

CLASCOTERONE AND MINOXIDIL COMBINATION THERAPY FOR USE IN TREATING HAIR LOSS

BACKGROUND

[0001] Alopecia is a group of disorders with multiple and varying etiologies that results in hair loss from the body. The most common form of alopecia is androgenetic alopecia (“AGA”). AGA is also commonly called alopecia androgenetica, male pattern baldness, or male-pattern or female-pattern hair loss. It has been reported that AGA affects roughly 50% of men over 40. This form of alopecia could eventually affect up to 80% of white men by the age of 70 and about half of all women. Hair loss is often a cause of great concern to affected subjects for cosmetic and psychological reasons, but it can also be an important sign of systemic disease.

[0002] Medical management of AGA includes surgical treatment options, including hair transplantation. This procedure has been performed successfully for decades. Hair transplantation involves harvesting intact hair follicles from within a safe donor area (SDA) of a patient’s scalp by either follicular unit strip surgery (FUSS) or follicular unit extraction (FUE). Although cosmetic results after surgery are often satisfactory, surgery can only be performed when a sufficient quantity of donor plugs (or follicles) is available to cover the balding area(s). Additionally, hair transplantation is generally reserved for patients who have experienced massive hair loss and for patients in whom AGA is not still evolving. In younger patients, for example, hair transplantation generally is not recommended because androgens, particularly dihydrotestosterone (DHT), can act on the newly transplanted follicles resulting in the same thinning and eventual hair loss that affected the originally present follicles.

[0003] In view of the deficiencies and drawbacks associated with surgical treatment options, there remains a need in the art for pharmacological therapies for treating hair loss, including alopecia and in particular, AGA.

BRIEF SUMMARY

[0004] Minoxidil, also known as 2,4-diamino-6-piperidinopyrimidine 3-oxide, is formulated as a topical drug product for treatment of AGA, typically at two strength levels – 2% (topical solution) and 5% (as a topical solution or foam). See, e.g., U.S. Patent Nos. 4,596,812 and 6,946,120, each of which is incorporated herein by reference in its entirety. To

exert its effect, minoxidil needs to be transformed into its active metabolite, minoxidil sulfate, by the enzyme sulfotransferase. This enzyme is present in the outer root sheath of anagen follicles. Disadvantageously, clinical trials have shown that the topical application of a 2% minoxidil solution to patients experiencing hair loss results in stimulated dense hair regrowth in fewer than about 5% of the patients and moderate hair regrowth in only about 30% of the patients. See e.g., E. A. Olsen, et al., "Topical Minoxidil in Early Male Pattern Baldness," *J. Amer. Acad. Derm.* 13, 185-192 (1985); and J. Roberts, "Androgenetic Alopecia: Treatment with Topical Minoxidil," *J. Amer. Acad. Derm.* 16(3) 705-710 (1987).

[0005] Cortisolone-17 α -propionate, also known as 17 α -propionyloxy-21-hydroxy-pregna-4-ene-3,20-dione and clascoterone, is a topical antiandrogen that displaces androgenic hormones from binding with their receptors. Cortisolone-17 α -propionate is known to be suitable for treating acne, alopecia, and other diseases of skin and cutaneous appendages. See, e.g., U.S. Patent Nos. 8,143,240 and 8,865,690, WO 2009/019138, and WO 2016/207778. The compound is also known to exist in several distinct crystalline polymorphs, each having unique properties. See, e.g., U.S. Patent No. 8,785,427. Each of these patents is incorporated herein by reference in its entirety.

[0006] It has been surprisingly discovered that hair loss, including alopecia, can be effectively treated with a combination of cortisolone-17 α -propionate and minoxidil. In some embodiments, a synergistic effect can be provided by the combination such that, surprisingly, a lower effective amount of each active can be used for effective treatment or the same amount of each active can be used to obtain higher combined synergy. As a result of this combination therapy, an advantageous clinical result can be realized after daily topical administration for an appropriate amount of time, such as a few days, weeks, or months.

[0007] Accordingly, the present disclosure provides a method of treating hair loss in a subject in need thereof, comprising topically administering to the subject an effective amount of cortisolone-17 α -propionate and an effective amount of minoxidil.

[0008] In some embodiments, cortisolone-17 α -propionate can be co-administered in an amount from at least 1 wt % to about 20 wt % along with an effective amount of minoxidil. In some embodiments, minoxidil can be co-administered in an amount from about 0.1 wt% to about 20 wt% along with an effective amount of cortisolone-17 α -propionate.

[0009] In some embodiments, the cortexolone-17 α -propionate and minoxidil are co-administered sequentially. In such embodiments, the cortexolone-17 α -propionate and minoxidil can be in separate pharmaceutical formulations. In other embodiments, the cortexolone-17 α -propionate and minoxidil can be co-administered simultaneously. In some embodiments, the cortexolone-17 α -propionate and minoxidil can be combined in the same pharmaceutical formulation.

[0010] In some embodiments, the pharmaceutical formulation can be a liquid or semi-solid formulation. In a further embodiment, the pharmaceutical formulation is a solution, a suspension, an emulsion, a microemulsion, a cream, a paste, a gel, an ointment, or a foam. In further embodiments, the pharmaceutical formulation is a solution. In some embodiments of the solution, the solution can comprise water, saline, a buffered saline solution, a polyol, a polyol ether, a C₁-C₇ alcohol, or a combination thereof.

[0011] In some embodiments of the method, the pharmaceutical formulation can further comprise at least one (e.g., 1, 2, 3, 4, 5, 6, 7, or 8) additive(s) selected from the group consisting of an acid, a buffer, an antioxidant, an emulsifier, a penetration enhancer, a moisturizer, a preservative, a chelating agent, and combinations thereof. In some embodiments, the cortexolone-17 α -propionate is co-administered in a pharmaceutical formulation comprising less than about 5 wt% water. In some embodiments, the cortexolone-17 α -propionate and minoxidil are combined in the same pharmaceutical formulation comprising less than about 5 wt% water. In some embodiments, the pharmaceutical formulation is co-administered topically once or twice daily.

[0012] In some embodiments of the method, the hair loss is alopecia. In some embodiments, the alopecia is androgenetic alopecia, alopecia areata, telogen effluvium, anagen effluvium, traction alopecia, or a combination of any of the foregoing. In some embodiments, the alopecia areata is selected from the group consisting of diffuse alopecia areata, alopecia areata monolocularis, alopecia areata multilocularis, ophiasis, alopecia totalis, and alopecia universalis. In some particular embodiments, the alopecia is androgenetic alopecia.

[0013] The present disclosure further provides a topical pharmaceutical formulation comprising cortexolone-17 α -propionate, minoxidil, and one or more pharmaceutically acceptable carriers. In some embodiments, the cortexolone-17 α -propionate is fully solubilized in the pharmaceutical formulation. In some embodiments, the pharmaceutical formulation

comprises cortexolone-17 α -propionate at a concentration from about 1 wt% to about 20 wt%, including from about 2 wt% to about about 15 wt%, from about 3 wt% to about about 10 wt%, or from about 4 wt% to about 7.5 wt%. In some embodiments, the pharmaceutical formulation comprises cortexolone-17 α -propionate at a concentration of about 1 wt%, about 2 wt%, about 3 wt%, about 4 wt%, about 5 wt%, about 6 wt%, about 7 wt%, about 7.5 wt%, about 8 wt%, about 9 wt%, or about 10 wt%. In some embodiments, the pharmaceutical formulation comprises minoxidil at a concentration from about 0.1 wt% to about 20 wt%, including from about 2 wt% to about 15 wt%, from about 3 wt% to about 10 wt%, from about 4 wt% to about about 7.5 wt%. In some embodiments, the pharmaceutical formulation comprises minoxidil at a concentration of about 1 wt%, about 2 wt%, about 3 wt%, about 4 wt%, about 5 wt%, about 6 wt%, about 7 wt%, about 7.5 wt%, about 8 wt%, about 9 wt%, about 10 wt%, about 11 wt%, about 12 wt%, about 13 wt%, about 14 wt%, about 15 wt%, about 16 wt%, about 17 wt%, about 18 wt%, about 19 wt%, or about 20 wt%. In some embodiments, the pharmaceutical formulation comprises a combination of cortexolone-17 α -propionate and minoxidil, each of them at a concentration from about 0.1 wt% to about 20 wt%, including from about 2 wt% to about 15 wt%, from about 3 wt% to about 10 wt%, or about from 4 wt% to about 7.5 wt%.

[0014] In some embodiments, the pharmaceutical formulation is a liquid or semi-solid formulation. In some embodiments, the pharmaceutical formulation is a solution, a suspension, an emulsion, a microemulsion, a cream, a paste, a gel, an ointment, or a foam. In some embodiments, the pharmaceutical formulation is a solution. In some of these embodiments, the solution comprises water, saline, a buffered saline solution, or a combination thereof. In some embodiments, the pharmaceutical formulation comprises less than about 5 percent water by weight.

[0015] In some embodiments, the one or more pharmaceutically acceptable carriers are selected from the group consisting of a polyol, a polyol ether, and a C₁-C₇ alcohol. In some embodiments, the C₁-C₇ alcohol is ethanol, isopropanol, methanol, or a combination thereof. In some embodiments, the C₁-C₇ alcohol is ethanol. In some embodiments, the polyol is selected from the group consisting of ethylene glycol, propylene glycol, glycerol, hexanetriol, and combinations thereof. In some embodiments, the polyol is propylene glycol. In some embodiments, the polyol ether is selected from the group consisting of polypropylene glycol, polyethylene glycol, polyethylene-polypropylene triblock copolymers, dipropylene glycol,

diethylene glycol monoethyl ether (Transcutol®), and combinations thereof. In some embodiments, the polyol ether is diethylene glycol monoethyl ether. In some embodiments, the polyol is propylene glycol, the polyol ether is diethylene glycol monoethyl ether, and the C₁-C₇ alcohol is ethanol.

[0016] In some embodiments, the pharmaceutical formulation further comprises at least one additive (e.g., 1, 2, 3, 4, 5, 6, 7, or 8) selected from an acid, a buffer, an antioxidant, an emulsifier, a penetration enhancer, a moisturizer, a preservative, a chelating agent, and combinations thereof. In some embodiments, the buffer is a phosphate buffer, citrate buffer, lactate buffer, or a combination thereof. In some embodiments, the antioxidant is selected from the group consisting of butylated hydroxytoluene (BHT), butylated hydroxyanisole (BHA), ascorbyl palmitate, ascorbic acid, alpha tocopherol, propyl gallate, 2,4,5-trihydroxybutyrophenone, 4-hydroxymethyl-2,6-di-tert-butylphenol, erythorbic acid, gum guaiac, thiodipropionic acid, dilauryl thiodipropionate, tert-butylhydroquinone, pharmaceutically acceptable salts or esters thereof, and combinations thereof. In some embodiments, the antioxidant is BHT, ascorbyl palmitate, or a combination of BHT and ascorbyl palmitate. In some embodiments, the emulsifier is selected from the group consisting of PEG-15 hydroxystearate (polyoxyl-15-hydroxystearate), PEG-30 stearate, PEG-40 laurate, PEG-40 oleate, a polysorbate (e.g., polysorbate 20, polysorbate 60, polysorbate 80), PEG-20 cetostearyl ether, polyoxyl 25 cetostearyl, cetomacrogol 1000, sorbitan monolaurate, sorbitan monopalmitate, sorbitan monooleate propylene glycol esters of fatty acids, polyglycerol esters of fatty acids, polyoxyl 5 castor oil, polyoxyl 15 castor oil, polyoxyl 35 castor oil, polyoxyl 40 hydrogenated castor oil, caprylocapryl polyoxyl-8 glycerides, caprylocaproyl polyoxylglycerides, lauroyl polyoxylglycerides, oleoyl polyoxylglycerides, and combinations thereof. In some embodiments, the emulsifier is a polysorbate, such as polysorbate 60, polysorbate 80, or a combination of polysorbate 60 and polysorbate 80. In some embodiments, the penetration enhancer is selected from the group consisting of a diol, a polyol, a fatty acid (e.g., myristic acid, palmitic acid, palmitoleic acid, stearic acid, oleic acid, linoleic acid, linolenic acid, or a combination thereof), a fatty alcohol, a fatty acid ester, an azone, a surfactant, a pyrrolidone, and combinations thereof. In some embodiments, the moisturizer is selected from the group consisting of a fatty alcohol, a fatty acid, a fatty acid ester, an oil, a polyethylene glycol, glycerin, an alpha hydroxy acid, and combinations thereof. In some

embodiments, the moisturizer is cetyl alcohol, cetearyl alcohol, stearyl alcohol, stearic acid, isopropyl myristate, isopropyl palmitate, cocoa butter, lanolin, liquid paraffin, shea butter, a silicone oil, castor oil, a polyethylene glycol, glycerin, lactic acid, glycolic acid, malic acid, citric acid, tartaric acid, or a combination thereof.

