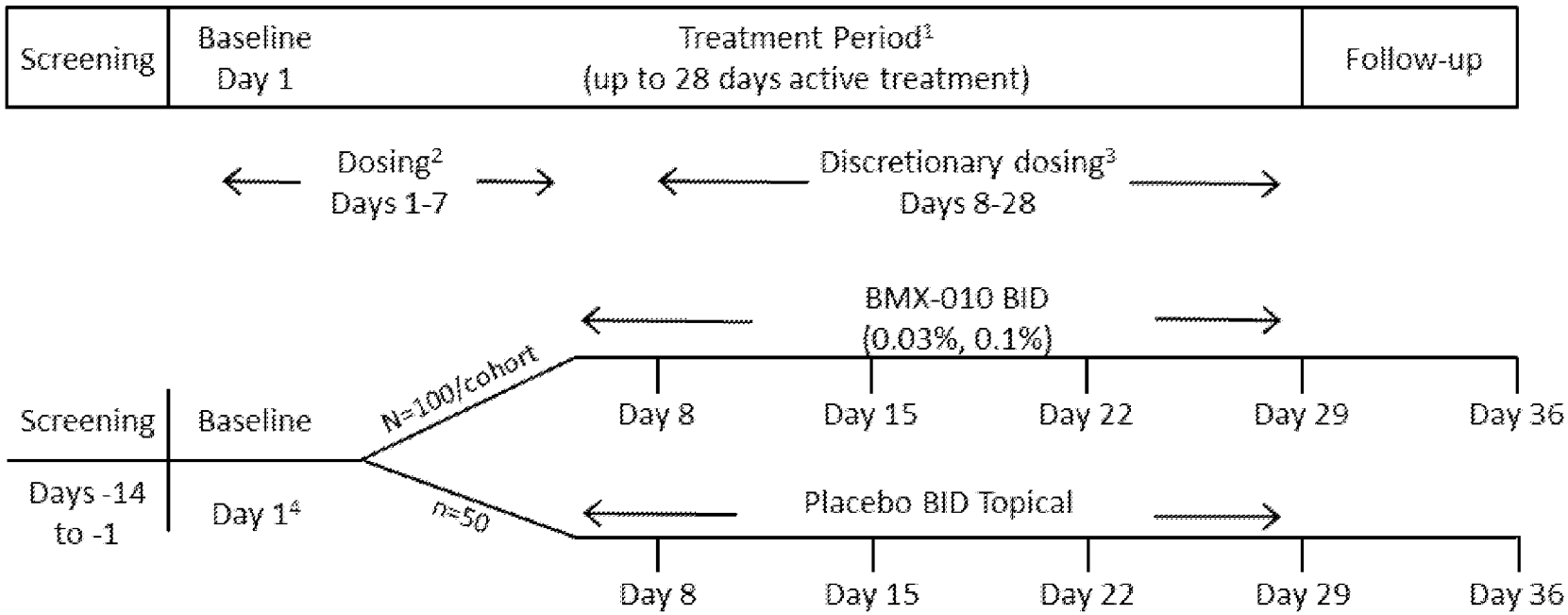

BMX-010 v. Eucrisa:
Approximation of Efficacy
BMX-010 full scoring range (clear → severe) is 12 points (modified EASI); Eucrisa full range is 5 points. Graphics are scaled to compare full ranges head to head.
Eucrisa Published Ph3 Data
Day 8
Day 15
P< 0.05
P< 0.05
BMX-010 top 2 doses, n=12
BMX-010
placebo

Fig. 8



[1] Treatment period will last for at least 7 and up to 28 days. Ability to stop before 28 days based on review of lesion and determination by clinical center investigator.

[2] Subjects will administer study drug BID and PRN for pruritus for an additional 2 times a day until the lesion is determined to be cleared based on the discretion of clinical center investigator. The 3 subjects receiving BMX-010 0.1% who participate in the PK portion of the study will have an additional visit on Day 9; the remaining subjects randomized to BMX-010 or Placebo will not. Subjects randomized to BMX-010 will be assigned concentrations of of 0.03% or 0.01%.

[3] Discretionary dosing period determined by clinical center investigator based on clearing of lesion.

[4] Randomization will occur after completion of all screening assessments. The first dose will be administered at the clinic on Day 1.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 18/38964

A. CLASSIFICATION OF SUBJECT MATTER
IPC(8) - A61K 31/409; A61K 31/555; C07D 487/22 (2018.01)
CPC - A61K 31/409; C07D 487/22; A61K 31/555

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

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
See Search History Document

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

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
See Search History Document

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X -- Y	US 2016/0324867 A1 (BIOMIMETIX JV, LLC) 10 November 2016 (10.11.2016); para [0002], [0009]-[0010], [0053]-[0057], [0071]-[0074], [0088], [0091], [0095]-[0098], [0100], [0103], [0109], [0124], [0129], [0133], [0135]-[0137], [0140]	1-2, 21, 38-40 ---------- 3, 22-23
Y	US 2011/0275606 A1 (BATINIC-HABERLE et al.) 10 November 2011 (10.11.2011); para [0060], [0062], [0069], [0075]	3
Y	US 2016/0324868 A1 (DUKE UNIVERSITY et al.) 10 November 2016 (10.11.2016); para [0068] -[0072], [0093]-[0094], [0130]-[0131]	22-23
A	US 2008/0021007 A1 (BATINIC-HABERLE et al.) 24 January 2008 (24.01.2008); see entire document	1-3, 21-23, 38-40
A	US 2004/0058902 A1 (BATINIC-HABERLE et al.) 25 March 2004 (25.03.2004); see entire document	1-3, 21-23, 38-40
A	US 2002/0042407 A1 (FRIDOVICH et al.) 11 April 2002 (11.04.2002); see entire document	1-3, 21-23, 38-40

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier application or patent but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
12 August 2018	17 SEP 2018
Name and mailing address of the ISA/US Mail Stop PCT, Attn: ISA/US, Commissioner for Patents P.O. Box 1450, Alexandria, Virginia 22313-1450 Facsimile No. 571-273-8300	Authorized officer: Lee W. Young PCT Helpdesk: 571-272-4300 PCT OSP: 571-272-7774

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 18/38964

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☒ Claims Nos.: 4-20, 24-37 and 41
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying additional fees, this Authority did not invite payment of additional fees.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.

☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.

☐ No protest accompanied the payment of additional search fees.