[0017] In certain embodiments, the present disclosure provides a method of treating alopecia, the method comprising topically administering to a subject in need thereof the topical pharmaceutical formulation described herein, wherein the topical administration of the pharmaceutical formulation for at least six months achieves a weighted average Hair Growth Assessment (HGA) score of about 0.30 in comparison with vehicle.

[0018] In certain embodiments, the present disclosure provides a method of treating alopecia, the method comprising topically administering to a subject in need thereof a topical pharmaceutical formulation described herein, wherein the topical administration of the pharmaceutical formulation for at least six months achieves a weighted average Investigator's Global Assessment (IGA) score of about 0.43 in comparison with vehicle.

[0019] In certain embodiments, the present disclosure provides a method of treating alopecia, the method comprising topically administering to a subject in need thereof a topical pharmaceutical formulation described herein, wherein the topical administration of the pharmaceutical formulation for at least six months is free from systemic antiandrogenic side-effects.

[0020] In certain embodiments, the present disclosure provides a method of treating alopecia, the method comprising topically administering to a subject in need thereof a topical pharmaceutical formulation described herein, wherein the topical administration of the pharmaceutical formulation provides:

[0021] a) a mean change from baseline in Target Area Hair Count equal to or higher than 9 hairs/cm² after 6 months of daily or BID application; or

[0022] b) a mean change from baseline in Target Area Hair Count equal to or higher than 10 hairs/cm² after 6 months of daily or BID application; or

[0023] c) a mean change from baseline in Target Area Hair Count equal to or higher than 11 hairs/cm² after 6 months of daily or BID application; or

[0024] d) a mean change from baseline in Target Area Hair Count equal to or higher than 12 hairs/cm² after 6 months of daily or BID application; or

- [0025] e) a weighted average HGA score equal to or higher than 0.20 after 6 months of daily or BID application; or
- [0026] f) a weighted average HGA score equal to or higher than 0.30 after 6 months of daily or BID application; or
- [0027] g) a weighted average HGA score equal to or higher than 0.40 after 6 months of daily or BID application; or
- [0028] h) a weighted average IGA score equal to or higher than 0.10 after 6 months of daily or BID application; or
- [0029] i) a weighted average IGA score equal to or higher than 0.20 after 6 months of daily or BID application; or
- [0030] j) a weighted average IGA score equal to or higher than 0.30 after 6 months of daily or BID application; or
- [0031] k) a favorable (positive) HGA score in at least about 10 % of subjects after 6 months of daily or BID application; or
- [0032] l) a favorable (positive) HGA score in at least about 20 % of subjects after 6 months of daily or BID application; or
- [0033] m) a favorable (positive) HGA score in at least about 30 % of subjects after 6 months of daily or BID application; or
- [0034] n) a favorable (positive) IGA score in at least about 10 % of subjects after 6 months of daily or BID application; or
- [0035] o) a favorable (positive) IGA score in at least about 20 % of subjects after 6 months of daily or BID application; or
- [0036] p) a favorable (positive) IGA score in at least about 30 % of subjects after 6 months of daily or BID application; or
- [0037] q) a favorable (positive) IGA score in at least about 40 % of subjects after 6 months of daily or BID application.
- [0038] In a further embodiment the topical pharmaceutical formulation of the present invention is for use in the treatment of hair loss in a subject in need thereof.

DETAILED DESCRIPTION

- [0039] The articles “a,” “an,” and “the” are used herein to refer to one or to more than one (i.e., to at least one) of the grammatical object of the article. By way of example, “an element” means one element or more than one element.
- [0040] As used herein, the term “about” means within an acceptable error range for the particular value as determined by one of ordinary skill in the art, which depends in part on how the value is measured or determined, i.e., the limitations of the measurement system. For example, “about” can mean within 3 or more than 3 standard deviations, per the practice in the art. Alternatively, “about” can mean a range of up to 10% (e.g., up to 5%, up to 1%) of a given value.
- [0041] As used herein, the phrase “active agent” refers to either cortexolone-17 α -propionate or minoxidil.
- [0042] The term “alopecia” as used herein refers to, collectively, or individually as specified, androgenetic alopecia (AGA), alopecia areata (including diffuse alopecia areata, alopecia areata monolocularis, alopecia areata multilocularis, ophiasis, alopecia totalis, and alopecia universalis), telogen effluvium, anagen effluvium, and traction alopecia.
- [0043] As used herein, the term “anhydrous” means substantially free of water, i.e., having less than about 5 wt% water, and, in certain embodiments as specified herein, less than about 3 wt% water.
- [0044] As used herein, the term “at least” prior to a number or series of numbers is understood to include the number associated with the term “at least,” and all subsequent numbers or integers that could logically be included, as clear from context. When at least is present before a series of numbers or a range, it is understood that “at least” can modify each of the numbers in the series or range. For example, “at least 3” means at least 3, at least 4, at least 5, etc. When at least is present before a component in a method step, then that component is included in the step, whereas additional components are optional.
- [0045] As used herein, the term “Bis In Die” or “BID” means “twice a day.”
- [0046] As used herein, the term “buffer” refers to a compound or group of compounds (e.g., a weak conjugate acid-base pair, such as a weak acid and its conjugate base or a weak base and its conjugate acid) that controls the pH of a solution within a desired range. In some

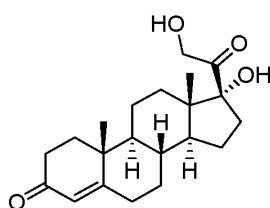
embodiments, the conjugate base can be added as a Group I or Group II salt. Examples of a buffer include, e.g., a phosphate buffer, citrate buffer, lactate buffer, or a combination thereof.

[0047] As used herein, the phrase “C₁-C₇ alcohol” refers to an alcohol having 1, 2, 3, 4, 5, 6, or 7 carbons that is suitable for use in a topical pharmaceutical formulation. Examples of such C₁-C₇ alcohols include, but are not limited to, methanol, ethanol, isopropanol, n-butanol, n-propanol, benzyl alcohol, and the like. Without wishing to be bound by any particular theory, it is believed that C₁-C₇ alcohols, and particularly short chain C₁-C₇ alcohols, like C₂-C₃ alcohols (e.g., ethanol, n-propanol, or isopropyl alcohol), contribute to the spreadability of the pharmaceutical formulations described herein.

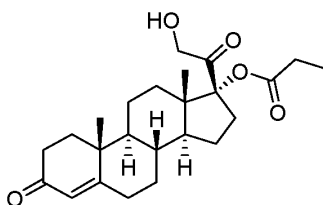
[0048] As used herein, the term “chelating agent” refers to a compound that can bind metal ions or metallic compounds. In some embodiments, a chelating agent can stabilize the formulation by preventing, e.g., oxidation or precipitation. Suitable chelating agents include, e.g., citric acid, phytic acid, sodium phytate, clioquinol, ethylenediaminetetraacetic acid (EDTA) (e.g., disodium EDTA, tetrasodium EDTA), etidronic acid, galactaric acid, tetrahydroxypropyl ethylenediamine, sodium metasilicate, or a combination thereof.

[0049] As used herein, the term “co-administration” means concurrent or sequential administration of two different active agents, i.e., cortexolone-17 α -propionate and minoxidil. In some embodiments, the active agents are administered close enough in time to each other that the first and second therapeutic agents are simultaneously present in subjects receiving the co-administration.

[0050] As used herein the term “cortexolone” (also known as “11-deoxycortisol” or “Reichstein’s substance”) refers to the compound having the structure:



[0051] As used herein, the term “cortexolone-17 α -propionate” refers to the compound 17 α -propionyloxy-21-hydroxy-pregna-4-ene-3,20-dione, which is also known as clascoterone and is equivalent to the chemical structure:



[0052] As used herein, the term “degradation product” refers to those compounds that result from the *in vitro* degradation of cortisone-17 α -propionate. Exemplary known cortisone-17 α -propionate degradation products include, but are not limited to, cortisone-21-propionate and cortisone.

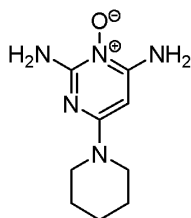
[0053] As used herein, the term “ester” refers to esterified organic solvents including, but not limited to, ethyl acetate and ethyl lactate.

[0054] As used herein, the term “ethanol,” refers to ethyl alcohol, i.e., CH₃CH₂OH, and includes pure (absolute) ethanol and 96° ethanol, the latter being ethanol containing water in an amount typically ranging from about 4% to about 5.1% by volume. In some embodiments, the ethanol is denatured alcohol, such as specially denatured (SD) alcohol, which includes a denaturing agent to prevent consumption.

[0055] As used herein, the term “fatty” refers to an aliphatic carbon chain that is either saturated or unsaturated. The chain is any suitable length, such as C₄-C₂₈, including more specifically C₁₀-C₂₀, C₁₂-C₂₂, and C₁₂-C₁₈ chain lengths.

[0056] As used herein, the term “gelling agent” refers to a pharmaceutically acceptable compound that can turn a water or oil phase into a gel. A gelling agent acts as a thickening agent, typically without imparting stiffness. The gelling agent can be an inorganic gelling agent, an organic gelling agent, a hydrogel, an organogel, or a combination thereof.

[0057] As used herein, the term “minoxidil” refers to the compound 2,4-diamino-6-piperidinopyrimidine 3-oxide, which is equivalent to the chemical structure:



In some embodiments, the minoxidil is present in the form of a salt. The salt can be, e.g., acetate, citrate, succinate, benzoate, hydrochloride, sulfate, phosphate, or lactate. In some embodiments, an acetate or lactate salt of minoxidil is used.

[0058] As used herein, the term “metabolite” refers to those compounds that result from the *in vivo* metabolism or degradation of an active agent, such as cortexolone-17 α -propionate or minoxidil. Exemplary known metabolites of cortexolone-17 α -propionate include, but are not limited to, cortexolone and tetrahydrocortexolone. Exemplary known metabolites of minoxidil include, but are not limited to, minoxidil sulfate.

[0059] As used herein, the term “moisturizer” refers to those compounds that impart moisture to skin, soften skin, or both. Exemplary moisturizers are emollients that include, e.g., a fatty alcohol, a fatty acid, a fatty acid ester, an oil, a polyethylene glycol, glycerin, an alpha hydroxy acid (e.g., lactic acid, glycolic acid, malic acid, citric acid, or tartaric acid), and combinations thereof. Specific examples of a moisturizer include, e.g., cetyl alcohol, ceteryl alcohol, stearyl alcohol, stearic acid, isopropyl myristate, isopropyl palmitate, cocoa butter, lanolin, liquid paraffin, shea butter, a silicone oil, castor oil, a polyethylene glycol, glycerin, lactic acid, glycolic acid, malic acid, citric acid, tartaric acid, or a combination thereof; preferably said moisturizer are selected from cetyl alcohol and stearyl alcohol.

[0060] As used herein the phrase “natural oil” refers to those oils isolable from natural sources. Exemplary natural oils include, but are not limited to, olive oil, jojoba oil, coconut oil, almond oil, cottonseed oil, safflower oil, sunflower oil, sesame oil, soybean oil, castor oil, calendula oil, and the like.

[0061] As used herein, the phrase “penetration enhancer” refers to those pharmaceutically acceptable compounds that increase penetration of the active agent through the dermis. Exemplary penetration enhancers include, e.g., hydroxypropyl β -cyclodextrin, polyoxyethylene alkyl ethers, polyoxyl glycerides, dimethyl sulfoxide, pyrrolidone, N-methyl-2-pyrrolidone, diethylene glycol monoethyl ether (e.g., TRANSCUTOL™, Gattefossé, France), dimethyl isosorbide, diethyl sebacate, azone, menthol, nerol, camphor, methyl salicylate, polysorbate 80 (e.g., TWEEN™ 80, Sigma-Aldrich, St. Louis, MO), SDS, benzalkonium chloride, polyoxyl 40 hydrogenated castor oil (e.g., CREMOPHOR™ RH40, KOLLIPHOR™ RH40, BASF, Germany), didecyldimethylammonium bromide (DDAB), didecyltrimethylammonium bromide (DTAB), fatty acids esters (e.g., isopropyl myristate,

isopropyl palmitate), fatty acids (e.g., oleic acid, palmitic acid, linoleic acid, and salts thereof), fatty alcohols (e.g., oleyl alcohol, myristyl alcohol, stearyl alcohol), medium-chain triglycerides, and combinations of any of the foregoing.

[0062] As used herein, and unless clear from the context in which it is used that it means otherwise, the term “pH” should be considered an “apparent pH” to acknowledge the fact that the behavior of a pH electrode in a complex multicomponent dermatological vehicle which is not totally aqueous in nature cannot be considered a “pH” in the strictest sense.

[0063] As used herein, the term “polyol” refers to organic molecules containing two or more hydroxyl groups. Exemplary polyols include, but are not limited to, ethylene glycol, propylene glycol, glycerol, hexanetriol, and the like, preferably propylene glycol,

[0064] As used herein, the term “polyol ether” refers to a polyol ether suitable for use in a topical pharmaceutical formulation. Exemplary polyol ethers include, but are not limited to, polypropylene glycol, polyethylene glycol, polyethylene-polypropylene triblock copolymers, dipropylene glycol, diethylene glycol monoethyl ether, and the like.

[0065] As used herein, the term “preservative” refers to a compound with antimicrobial activity, such as an antibacterial or antifungal. Suitable preservatives include, e.g., a paraben (e.g., methyl paraben, ethyl paraben, propyl paraben, butyl paraben), a benzoate (e.g., sodium benzoate), a sorbate (e.g., potassium sorbate), a quaternary ammonium compound (e.g., benzalkonium chloride, benzethonium chloride), an alcohol (e.g., chlorobutanol, benzyl alcohol, ethanol, phenol, m-cresol, chlorocresol), sodium metabisulfite, imidazolidinyl urea, glycerin, propylene glycol, or a combination thereof.

[0066] As used herein, the term “solvent” means one or a mixture of more than one pharmaceutically acceptable solvents suitable for topical application, including without limitation, the scalp, that is used to solubilize cortexolone-17 α -propionate and/or minoxidil in a formulation described herein.

[0067] As used herein “tetrahydrocortexolone” refers to the compound having the Chemical Abstract Service (CAS) Registry Number 68-60-0.

[0068] As used herein, the terms “treat,” “treating,” and “treatment” refer to any indicia of success in the treatment or amelioration of an injury, disease, or condition, including any objective or subjective parameter such as abatement; remission; diminishing of one or more symptoms or making the injury, disease, or condition more tolerable to the subject; slowing in

the rate of degeneration or decline; or improving a subject's physical or mental well-being. The treatment or amelioration of symptoms can be based on objective or subject parameters, including the results of a physical examination, neuropsychiatric examinations, or psychiatric evaluation.

[0069] As used herein, the term “preventing” refers to keeping from happening or existing, or alternatively delaying the onset or recurrence of a disease, disorder, or condition to which such term applies, or of one or more symptoms associated with a disease, disorder, or condition. The term “preventing” also refers to reducing the incidence of a disease, disorder, or condition. The term “prevention” refers to the act of preventing.

[0070] As used herein, the term “sequentially” means that to a subject, a first active agent is co-administered to the subject in a first period of time followed by an administration of a second active agent in a second period of time. In other words the term “sequentially” includes a first therapy in a first period of time followed by a second therapy in a second period of time. The first and second time periods can be separated on the order of seconds, minutes, hours, or days, as needed. In some embodiments, the first and second time periods are separated by seconds (e.g., about 60 seconds or less, about 30 seconds or less).

[0071] As used herein, the term “subject” typically is directed to a mammal. In some embodiments, the subject to be treated is a human.

[0072] As used herein, the phrase “wt%” is intended to encompass and disclose embodiments wherein the wt% is wt% by volume (w/v) and percentage of weight by total weight (w/w) for a given value. By way of example, an embodiment comprising 10 wt% of element “X” discloses embodiments comprising both 10 wt% “X” (w/v) and 10 wt% “X” (w/w). Similarly, and again by way of example, an embodiment comprising 10 wt% “X,” 20 wt% “Y,” and 60 wt% “Z,” discloses embodiments comprising: a) 10 wt% “X” (w/v), 20 wt% “Y” (w/v), and 60 wt% “Z” (w/v); and b) 10 wt% “X” (w/w), 20 wt% “Y” (w/w), and 60 wt% “Z” (w/w). The foregoing notwithstanding, in some embodiments, a value will be marked specifically “(w/w)” or “(w/v).” In those instances, the value should be interpreted as disclosing only the labeled value, i.e. only (w/w) or only (w/v) – but not both.

[0073] As used herein, the terms “comprises,” “comprising,” “having,” “including,” “containing,” and the like are open-ended terms meaning “including, but not limited to.” To the extent a given embodiment disclosed herein “comprises” certain elements, it should be

understood that present disclosure also specifically contemplates and discloses embodiments that “consist essentially of” those elements and that “consist of” those elements.

[0074] As used herein the terms “consists essentially of,” “consisting essentially of,” and the like are to be construed as a semi-closed terms, meaning that no other ingredients which materially affect the basic and novel characteristics of an embodiment are included.

[0075] As used herein, the terms “consists of,” “consisting of,” and the like are to be construed as closed terms, such that an embodiment “consisting of” a particular set of elements excludes any element, step, or ingredient not specified in the embodiment.

[0076] As used herein, the terms “Target Area Hair Count” or “TAHC” refer to the change, from baseline, in the number of non-vellus hairs in a target area of the scalp. The target area can be, for example, 1 cm² or a circle of a diameter of 1 inch (5.1 cm²).

[0077] As used herein, the terms “Hair Growth Assessment” or “HGA” refer to a score given by the subject comparing the baseline standardized global photo of the subject’s scalp with a “real time” standardized global photo.

[0078] As used herein, the terms “Investigator’s Global Assessment” or “IGA” refer to a score given by an evaluator comparing the baseline standardized global photo of the subject’s scalp with a “real time” standardized global photo.

The Method

[0079] The present disclosure provides a method of treating hair loss, such as alopecia, in a subject in need thereof, comprising topically administering to the subject an effective amount of cortexolone-17 α -propionate and an effective amount of minoxidil. Topical administration comprises application of cortexolone-17 α -propionate and minoxidil to the skin and/or the scalp of the subject, as described herein.

[0080] In preferred embodiments, the subject can be a mammal, such as a human.

[0081] In some embodiments, the hair loss can be associated with alopecia. Alopecia can include, e.g., androgenetic alopecia (AGA), alopecia areata (including diffuse alopecia areata, alopecia areata monocularis, alopecia areata multilocularis, ophiasis, alopecia totalis and alopecia universalis), telogen effluvium, anagen effluvium, and traction alopecia. In some embodiments, the alopecia to be treated can be AGA.

[0082] In some embodiments, the cortexolone-17 α -propionate and minoxidil are co-administered sequentially in that a first active agent can be administered to the subject in a first period of time followed by an administration of the second active agent in a second period of time. The particular order of administration is not limited. In some embodiments, the cortexolone-17 α -propionate can be administered first, and the minoxidil can be administered second. In other embodiments, the minoxidil can be administered first, and the cortexolone-17 α -propionate can be administered second. The time period between the two administering steps can be separated on the order of seconds, minutes, hours, or days, as needed. In some embodiments, the first and second administering steps can be separated by seconds (e.g., about 60 seconds or less, about 30 seconds or less).

[0083] In certain embodiments, the present disclosure provides a method of treating alopecia, the method comprising topically administering to a subject in need thereof a topical pharmaceutical formulation described herein, wherein the topical administration of the pharmaceutical formulation for at least six months achieves a weighted average Hair Growth Assessment (HGA) score of about 0.30 in comparison with vehicle.

[0084] In certain embodiments, the present disclosure provides a method of treating alopecia, the method comprising topically administering to a subject in need thereof a topical pharmaceutical formulation described herein, wherein the topical administration of the pharmaceutical formulation for at least six months achieves a weighted average Investigator's Global Assessment (IGA) score of about 0.43 in comparison with vehicle.

[0085] In certain embodiments, the present disclosure provides a method of treating alopecia, the method comprising topically administering to a subject in need thereof a topical pharmaceutical formulation described herein, wherein the topical administration of the pharmaceutical formulation for at least six months does not result in systemic antiandrogenic side-effects in the subject.

[0086] In certain embodiments, the present disclosure provides a method of treating alopecia, the method comprising topically administering to a subject in need thereof a topical pharmaceutical formulation described herein, wherein the topical administration of the pharmaceutical formulation provides:

[0087] a) a mean change from baseline in Target Area Hair Count equal to or higher than 9 hairs/cm² after 6 months of daily or BID application; or

- [0088] b) a mean change from baseline in Target Area Hair Count equal to or higher than 10 hairs/cm² after 6 months of daily or BID application; or
- [0089] c) a mean change from baseline in Target Area Hair Count equal to or higher than 11 hairs/cm² after 6 months of daily or BID application; or
- [0090] d) a mean change from baseline in Target Area Hair Count equal to or higher than 12 hairs/cm² after 6 months of daily or BID application; or
- [0091] e) a weighted average HGA score equal to or higher than 0.20 after 6 months of daily or BID application; or
- [0092] f) a weighted average HGA score equal to or higher than 0.30 after 6 months of daily or BID application; or
- [0093] g) a weighted average HGA score equal to or higher than 0.40 after 6 months of daily or BID application; or
- [0094] h) a weighted average IGA score equal to or higher than 0.10 after 6 months of daily or BID application; or
- [0095] i) a weighted average IGA score equal to or higher than 0.20 after 6 months of daily or BID application; or
- [0096] j) a weighted average IGA score equal to or higher than 0.30 after 6 months of daily or BID application; or
- [0097] k) a favorable (positive) HGA score in at least about 10 % of subjects after 6 months of daily or BID application; or
- [0098] l) a favorable (positive) HGA score in at least about 20 % of subjects after 6 months of daily or BID application; or
- [0099] m) a favorable (positive) HGA score in at least about 30 % of subjects after 6 months of daily or BID application; or
- [0100] n) a favorable (positive) IGA score in at least about 10 % of subjects after 6 months of daily or BID application; or
- [0101] o) a favorable (positive) IGA score in at least about 20 % of subjects after 6 months of daily or BID application; or
- [0102] p) a favorable (positive) IGA score in at least about 30 % of subjects after 6 months of daily or BID application; or

- [0103] q) a favorable (positive) IGA score in at least about 40 % of subjects after 6 months of daily or BID application.

Pharmaceutical Formulations

- [0104] In some embodiments, the cortexolone-17 α -propionate and minoxidil can be co-administered sequentially. In such embodiments, the cortexolone-17 α -propionate and minoxidil can be provided in separate pharmaceutical formulations. Each pharmaceutical formulation can be as described herein.
- [0105] In other embodiments, the cortexolone-17 α -propionate and minoxidil can be co-administered simultaneously (i.e., concomitantly). In some embodiments, the cortexolone-17 α -propionate and minoxidil can be provided in the same pharmaceutical formulation (e.g., a combination formulation).
- [0106] The pharmaceutical formulation can be in any form suitable for topical administration. In some embodiments, the pharmaceutical formulation can be a liquid or semi-solid formulation depending on the carriers and excipients that can be present, as described herein. Examples of the liquid or semi-solid formulation include, e.g., a solution, a suspension, an emulsion, a microemulsion, a cream, a paste, a gel, an ointment, or a foam. In preferred embodiments, the pharmaceutical formulation can be a solution.
- [0107] In some embodiments, the formulation can be a cream. In some embodiments, the cream can comprise equal parts oil and water in the form of an emulsion.
- [0108] In some embodiments, the formulation can be a paste. In some embodiments, the paste can comprise a fatty acid (e.g., myristic acid, palmitic acid, palmitoleic acid, stearic acid, oleic acid, linoleic acid, linolenic acid, or a combination thereof), an oil, or a combination thereof.
- [0109] In some embodiments, the formulation can be a gel that includes at least one gelling agent. The gelling agent can be, e.g., an inorganic gelling agent (e.g., aluminum hydroxide gel, bentonite magma), an organic gelling agent (e.g., a carbomer polymer, tragacanth), a hydrogel (e.g., an organic hydrogel, a natural or synthetic gum, or an inorganic hydrogel), an organogel (e.g., a hydrocarbon type, a vegetable fat, a soap based grease, or a hydrophilic organogel), or a combination thereof. The organic hydrogel can include, e.g., pectin paste and tragacanth jelly. The natural or synthetic gum can include, e.g., methylcellulose, sodium

carboxymethyl cellulose, and poloxamer. The inorganic hydrogel can include, e.g., bentonite gel, smectite (e.g., VEEGUM™, Vanderbilt Minerals, LLC, Norwalk, CT), or silica. The hydrocarbon type organogel can include, e.g., petrolatum and mineral oil/polyethylene gel. The vegetable fat type organogel can include, e.g., cocoa butter. The soap-based grease type organogel can include, e.g., aluminum stearate with heavy mineral oil gel. The hydrophilic organogels can include, e.g., carbowax bases, such as polyethylene glycol (PEG) ointment.

[0110] In some embodiments, the gelling agent can be a carbomer polymer. The term “carbomer” is a generic name for high molecular weight polymer of acrylic acid lightly crosslinked with allyl ethers of polyalcohols (e.g., allyl sucrose, allyl pentaerythritol). The term also can be used to describe CARBOPOL™ polymers (Lubrizol Corp., Wickliffe, OH).

[0111] In some embodiments, the formulation can be an ointment. In some embodiments, the ointment can comprise a hydrocarbon (e.g., paraffin, petrolatum), lanolin, beeswax, a macrogol, a polyethylene glycol, an emulsifying wax, an alkyltrimethylammonium bromide (e.g., a cetrimide), a vegetable oil (e.g., olive oil, jojoba oil, coconut oil, almond oil, cottonseed oil, safflower oil, sunflower oil, sesame oil, soybean oil, castor oil, or calendula oil), or a combination thereof. In some embodiments, the ointment can comprise about 20 wt% or less of water.

[0112] In some embodiments, the formulation can be a foam. A foam formulation can be used in combination with one or more acceptable propellants, such as propane, butane, isobutene, nitrogen, Propellant P75 and the like.

The Solvent

[0113] In some embodiments of when the pharmaceutical formulation can be a solution, the pharmaceutical formulation can comprise water, saline (e.g., a sodium chloride salt solution), a buffered saline solution (e.g., a phosphate-buffered saline solution), or a combination thereof.

[0114] In some embodiments, the pharmaceutical formulation can be considered anhydrous and can contain less than about 5 percent by weight (wt%) (e.g., less than about 4 wt%, less than about 3 wt%, less than about 2 wt%, or less than about 1 wt%) of water.

[0115] In some embodiments, particularly in embodiments that contain less than about 5 wt% water, the cortexolone-17 α -propionate can be fully solubilized in the pharmaceutical

formulation. The topical pharmaceutical formulation can comprise one or more pharmaceutically acceptable carriers (e.g., solvents) in addition to or in place of water, such as a polyol, a polyol ether, a C₁-C₇ alcohol, and combinations thereof.

[0116] In some embodiments, the pharmaceutical formulation can comprise a solvent selected from the group comprising or the group consisting of: water, a C₁-C₇ alcohol, a polyol ether, a polyol, polyvinyl alcohol (PVA), polyvinyl pyrrolidone (PVP), a natural oil, an ester, tricaprylin (2,3-di(octanoyloxy)propyl octanoate), a medium-chain triglyceride, caprylocaproyl polyoxyl-8 glycerides, and combinations of any of the foregoing. In preferred embodiments, the one or more pharmaceutically acceptable carriers are selected from the group consisting of a polyol, a polyol ether, a C₁-C₇ alcohol, and combinations thereof.

[0117] In some embodiments, the pharmaceutical formulation can comprise at least about 50 wt% solvent (e.g., water, saline, a buffered saline solution, a polyol, a polyol ether, a C₁-C₇ alcohol, or a combination thereof). In other embodiments, the pharmaceutical formulation can comprise at least about 60 wt% solvent. In other embodiments, the pharmaceutical formulation can comprise at least about 70 wt% solvent. In other embodiments, the pharmaceutical formulation can comprise at least about 80 wt% solvent. In other embodiments, the pharmaceutical formulation can comprise at least about 85 wt% solvent, at least about 90 wt% solvent, at least about 91 wt% solvent, at least about 92 wt% solvent; at least about 93 wt% solvent; at least about 94 wt% solvent; or at least about 95 wt% solvent.

[0118] In some embodiments, the solvent can comprise a mixture of a C₁-C₇ alcohol, a polyol ether, and a polyol. In such embodiments, the pharmaceutical formulation can comprise from about 10 to about 50 wt% of the polyol ether; from about 5 wt% to about 55 wt% of the polyol; and about 5 to about 50 wt% of the C₁-C₇ alcohol. In some embodiments, the mixture of the C₁-C₇ alcohol, the polyol ether, and the polyol can be present at about a 1:1:1 ratio on a w/w/w basis. In some embodiments, each of the C₁-C₇ alcohol, the polyol ether, and the polyol can be present at about 30 wt%.

[0119] In some embodiments, the pharmaceutical formulation can comprise from about 15 to about 45 wt% of the polyol ether; from about 20 to about 40 wt% of the polyol ether; from about 25 to about 35 wt% of the polyol ether; or from about 30 to about 35 wt% of the polyol ether. In some embodiments, the pharmaceutical formulation can comprise about 30 wt% of

the polyol ether. In other embodiments, the pharmaceutical formulation can comprise about 32 wt% of the polyol ether.

[0120] In some embodiments, the polyol ether can be selected from the group comprising or the group consisting of: polyethylene glycol, polypropylene glycol, polyethylene-polypropylene triblock copolymers, dipropylene glycol, diethylene glycol monoethyl ether (TRANSCUTOL™, Gattefossé, France), and combinations thereof.

[0121] When the polyol ether can be a polyethylene glycol (PEG), the PEG can have a number average molecular weight (M_n) that can be about 200 g/mol to about 6,000 g/mol. In some embodiments, the PEG can be selected from the group comprising or the group consisting of: PEG 200, PEG 300, PEG 400, PEG 540, and PEG 600. In some embodiments, the polyol ether can be PEG 200. In other embodiments, the polyol ether can be PEG 400. In still other embodiments, the polyol ether can be diethylene glycol monoethyl ether.

[0122] In some embodiments, the polyol can be selected from the group comprising or the group consisting of: propylene glycol, ethylene glycol, glycerol, hexanetriol, and combinations thereof. In some embodiments, the polyol can be glycerol. In preferred embodiments, the polyol can be propylene glycol.

[0123] In some embodiments, the polyol can be present in an amount ranging from about 5 wt% to about 55 wt% of the total formulation; from about 10 wt% to about 50 wt% of the total formulation; from about 20 wt% to about 45 wt% of the total formulation; and In some embodiments, from about 25 wt% to about 40 wt%. In a particular embodiment, the polyol can comprise about 30 wt% of the total formulation. In a further embodiment, the polyol comprising about 30 wt% of the total formulation can be propylene glycol.

[0124] In some embodiments, the pharmaceutical formulation can comprise from about 5 to about 50 wt% of the C₁-C₇ alcohol. In some embodiments, the pharmaceutical formulation can comprise from about 15 to about 45 wt% of the C₁-C₇ alcohol; from about 20 to about 40 wt% of the C₁-C₇ alcohol; or from about 25 to about 35 wt% of the C₁-C₇ alcohol. In some embodiments, the pharmaceutical formulation can comprise about 30 wt% of the C₁-C₇ alcohol. In still further embodiments, the pharmaceutical formulation can comprise the C₁-C₇ alcohol in an amount ranging from about 10 wt% to about 40 wt%, or from about 15 wt% to about 35 wt%.

- [0125] In some embodiments, the C₁-C₇ alcohol can be selected from the group comprising or the group consisting of methanol, ethanol, isopropanol, n-butanol, n-propanol, and benzyl alcohol. In preferred embodiments, the C₁-C₇ alcohol can be ethanol. In some embodiments, the ethanol comprises about 30 wt% of the total formulation. In other embodiments, the C₁-C₇ alcohol can be isopropanol.
- [0126] In some embodiments, the C₁-C₇ alcohol can contain a small water fraction, generally in the range of from about 4 percent to about 5.1 percent by volume. In embodiments wherein the pharmaceutical formulation can be anhydrous, the C₁-C₇ alcohol having from about 4 percent to about 5.1 percent water by volume can be present in the pharmaceutical formulation in an amount such that the water content in the finished formulation itself can be less than about 5 wt% or less than about 3 wt%.
- [0127] In some embodiments, the solvent can comprise a polyol, a polyol ether, and a C₁-C₇ alcohol. In some embodiments, the solvent can comprise ethanol as the C₁-C₇ alcohol, diethylene glycol monomethyl ether as the polyol ether, and propylene glycol as the polyol. These solvents can be present in any acceptable ratio, but typically are present such that each is about 25 to about 35 wt% of the pharmaceutical formulation.

Other Components

- [0128] In some embodiments, the pharmaceutical formulation can further comprise at least one additive selected from an acid, a buffer, an antioxidant, an emulsifier, a penetration enhancer, a moisturizer, a preservative, a chelating agent, and combinations thereof.
- [0129] In some embodiments, the pharmaceutical formulation can comprise from about 0.1 wt% to about 50 wt% of each additive (e.g., an acid, a buffer, an antioxidant, an emulsifier, a penetration enhancer, a moisturizer, a preservative, a chelating agent) relative to the total weight of the composition (i.e., making up 100 wt%). For example, each additive can be present in the pharmaceutical formulation in an amount from about 0.1 wt% to about 45 wt%, about 0.1 wt% to about 40 wt%, about 0.1 wt% to about 35 wt%, about 0.1 wt% to about 30 wt%, about 0.1 wt% to about 25 wt%, about 0.1 wt% to about 20 wt%, about 0.1 wt% to about 15 wt%, about 0.1 wt% to about 10 wt%, about 0.1 wt% to about 5 wt%, about 0.1 wt% to about 2 wt%, about 0.5 wt% to about 50 wt%, about 0.5 wt% to about 45 wt%, about 0.5 wt% to about 40 wt%, about 0.5 wt% to about 35 wt%, about 0.5 wt% to about 30 wt%, about 0.5

wt% to about 25 wt%, about 0.5 wt% to about 20 wt%, about 0.5 wt% to about 15 wt%, about 0.5 wt% to about 10 wt%, about 0.5 wt% to about 5 wt%, about 0.5 wt% to about 2 wt%, about 1 wt% to about 50 wt%, about 1 wt% to about 45 wt%, about 1 wt% to about 40 wt%, about 1 wt% to about 35 wt%, about 1 wt% to about 30 wt%, about 1 wt% to about 25 wt%, about 1 wt% to about 20 wt%, about 1 wt% to about 15 wt%, about 1 wt% to about 10 wt%, about 1 wt% to about 5 wt%, about 1 wt% to about 2 wt%, about 50 wt%, about 48 wt%, about 46 wt%, about 44 wt%, about 42 wt%, about 40 wt%, about 38 wt %, about 36 wt%, about 34 wt%, about 2 wt%, about 30 wt%, about 28 wt%, about 26 wt%, about 24 wt%, about 22 wt%, about 20 wt%, about 18 wt%, about 16 wt%, about 14 wt%, about 12 wt%, about 10 wt%, about 8 wt%, about 6 wt%, about 5 wt%, about 4 wt%, about 3 wt%, about 2 wt%, about 1 wt%, about 0.9 wt%, about 0.8 wt%, about 0.7 wt%, about 0.6 wt%, about 0.5 wt%, about 0.4 wt%, about 0.3 wt%, about 0.2 wt%, or about 0.1 wt% of the total weight of the composition.

[0130] In some embodiments, the pharmaceutical formulation can include an acid to help solubilize one or both of the active agents, to maintain a desired pH, or both. Any suitable acid can be used, such as a mineral acid (e.g., hydrochloric acid, sulfuric acid, nitric acid, or phosphoric acid), an organic acid (e.g., citric acid, acetic acid, succinic acid, or maleic acid), or mixtures thereof. Examples of suitable acid additives include, e.g., 1-hydroxy-2-naphthoic acid; 2,2-dichloroacetic acid; 2-hydroxyethanesulfonic acid; 2-oxoglutaric acid; 4-acetamidobenzoic acid; 4-aminosalicylic acid; acetic acid; adipic acid; L-ascorbic acid; L-aspartic acid; benzenesulfonic acid; benzoic acid; (+)-camphoric acid; (+)-camphor-10-sulfonic acid; capric acid (decanoic acid); caproic acid (hexanoic acid); caprylic acid (octanoic acid); carbonic acid; cinnamic acid; citric acid; cyclamic acid; dodecylsulfuric acid; ethane-1,2-disulfonic acid; ethanesulfonic acid; formic acid; fumaric acid; galactaric acid; gentisic acid; D-glucoheptonic acid; D-gluconic acid; D-glucuronic acid; glutamic acid; glutaric acid; glycerophosphoric acid; glycolic acid; hippuric acid; hydrobromic acid; hydrochloric acid; isobutyric acid; lactic acid; lactobionic acid; lauric acid; maleic acid; L-malic acid; malonic acid; mandelic acid; methanesulfonic acid; naphthalene-1,5-disulfonic acid; naphthalene-2-sulfonic acid; nicotinic acid; nitric acid; oleic acid; oxalic acid; palmitic acid; pamoic acid; phosphoric acid; propionic acid; L-pyroglutamic acid; salicylic acid; sebacic acid; stearic acid; succinic acid; sulfuric acid; L-tartaric acid; thiocyanic acid; p-toluenesulfonic acid; and

undecylenic acid. In some embodiments, acetic acid, citric acid, or lactic acid can be added to the pharmaceutical formulation.

[0131] In some embodiments, the acid can be added in a sufficient amount so that the pH of the pharmaceutical formulation can be about 7.0 or less (e.g., about 4 to about 7.0, about 4 to about 6.5, about 4 to about 6, about 4 to about 5.5, about 4 to about 5, about 4.5 to about 7.0, about 4.5 to about 6.5, about 4.5 to about 6, about 4.5 to about 5.5, about 4.5 to about 5, about 5 to about 7.0, about 5 to about 6.5, about 5 to about 6, about 5 to about 5.5, about 5.5 to about 7.0, about 5.5 to about 6.5, about 5.5 to about 6, about 6 to about 7.0, or about 6 to about 6.5).

[0132] In some embodiments, the pharmaceutical formulation can include a buffer to help maintain the pH of the formulation within a desired range. In some embodiments, the buffer can be a phosphate buffer, citrate buffer, lactate buffer, or a combination thereof. In some embodiments, the formulation can comprise phosphoric acid, citric acid, lactic acid, or a combination thereof.

[0133] Because oxidation can result in degradation of the active agent, in some embodiments, the pharmaceutical formulation can include of an antioxidant. In some embodiments, the antioxidant can be, e.g., butylated hydroxytoluene (BHT), butylated hydroxyanisole (BHA), ascorbyl palmitate, ascorbic acid, alpha tocopherol, propyl gallate, 2,4,5-trihydroxybutyrophenone, 4-hydroxymethyl-2,6-di-tert-butylphenol, erythorbic acid, gum guaiac, thiodipropionic acid, dilauryl thiodipropionate, tert-butylhydroquinone, pharmaceutically acceptable salts or esters thereof, and combinations thereof. In some embodiments, the antioxidant can be ascorbyl palmitate, BHA, BHT, or a combination thereof. In some embodiments, the antioxidant can be BHT, ascorbyl palmitate, or a combination of BHT and ascorbyl palmitate.

[0134] In some embodiments, the pharmaceutical formulation can include up to about 1 wt% an antioxidant. In some embodiments, the pharmaceutical formulation can include up to about 0.5 wt% of an antioxidant or include about 0.5 wt% antioxidant.

[0135] In some embodiments, the pharmaceutical formulation can include an emulsifier, particularly to provide a solution, a suspension, an emulsion, or a microemulsion. Without wishing to be bound to any particular theory, it is believed that emulsifiers, when present, assist or facilitate dissolution of any solid substances, such as an active agent, in the pharmaceutical formulation. In other embodiments, however, the emulsifier can be present to facilitate

incorporation of two non-miscible liquids into each other (e.g., to form an emulsion or microemulsion).

[0136] In other embodiments, and without wishing to be bound by any particular theory, an emulsifier can increase product spreadability. For example, and without wishing to be bound to a particular theory, when the pharmaceutical formulation is a liquid solution, the presence of a suitable amount of an emulsifier is believed to decrease the surface tension between the pharmaceutical formulation and the lipid environment of the superficial layer of the skin and/or scalp. This makes it easier to spread the pharmaceutical formulation and is believed to assist penetration of the active agent(s) into skin (including the scalp), hair follicles, or both.

[0137] In some embodiments, the emulsifier can be selected from the group comprising or the group consisting of: polyethylene glycol (PEG)-fatty acid monoesters such as PEG-15 hydroxystearate (also known as polyoxyl-15-hydroxystearate), PEG-30 stearate, PEG-40 laurate, PEG-40 oleate and the like; polyoxyethylene sorbitan fatty acid esters (polysorbates) such as polysorbate 20, polysorbate 60, polysorbate 80, and the like; polyoxyethylene alkyl ethers such as PEG-20 cetostearyl ether, polyoxyl 25 cetostearyl, cetomacrogol 1000 and the like; sorbitan fatty acid esters such as sorbitan monolaurate, sorbitan monopalmitate, sorbitan monooleate, and the like; propylene glycol esters of fatty acids; polyglycerol esters of fatty acids; polyoxyethylene castor oil derivatives such as polyoxyl 5 castor oil, polyoxyl 15 castor oil, polyoxyl 35 castor oil, polyoxyl 40 hydrogenated castor oil and the like; caprylocapryl polyoxyl-8 glycerides; polyoxylglycerides such as caprylocaproyl polyoxylglycerides, lauroyl polyoxylglycerides, oleoyl polyoxylglycerides, and the like; polyoxyethylene lauryl alcohol; along with combinations of any of the foregoing. In some embodiments, the emulsifier can be polyoxyl 40 hydrogenated castor oil, polyoxyl-15-hydroxystearate, polysorbate 60, polysorbate 80, or a combination thereof. In preferred embodiments, the emulsifier can be a polysorbate, such as polysorbate 60, polysorbate 80, or a combination of polysorbate 60 and polysorbate 80.

[0138] In some embodiments, the pharmaceutical formulation can include the emulsifier in an amount of up to about 5 wt% of the total formulation (e.g., up to about 4 wt%, up to about 3 wt%, up to about 2 wt%). In some embodiments, the emulsifier can be present in an amount ranging from 0.05 to 5 wt% (e.g., from about 0.05 wt% to about 4 wt%, from about 0.05 wt%

to about 3 wt%, from about 0.05 wt% to about 2 wt%). In preferred embodiments, the pharmaceutical formulation can include the emulsifier in an amount of about 0.1 wt%, about 0.2 wt%, about 0.3 wt%, about 0.4 wt%, about 0.5 wt%, about 0.6 wt%, about 0.7 wt%, about 0.8 wt%, about 0.9 wt%, about 1 wt%, about 1.5 wt%, about 2 wt%, about 2.5 wt%, about 3 wt%, about 3.5 wt%, about 4 wt%, about 4.5 wt%, or about 5 wt%. In still further embodiments, the pharmaceutical formulation can include the emulsifier in an amount up to about 0.1 wt% or it can include about 0.1 wt% emulsifier. In still further embodiments, the emulsifier can be present in the pharmaceutical formulation at about 0.1 wt%.

[0139] In some embodiments, the pharmaceutical formulation can include one or more penetration enhancers. Without wishing to be bound by a particular theory, penetration enhancers are believed to beneficially affect delivery of the active agent(s) into the skin (including the scalp) and/or the hair follicles. Advantageously, and in some embodiments, the solvent or some component(s) of the solvent act as a penetration enhancer. For example, in embodiments wherein the pharmaceutical formulation comprises ethanol and/or diethylene glycol monoethyl ether, these solvents can also act to enhance penetration of the active agent into the skin (including the scalp), the hair follicles, or both. The presence of ethanol and/or diethylene glycol monoethyl ether notwithstanding, the pharmaceutical formulations described herein can further include additional penetration enhancers.

[0140] In some embodiments, the penetration enhancer can be selected from the group consisting of hydroxypropyl β -cyclodextrin, a diol, a polyol, a fatty acid (e.g., myristic acid, palmitic acid, palmitoleic acid, stearic acid, oleic acid, linoleic acid, linolenic acid, or a combination thereof), a fatty alcohol, a fatty acid ester, a surfactant, a pyrrolidone, and combinations thereof. Examples of further penetration enhancer that can be incorporated into formulations described herein include, but are not limited to, polyoxymethylene alkyl ethers, polyoxyl glycerides, dimethyl sulfoxide, pyrrolidone, N-methyl-2-pyrrolidone, diethylene glycol monoethyl ether (e.g., TRANSCUTOL™, Gattefossé, France), dimethyl isosorbide, diethyl sebacate, azone, menthol, nerol, camphor, methyl salicylate, polysorbate 80 (e.g., TWEEN™ 80, Sigma-Aldrich, St. Louis, MO), SDS, benzalkonium chloride, polyoxyl 40 hydrogenated castor oil (e.g., CREMOPHOR™ RH40, KOLLIPHOR™ RH40, BASF, Germany), didecyldimethylammonium bromide (DDAB), didecyltrimethylammonium bromide (DTAB), fatty acids esters (e.g., isopropyl myristate, isopropyl palmitate), fatty acids

(e.g., oleic acid, palmitic acid, linoleic acid, and salts thereof), fatty alcohols (e.g., oleyl alcohol, myristyl alcohol, and stearyl alcohol), medium-chain triglycerides, and combinations of any of the foregoing.

[0141] In some embodiments, the penetration enhancer can be dimethyl isosorbide. In other embodiments, the penetration enhancer can be a mixture comprising dimethyl isosorbide and diethylene glycol monoethyl ether. In other embodiments, the penetration enhancer can be dimethyl sulfoxide.

[0142] In some embodiments, the penetration enhancer can be present in an amount ranging from about 1 wt% to about 50 wt% with respect to the total weight of the pharmaceutical formulation. In other embodiments, the penetration enhancer can be present from about 2 wt% to about 40 wt% with respect to the total weight of the pharmaceutical formulation; or from about 5 wt% to about 35 wt% with respect to the total weight of the pharmaceutical formulation. According to some embodiments, the penetration enhancer can be present in the pharmaceutical formulation described herein in an amount of about 1% wt%, about 2 wt%, about 5 wt%, about 10 wt%, about 15 wt%, about 20 wt%, about 25 wt%, about 30 wt%, about 35 wt%, about 40 wt%, about 45 wt%, or about 50 wt% with respect to the total weight of the pharmaceutical formulation.

[0143] In some embodiments, the pharmaceutical formulation can include one or more moisturizers. Without wishing to be bound by a particular theory, a moisturizer is believed to impart moisture and/or softness into the skin (including the scalp), particularly when a component known to dry the skin, such as an alcohol, are also present in the formulation. In some embodiments, the moisturizer can be a fatty alcohol, a fatty acid (e.g., myristic acid, palmitic acid, palmitoleic acid, stearic acid, oleic acid, linoleic acid, linolenic acid, or a combination thereof), a fatty acid ester, an oil, a polyethylene glycol, glycerin, an alpha hydroxy acid, or a combination thereof. In some embodiments, the moisturizer can be cetyl alcohol, cetearyl alcohol, stearyl alcohol, stearic acid, isopropyl myristate, isopropyl palmitate, cocoa butter, lanolin, liquid paraffin, shea butter, a silicone oil, castor oil, a polyethylene glycol, glycerin, lactic acid, glycolic acid, malic acid, citric acid, tartaric acid, or a combination thereof. In some embodiments, the moisturizer can be cetyl alcohol, stearyl alcohol, or a combination of cetyl alcohol and stearyl alcohol.

[0144] In some embodiments, the pharmaceutical formulation can include one or more preservatives (e.g., an antibacterial, an antifungal). Suitable preservatives include, e.g., a paraben (e.g., methyl paraben, ethyl paraben, propyl paraben, butyl paraben), a benzoate (e.g., sodium benzoate), a sorbate (e.g., potassium sorbate), a quaternary ammonium compound (e.g., benzalkonium chloride, benzethonium chloride), an alcohol (e.g., chlorobutanol, benzyl alcohol, ethanol, phenol, m-cresol, chloro cresol), sodium metabisulfite, imidazolidinyl urea, glycerin, propylene glycol, or a combination thereof.

[0145] In some embodiments, the pharmaceutical formulation can include one or more chelating agents. Suitable chelating agents include, e.g., citric acid, phytic acid, sodium phytate, clioquinol, ethylenediaminetetraacetic acid (EDTA) (e.g., disodium EDTA, tetrasodium EDTA), etidronic acid, galactaric acid, tetrahydroxypropyl ethylenediamine, sodium metasilicate, or a combination thereof.

Modes of Administration

[0146] The pharmaceutical formulations described herein can be co-administered according to varying schedules. In one embodiment, the mode of administration of the pharmaceutical formulation can be continuous. For example, the pharmaceutical formulations can be applied topically once a day, twice daily, three times a day, four times a day, or more, as specified by a physician. In some embodiments, a formulation described herein can be applied topically once a day or twice daily. According to a particular embodiment, the pharmaceutical formulation described herein can be applied topically once a day. According to another embodiment, the pharmaceutical formulation described herein can be applied topically twice daily.

[0147] In some embodiments, a dosing regimen can be tapered. That is, the pharmaceutical formulation can be applied once a day for a first period of time, twice daily thereafter for a second period of time, three times a day thereafter for a third period of time, and so on. In a particular embodiment, the pharmaceutical formulation can be applied once a day on the first day, and twice daily thereafter, with the appropriate duration of treatment determined by a subject's physician. In an alternative embodiment, tapered administration can comprise administering the pharmaceutical formulation in a reducing schedule starting from multiple administrations per day for an appropriate period of time and reducing the number of

administrations over an appropriate period of time until a maintenance scheduled can be achieved. It is within the skill of a physician of ordinary skill in the art armed with the present disclosure to determine the appropriate starting point, reducing taper, and maintenance schedule.

[0148] In some embodiments, the pharmaceutical formulation can be applied over the course of a period of days, weeks, or months. For example, the pharmaceutical formulation can be applied one, two, three, four, or five times a day for up to: 1, 2, 3, 4, 5, 6, or 7 days (i.e., about 1 week); about 2 weeks, about 3 weeks, or about 4 weeks; about 2 months, about 3 months, about 4 months, about 5 months, about 6 months, about 7 months, about 8 months, about 9 months, about 10 months, about 11 months, about a year (i.e., about 12 months), about 13 months, about 14 months, about 15 months, about 16 months, about 17 months, about 18 months, about 19 months, about 20 months, about 21 months, about 22 months, about 23 months, or about 24 months. According to a particular embodiment, the pharmaceutical formulation can be applied once on the first day and twice daily thereafter for about 4 weeks.

[0149] In another embodiments, the pharmaceutical formulation can be topically applied to the scalp once a day for 1 month, once a day for 2 months, once a day for 3 months, once a day for 4 months, once a day 5 months, once a day for 6 months, once a day for 8 months, once a day for 12 months, once a day for 14 months, once a day for 16 months, once a day for 18 months, once a day for 20 months, once a day for 22 months, or once a day for 24 months. In some embodiments, the pharmaceutical formulation can be topically applied to the scalp once daily for 6 months. In some embodiments, the pharmaceutical formulation can be topically applied to the scalp once daily for 12 months.

[0150] In other embodiments, the pharmaceutical formulation can be topically applied to the scalp twice daily for: about 1 month; for about 2 months; for about 3 months; for about 4 months; for about 5 months; for about 6 months, for about 8 months, for about 12 months, for about 14 months, for about 16 months, for about 18 months, for about 20 months, for about 22 months, or for about 24 months. In some embodiments, the pharmaceutical formulation can be topically applied to the scalp twice daily for 6 months. In some embodiments, the pharmaceutical formulation can be topically applied to the scalp twice daily for 12 months.

[0151] In other embodiments, the pharmaceutical formulation can be applied more than twice daily (i.e., 3 times a day (TID), 4 times a day (QID), etc.) for: about 1 month; for about

2 months; for about 3 months; for about 4 months; for about 5 months; for about 6 months, for about 8 months, for about 12 months, for about 14 months, for about 16 months, for about 18 months, for about 20 months, for about 22 months, or for about 24 months. In some embodiments, the pharmaceutical formulation can be topically applied to the scalp more than twice daily (i.e., TID, QID, etc.) for 6 months. In some embodiments, the pharmaceutical formulation can be topically applied to the scalp more than twice daily (i.e., TID, QID, etc.) for 12 months.

[0152] In another embodiment, the mode of administration of the pharmaceutical formulations can be cyclic. For example, the pharmaceutical formulation can first be applied in a continuous way as described above for a desired period of time, the application can then be discontinued for a period of time, such as a few days, and then the application of the pharmaceutical formulations can be started again, as described above. The treatment period can include one or more cycles which can be the same or different. In some embodiments, the treatment period can be as follows: a) the pharmaceutical formulation can be topically applied to the scalp for a period of time, such as 4 months, by continuous administration, b) the application can be discontinued for a few days (e.g., 2 to 5 days), and 3) the topical application can be continued for an additional period of time, such as 6 months.

[0153] In some embodiments, the mode of administration can be cyclic in that cortisone-17 α -propionate and minoxidil can be co-administered sequentially. For example, a pharmaceutical formulation comprising cortisone-17 α -propionate can be administered first for a first period of time, and a pharmaceutical composition comprising minoxidil can be administered second for a second period of time. In other embodiments, a pharmaceutical composition comprising minoxidil can be administered first and a pharmaceutical composition comprising cortisone-17 α -propionate can be administered second. The time period between when the first pharmaceutical composition can be administered, and the second pharmaceutical composition can be administered, can be any suitable time period. For example, the time between each administration can be on the order of seconds, minutes, hours, or days, as needed. In some embodiments, administration of the first and second pharmaceutical compositions can be separated by seconds (e.g., about 60 seconds or less, about 30 seconds or less). In some embodiments, administration of the first and second pharmaceutical compositions can be separated by hours (e.g., about 1 hour or less, about 2 hours or less, about 3 hours or less, about

5 hours or less, about 8 hours or less, about 12 hours or less, about 24 hours or less). In some embodiments, administration of the first and second pharmaceutical compositions can be separated by days (e.g., about 1 day, about 2 days, about 3 days, about 4 days, about 5 days, about 6 days, or about 7 days). In some embodiments, administration of the first and second pharmaceutical compositions can be separated by weeks (e.g., about 1 week, about 2 weeks, about 3 weeks, or about 4 weeks).

[0154] In some embodiments, a first pharmaceutical formulation comprising either cortexolone-17 α -propionate or minoxidil can be administered for a first period of time, in which the first time period can be on the order of days or weeks. During the first period of time, the first pharmaceutical formulation can be administered multiple times to the skin or scalp, as described herein, before a second pharmaceutical formulation comprising the other active agent can be administered in a second period of time. Similar to the first period of time, the second time period can be on the order of days or weeks. For example, a first pharmaceutical formulation comprising cortexolone-17 α -propionate can be administered for a first period of time (e.g., about 1 day or more, about 2 days or more, about 7 days or more, about 2 weeks or more, about 3 weeks or more, or about 4 weeks or more). A second pharmaceutical formulation comprising minoxidil can be administered for a second period of time (e.g., about 1 day or more, about 2 days or more, about 7 days or more, about 2 weeks or more, about 3 weeks or more, or about 4 weeks or more). In some embodiments, a subject can alternate (e.g., cycle between) administration between the first and second pharmaceutical formulations for a given time period to effect treatment.

[0155] The “effective amount” of each active agent is an amount that provides a desired outcome (e.g., to induce hair growth and/or regrowth). In some embodiments, the pharmaceutical formulation can comprise cortexolone-17 α -propionate, minoxidil, or both active agents at a concentration of from about 0.1 wt% to about 20 wt%. For example, the pharmaceutical formulation can comprise cortexolone-17 α -propionate, minoxidil, or both active agents at a concentration of about 0.1 wt% or more (e.g., about 0.2 wt% or more, about 0.3 wt% or more, about 0.4 wt% or more, about 0.5 wt% or more, about 0.6 wt% or more, about 0.7 wt% or more, about 0.8 wt% or more, about 0.9 wt% or more, about 1 wt% or more, about 1.2 wt% or more, about 1.4 wt% or more, about 1.6 wt% or more, about 1.8 wt% or more, about 2 wt% or more, about 2.2 wt% or more, about 2.4 wt% or more, about 2.6 wt% or

more, about 2.8 wt% or more, about 3 wt% or more, about 3.2 wt% or more, about 3.4 wt% or more, about 3.6 wt% or more, about 3.8 wt% or more, about 4 wt% or more, about 4.2 wt% or more, about 4.4 wt% or more, about 4.6 wt% or more, about 4.8 wt% or more, about 5 wt% or more, about 5.2 wt% or more, about 5.4 wt% or more, about 5.6 wt% or more, about 5.8 wt% or more, about 6 wt% or more, about 6.2 wt% or more, about 6.4 wt% or more, about 6.6 wt% or more, about 6.8 wt% or more, about 7 wt% or more, about 7.2 wt% or more, about 7.4 wt% or more, about 7.6 wt% or more, about 7.8 wt% or more, about 8 wt% or more, about 8.2 wt% or more, about 8.4 wt% or more, about 8.6 wt% or more, about 8.8 wt% or more, about 9 wt% or more, about 9.2 wt% or more, about 9.4 wt% or more, about 9.6 wt% or more, about 9.8 wt% or more, about 10 wt% or more, about 10.5 wt% or more, about 11 wt% or more, about 11.5 wt% or more, about 12 wt% or more, about 12.5 wt% or more, about 13 wt% or more, about 13.5 wt% or more, about 14 wt% or more, about 14.5 wt% or more, about 15 wt% or more, about 15.5 wt% or more, about 16 wt% or more, about 16.5 wt% or more, about 17 wt% or more, about 17.5 wt% or more, about 18 wt% or more, about 18.5 wt% or more, about 19 wt% or more, or about 19.5 wt% or more) to about 20 wt% or less (e.g., about 19.5 wt% or less, about 19 wt% or less, about 18.5 wt% or less, about 18 wt% or less, about 17.5 wt% or less, about 17 wt% or less, about 16.5 wt% or less, about 16 wt% or less, about 15.5 wt% or less, about 15 wt% or less, about 14.5 wt% or less, about 14 wt% or less, about 13.5 wt% or less, about 13 wt% or less, about 12.5 wt% or less, about 12 wt% or less, about 11.5 wt% or less, about 11 wt% or less, about 10.5 wt% or less, about 10 wt% or less, about 9.5 wt% or less, about 9 wt% or less, about 8.5 wt% or less, about 8 wt% or less, about 7.5 wt% or less, about 7 wt% or less, about 6.5 wt% or less, about 6 wt% or less, about 5.8 wt% or less, about 5.6 wt% or less, about 5.4 wt% or less, about 5.2 wt% or less, about 5 wt% or less, about 4.8 wt% or less, about 4.6 wt% or less, about 4.4 wt% or less, about 4.2 wt% or less, about 4 wt% or less, about 3.8 wt% or less, about 3.6 wt% or less, about 3.4 wt% or less, about 3.2 wt% or less, about 3 wt% or less, about 2.8 wt% or less, about 2.6 wt% or less, about 2.4 wt% or less, about 2.2 wt% or less, about 2 wt% or less, about 1.8 wt% or less, about 1.6 wt% or less, about 1.4 wt% or less, about 1.2 wt% or less, about 1 wt% or less, about 0.9 wt% or less, about 0.8 wt% or less, about 0.7 wt% or less, about 0.6 wt% or less, about 0.5 wt% or less, about 0.4 wt% or less, about 0.3 wt% or less, or about 0.2 wt% or less). In preferred embodiments, the pharmaceutical formulation can comprise cortexolone-17 α -propionate, minoxidil, or both

active agents at a concentration of from about 0.5 wt% to about 18 wt% or about 1 wt% to about 15 wt% or about 1.5 wt% to about 15 wt% or about 2 wt% to about 12 wt% or about 2.5 wt% to about 10 wt% or about 2.5 wt% to about 8 wt% or about 3 wt% to about 7 wt%.

[0156] In some embodiments, the pharmaceutical formulation can comprise cortexolone-17 α -propionate at a concentration from about 1 wt% to about 20 wt%. In some embodiments, the pharmaceutical formulation can comprise minoxidil at a concentration from about 0.1 wt% to about 20 wt%. In some embodiments, the pharmaceutical formulation can be a solution that can comprise cortexolone-17 α -propionate at a concentration from about 1 wt% to about 20 wt% and minoxidil at a concentration from about 0.1 wt% to about 20 wt%. In preferred embodiments, the pharmaceutical formulation can be a solution that can comprise about 5 wt% cortexolone-17 α -propionate and about 5 wt% minoxidil.

[0157] In some embodiments, the amount of cortexolone-17 α -propionate in a single application can range from about 20 mg to about 400 mg. In other embodiments, the amount of cortexolone-17 α -propionate in a single application can range from about 20 mg to about 350 mg. In other embodiments, the amount of cortexolone-17 α -propionate in a single application can range from about 20 mg to about 300 mg. In other embodiments, the amount of cortexolone-17 α -propionate in a single application can range from about 20 mg to about 250 mg.

[0158] In some embodiments, the amount of cortexolone-17 α -propionate in a single application can range from about 20 mg to about 200 mg. In other embodiments, the amount of cortexolone-17 α -propionate in a single application can range from about 20 mg to about 170 mg. In other embodiments, the amount of cortexolone-17 α -propionate in a single application can range from about 20 mg to about 150 mg. In some embodiments, the amount of cortexolone-17 α -propionate in a single application can range from about 20 mg to about 100 mg. In some embodiments, the amount of cortexolone-17 α -propionate in a single application can be about 20 mg, about 25 mg, about 30 mg, about 35 mg, about 40 mg, about 45 mg, about 50 mg, about 55 mg, about 60 mg, about 75 mg, about 80 mg, about 85 mg, about 90 mg, or about 100 mg. In another embodiment, the amount of cortexolone-17 α -propionate in a single application can be about 25 mg. In another embodiment, the amount of cortexolone-17 α -propionate in a single application can be about 30 mg. In yet another embodiment, the amount of cortexolone-17 α -propionate in a single application can be about 50 mg. In yet another

embodiment, the amount of cortexolone-17 α -propionate in a single application can be about 75 mg. In yet another embodiment, the amount of cortexolone-17 α -propionate in a single application can be about 80 mg. In yet another embodiment, the amount of cortexolone-17 α -propionate in a single application can be about 100 mg. In other embodiments, the amount of cortexolone-17 α -propionate in a single application can be about 110 mg, about 111 mg, about 112 mg, about 113 mg, about 114 mg, about 115 mg, about 116 mg, about 117 mg, about 118 mg, about 119 mg, or about 200 mg. In yet another embodiment, the amount of cortexolone-17 α -propionate in a single application can be about 150 mg.

[0159] In some embodiments, the amount of minoxidil in a single application can range from about 2 mg to about 20 mg. In other embodiments, the amount of minoxidil in a single application can range from about 2 mg to about 15 mg. In other embodiments, the amount of minoxidil in a single application can range from about 2 mg to about 10 mg. In other embodiments, the amount of minoxidil in a single application can range from about 2 mg to about 5 mg.

[0160] In some embodiments, the pharmaceutical formulation can be self-administered by the subject once a day or twice daily. In some embodiments, when the pharmaceutical formulation can be in liquid form having a cortexolone-17 α -propionate concentration of about 5 wt% and a minoxidil concentration of about 5 wt%, the pharmaceutical formulation can be self-administered once a day or twice daily at a dose ranging from about 0.2 to about 2.0 ml, from about 0.5 to about 1.5 ml, and in further embodiments at about 1 mL or about 1.5 mL.

[0161] In some embodiments, when the pharmaceutical formulation can be in liquid form having a cortexolone-17 α -propionate concentration of about 2.5 wt% and a minoxidil concentration of about 2 wt%, the pharmaceutical formulation can be self-administered once a day or twice daily at a dose ranging from about 0.2 to about 2.0 ml, from about 0.5 to about 1.5 ml, and in further embodiments at about 1 mL or about 1.5 mL.

[0162] In some embodiments, when the pharmaceutical formulation can be in liquid form having a cortexolone-17 α -propionate concentration of about 3 wt% and a minoxidil concentration of about 3 wt%, the pharmaceutical formulation can be self-administered once a day or twice daily at a dose ranging from about 0.2 to about 2.0 ml, from about 0.5 to about 1.5 ml, and in further embodiments at about 1 mL or about 1.5 mL.

[0163] In some embodiments, when the pharmaceutical formulation can be in liquid form having a cortexolone-17 α -propionate concentration of about 7.5 wt% and a minoxidil concentration of about 1.5 wt%, the pharmaceutical formulation can be self-administered once a day or twice daily at a dose ranging from about 0.2 to about 2.0 ml, from about 0.5 to about 1.5 ml, and in further embodiments at about 1 mL or about 1.5 mL.

[0164] The pharmaceutical formulation described herein can be applied to any body surface in need of treatment, such as a skin region susceptible to induction of hair growth. Suitable skin regions include e.g., scalp, face (e.g., the eyebrow, eyelashes, upper lip, lower lip, chin, cheeks, beard area, or mustache area), arms, armpits, legs, chest, abdomen, or any combination of the foregoing. In some embodiments, treatment is not delivered to the face. In other embodiments, the pharmaceutical formulation can be applied to the scalp.

Kit

[0165] The present disclosure further provides a kit comprising one or more topical pharmaceutical formulations in various forms, as described herein. The kit can contain one or more liquid or semi-solid formulations suitable for administration. The kit can further comprise a device for administration, such as a dropper, a pipette, or an injection device (e.g., manual or electronic driven), for use by a person skilled in the art. The kit can further include instructions for preparing and administering the one or more pharmaceutical formulations. The instruction can be in various formats, such as a printed matter, magnetic disk, magnetic tape, compact disc, flash memory, or other media suitable for conveying the appropriate information.

[0166] In some embodiments, the kit can comprise a pharmaceutical formulation comprising cortexolone-17 α -propionate as a first component and a pharmaceutical formulation comprising minoxidil as a second component. The kit can further comprise instructions for use of the first and second components. In some embodiments, the first component and the second component can be combined just before use (e.g., within 1 hour before use, within 45 min before use, within 30 min before use, within 20 min before use, within 15 min before use, within 10 min before use, or within 5 min before use) and applied to the skin or scalp as a single combined formulation. In some embodiments, both the first and second components are solutions. In some embodiments, one or both of the first and second components can be a gel.

In some embodiments, one or both of the first and second components can be a cream. In some embodiments, one or both of the first and second components can be a foam.

[0167] In some embodiments, the kit can comprise cortexolone-17 α -propionate in solid form as a first component and a pharmaceutical formulation comprising minoxidil as a second component. The kit can further comprise instructions for using the first and second components. In some embodiments, the cortexolone-17 α -propionate in solid form can be a powder, a fast-disintegrating tablet, a granule, a granulate, and the like. Preferably, the cortexolone-17 α -propionate is in powder form. In some embodiments, the cortexolone-17 α -propionate in solid form can be stored separately from the container containing the pharmaceutical formulation comprising minoxidil. In such embodiments, cortexolone-17 α -propionate in solid form can be stored within a capped vial or closed bottle.

[0168] In some embodiments, the cortexolone-17 α -propionate in solid form can be stored within the same container containing the pharmaceutical formulation comprising minoxidil. According to such embodiments, the cortexolone-17 α -propionate in solid form can be stored in a constituent part of the container containing the pharmaceutical formulation comprising minoxidil, which is designed to prevent contact between the two active agents. In some embodiments, the constituent part of the container, which is designed to prevent the contact between the cortexolone-17 α -propionate in solid form and the pharmaceutical formulation comprising minoxidil, can be a cap containing a storage chamber for a solid substance (e.g., a reservoir cap), or a chamber separated from the main chamber containing the pharmaceutical formulation comprising minoxidil. In some embodiments, the container containing the pharmaceutical formulation comprising minoxidil can be capped with a reservoir cap containing cortexolone-17 α -propionate in solid form, which is equipped with a cutting device activated by the subject pushing, twisting, or pulling the cap itself. According to such embodiment, activating the cutting device in the reservoir cap allows cortexolone-17 α -propionate in solid form to come into contact with the pharmaceutical formulation comprising minoxidil.

[0169] In some embodiments, the first component and the second component can be combined just before use (e.g., within 1 hour before use, within 45 min before use, within 30 min before use, within 20 min before use, within 15 min before use, within 10 min before use, or within 5 min before use) and applied to the skin or scalp as a single combined formulation.

In some embodiments, the first component can be in solid form and the second component can be a solution. In some embodiments, the first component can be in solid form and the second component can be a gel. In some embodiments, the first component can be in solid form and second component can be a cream. In some embodiments, the first component can be in solid form and the second component can be a foam.

[0170] In some embodiments, the kit can comprise minoxidil in solid form as a first component and a pharmaceutical formulation comprising cortexolone-17 α -propionate as a second component. The kit can further comprise instructions for using the first and second components. In some embodiments, the minoxidil in solid form can be a powder, a fast-disintegrating tablet, a granule, a granulate, and the like. In some embodiments, the minoxidil in solid form can be stored separately from the container containing the pharmaceutical formulation comprising cortexolone-17 α -propionate. In such embodiments, minoxidil in solid form can be stored within a capped vial or closed bottle.

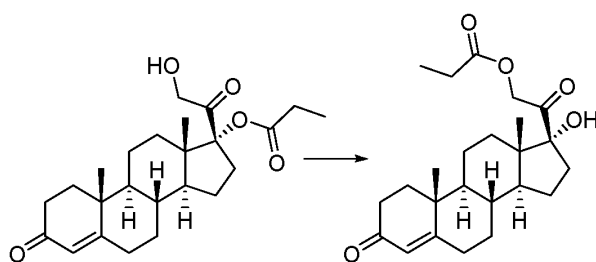
[0171] In some embodiments, the minoxidil in solid form can be stored within the same container containing the pharmaceutical formulation comprising cortexolone-17 α -propionate. According to such embodiments, the minoxidil in solid form can be stored in a constituent part of the container containing the pharmaceutical formulation comprising cortexolone-17 α -propionate, which is designed to prevent the contact between the two. In some embodiments, the constituent part of the container, which is designed to prevent the contact between the minoxidil in solid form and the pharmaceutical formulation comprising cortexolone-17 α -propionate, can be a cap containing a storage chamber for a solid substance (e.g., a reservoir cap), or a chamber separated from the main chamber containing the pharmaceutical formulation comprising cortexolone-17 α -propionate. In some embodiments, the container containing the pharmaceutical formulation comprising cortexolone-17 α -propionate can be capped with a reservoir cap containing minoxidil in solid form, which is equipped with a cutting device activated by the subject pushing, twisting, or pulling the cap itself. According to such embodiment, activating the cutting device in the reservoir cap allows minoxidil in solid form to come into contact with the pharmaceutical formulation comprising cortexolone-17 α -propionate. In some embodiments, the first component and the second component can be combined just before use (e.g., within 1 hour before use, within 45 min before use, within 30 min before use, within 20 min before use, within 15 min before use, within 10 min before use,

or within 5 min before use) and applied to the skin or scalp as a single combined formulation. In some embodiments, the first component can be in solid form and the second component can be a solution. In some embodiments, the first component can be in solid form and the second component can be a gel. In some embodiments, the first component can be in solid form and the second component can be a cream. In some embodiments, the first component can be in solid form and the second component can be a foam.

Storage Stability

[0172] Storage stability is an important metric for pharmaceutical products. In general, greater stability means that a given formulation is both easier to transport and store, increasing the likelihood that it will be stocked by pharmacies and that subjects will not have to be concerned with special storage instructions. In some embodiments, the pharmaceutical formulation described herein can have a desirable stability profile allowing for storage of the final formulation for at least about 3 months, at least about 6 months, at least about 9 months, at least about 12 months, at least about 15 months, at least about 18 months, at least about 21 months, or at least about two years – each at room (about 20 °C) or refrigerated temperatures (e.g., about 4 °C).

[0173] For example, one of the main degradation pathways of cortexolone-17 α -propionate is transesterification to cortexolone-21-propionate (17 α -hydroxy-21-propionyloxy-pregna-4-ene-3,20-dione):



[0174] In some embodiments, maintaining the pharmaceutical formulations disclosed herein at an acidic pH, including a pH of less than 7.0 (e.g., less than about 6.5, less than about 6, less than about 5.5, less than about 5, less than about 4.5, between about 4 and about 7, between about 4 and about 6.5, between about 4 and about 6, between about 4 and 5.5, between about 4 and 5, between about 4 and about 4.5, or at about 6.5, about 6, about 5.5, about 5, about

4.5, or about 4), can slow this degradation process. In some embodiments, the pH can be about 4. The appropriate pH can be obtained via addition of a suitable amount of a pH modifier, such as the acids described herein.

[0175] In some embodiments, the pharmaceutical formulations described herein can, at room (about 20 °C) or refrigerated (e.g., about 4 °C) temperatures, have less than about 5 wt% cortexolone-21-propionate or other degradation products after storage for a period of about 24 months.

[0176] FIGURES

[0177] Figure 1. : IL-6 concentration in Human Hair Follicle Dermal Papilla cells (HFDPC) cell cultures following 24 hours of drug treatment.

[0178] Figure 2: Side-by-side comparison of IL-6 concentrations for clascoterone + DHT groups vs clascoterone + DHT + minoxidil groups in HFDPC

EXAMPLES

[0179] The pharmaceutical formulations described herein are now further detailed with reference to the following examples. These examples are provided for the purpose of illustration only and the embodiments described herein should in no way be construed as being limited to these examples. Rather, the embodiments should be construed to encompass any and all variations which become evident as a result of the teaching provided herein.

[0180] Example 1: Anhydrous 5% w/w Solution of Cortexolone-17 α -propionate

[0181] A 5 wt% (w/w) solution of cortexolone-17 α -propionate having the components shown in Table 1, below, was prepared by solubilizing the active agent in the mixture of solvents followed by the addition of the emulsifier (polysorbate 80).

Table 1

Component	Amount (g/100 g)
Cortexolone-17 α -propionate	5.26
Diethylene glycol monoethyl ether	31.75
Alcohol (Ethanol)	31.75
Polysorbate 80	0.11
Propylene glycol	31.12
Citric acid monohydrate	0.04

[0182] This formulation provided the stability profile (40 °C and 75% relative humidity (RH)) shown in Table 2.

Table 2

Time point	Cortexolone-17 α -propionate (wt %)	Cortexolone 21-propionate (wt %)*	Total impurities (wt %)*
0	5.108	0.07	0.13
1 month	5.046	1.08	1.19
3 months	4.989	2.78	3.11
6 months	4.847	4.76	5.23

*Cortexolone-21-propionate contents calculated as (% (w/w) of cortexolone-21-propionate) / (% (w/w) of cortexolone-17 α -propionate x 100)

[0183] **Example 2: 5% w/w Foam of Minoxidil**

[0184] A 5 wt% (w/w) foam of minoxidil having the components shown in Table 3 can be prepared.

Table 3

Component	Amount (g/100 g)
Minoxidil	5.0
Cetyl alcohol	2.2
Stearyl alcohol	1
Ethanol	51.8
Polysorbate 60	0.4
Polyoxyethylene lauryl alcohol	1
Propylene glycol	5
Propellant P75	4.3
Acetic acid	q.s. pH 6.0
Purified water	q.s. to 100g

q.s.: quantum satis

[0185] **Example 3: 5% w/w Solution of Minoxidil**

[0186] A 5 wt% (w/w) solution of minoxidil having the components shown in Table 4 can be prepared.

Table 4

Component	Amount (g/100 g)
Minoxidil	5.0
Propylene glycol	35
Ethanol	48
Water	q.s. to 100 g

[0187] Ethanol and propylene glycol are mixed and heated to 60-70 °C; once the temperature is within the above range (60-70 °C), minoxidil is added and the mixture is kept under stirring until minoxidil is completely solubilized. Thereafter, water is added slowly to the mixture under stirring and keeping the temperature in the range 60-70 °C, until final weight is reached. Thereafter, the mixture is slowly cooled to room temperature under stirring.

[0188] **Example 4: Solution of Minoxidil (2.5% w/w) and of cortexolone-17 α -propionate (2.5% w/w)**

[0189] A solution of minoxidil (2.5% w/w) and cortexolone-17 α -propionate (2.5% w/w) having the components shown in Table 5 can be prepared.

Table 5

Component	Amount (g/100 g)
Minoxidil	2.5
Cortexolone-17 α -propionate	2.5
Propylene glycol	35
Ethanol	48
Water	q.s. to 100 g

[0190] Ethanol and propylene glycol are mixed and heated to 60-70 °C; once the temperature is within the above range (60-70 °C), minoxidil is added and the mixture is kept under stirring until minoxidil is completely solubilized. Then, cortexolone-17 α -propionate is added and the mixture is kept under stirring until minoxidil is completely solubilized. Thereafter, water is added slowly to the mixture under stirring and keeping the temperature in the range 60-70 °C, until final weight is reached. Thereafter, the mixture is slowly cooled to room temperature under stirring.

[0191] Example 5: Kit containing a Solution of Minoxidil (5.0% w/w) and Cortisolone-17 α -propionate in Solid Form

[0192] A 5 wt% (w/w) solution of minoxidil having the components shown in Table 6 can be prepared.

Table 6

Component	Amount (g/100 g)
Minoxidil	5.0
Propylene glycol	35
Ethanol	48
Water	q.s. to 100 g

[0193] Ethanol and propylene glycol are mixed and heated to 60-70 °C; once the temperature is within the above range (60-70 °C), minoxidil is added and the mixture is kept under stirring until complete minoxidil is completely solubilized. Thereafter, water is added slowly to the mixture under stirring and keeping the temperature in the range 60-70 °C, until final weight is reached. Thereafter, the mixture is slowly cooled to room temperature under stirring. The solution containing minoxidil is then filled in 60 mL glass bottles. Cortisolone-17 α -propionate in powder form is filled into the storage container of reservoir caps (about 3 g per cap). The 60 mL bottles containing the minoxidil solution are then capped with the reservoir caps filled in with cortisolone-17 α -propionate powder.

[0194] Example 6: Kit containing a Solution of Cortisolone-17 α -propionate (5.0% w/w) and Minoxidil in Solid Form

[0195] A 5 wt% (w/w) solution of cortisolone-17 α -propionate having the components shown in Table 7 can be prepared.

Table 7

Component	Amount (g/100 g)
Cortisolone-17 α -propionate	5.26
Diethylene glycol monoethyl ether	31.75
Alcohol (Ethanol)	31.75
Polysorbate 80	0.11
Propylene glycol	31.12
Citric acid monohydrate	0.04

[0196] A 5 wt% (w/w) solution of cortexolone-17 α -propionate having the components shown in Table 7 was prepared by solubilizing the active agent in the mixture of solvents followed by the addition of the emulsifier (polysorbate 80). The solution containing cortexolone-17 α -propionate is then filled in 60 mL glass bottles. Minoxidil in powder form is filled into the storage container of reservoir caps (about 3 g per cap). The 60 mL bottles containing the cortexolone-17 α -propionate solution are then capped with the reservoir caps filled in with minoxidil powder.

[0197] **Example 7. Clascoterone and Minoxidil Combination Treatment Synergistically Inhibits IL-6 Secretion in Human Hair Follicle Dermal Papilla cells (HFDPC)**

[0198] Clascoterone is a potent anti-androgen that blocks the effects of the androgen receptor in human hair follicles. Topical administration demonstrates clinically meaningful efficacy in AGA. Part of its mechanism-of-action is to inhibit androgen-induced IL-6 secretion from HFDPC, and this reduces IL-6 induced hair follicle damage. As such, IL-6 secretion from these cells is a relevant efficacy biomarker that correlates with hair growth.

[0199] Minoxidil is a K_{ATP} channel modulator that demonstrates topical efficacy in AGA. There are no reports of its effects on IL-6 secretion in HFDPC.

[0200] In this study the combination of clascoterone with minoxidil on inhibition of IL-6 secretion from HFDPC was better than expected. That is, the combined efficacy was greater than just adding the efficacy of each agent alone.

[0201] The results suggest that the synergistic combination of topical clascoterone and topical minoxidil should provide significantly increased efficacy when used in AGA patients.

[0202] **Background**

[0203] The bulk of the hair follicle is composed of keratinocytes, the epithelial cells that comprise the hair shaft itself as well as the encircling inner and outer root sheaths. However, a specialized mesenchymal population, the dermal papilla (DP), plays a critical role in directing the activities of these keratinocytes to form the follicle and generate the hair shaft (Greco et al. 2009). Active communication between the DP or its precursors and the epithelial compartment regulate many aspects of follicle biology. The DP influences the size and shape of the hair shaft through the generation of signals that act on keratinocytes.

[0204] In androgenetic alopecia the reduction in the size of the hair follicle associated with progressive hair thinning and loss includes a failure to maintain DP cell function (Elliott et al. 1999). Several observations suggest that this arises from a primary defect in the DP. One of the key paracrine factors that are produced by balding DP cells in male pattern baldness is the cytokine IL-6.

[0205] IL-6, in response to dihydrotestosterone (DHT), is upregulated in balding DP cells compared with non-balding DP cells. (Kwack et al. 2012); IL-6 receptors are expressed in follicular keratinocytes, including matrix cells. Recombinant human IL-6 (rhIL-6) inhibited hair shaft elongation and suppressed proliferation of matrix cells in cultured human hair follicles. Moreover, rhIL-6 injection into the hypodermis of mice during anagen (hair growth phase) caused premature onset of catagen (growth inhibition). As such, DHT-inducible IL-6 inhibits hair growth as a paracrine mediator from the DP (Kwack et al. 2012).

[0206] There are three classes of drugs that are effective in arresting the progression of hair loss, anti-androgens (e.g., Clascoterone), 5- α reductase type 2 inhibitors (e.g., Finasteride) and K_{ATP} channel openers (e.g., Minoxidil). These compounds act on DP cells in cell cultures or isolated hair follicles (Kaufman et al. 1998; Randall 2008; Shorter et al. 2008).

[0207] It has been demonstrated that clascoterone can inhibit DHT-induced IL-6 expression in dermal papilla cells (Rosette et al. 2019). However, it is not known if minoxidil can modulate IL-6 expression in DP cells or if the combination of clascoterone and minoxidil can demonstrate greater efficacy than either agent alone.

[0208] **Experimental section**

[0209] Cell lines

[0210] Human Hair Follicle Dermal Papilla cells (HFDPC) from the vertex region of human scalp were obtained from Cell Applications (San Diego, CA). Cells were propagated in complete Hair Follicle Dermal Papilla Cell Basal Media (Cell Applications, San Diego, CA) and 10% fetal bovine serum (Gibco, Gaithersburg, MD). All flasks and plates used were collagen-coated. Collagen was obtained from Cell Applications (San Diego, CA) and used as per the manufacturer's instructions. For analysis of IL-6 secretion the cells were trypsinized and seeded (2×10^5 cells per well) into collagen-coated 24-well plates containing Hair Follicle Dermal Papilla Cell Basal Media and 5% charcoal-dextran filtered serum (DCC-FBS) (Omega Scientific, Tarzana, CA) and incubated overnight. Experiments were done in triplicate wells.

The next day media was removed and fresh Basal media + 5% DCC-FBS containing the compounds and DHT were added and incubated for 24 hours. All cell incubations were performed at 37°C and 5% CO₂. For the concentrations of compounds used in these experiments it was determined that there was no significant effect on the proliferation of the cells (data not shown).

[0211] Compounds

[0212] Clascoterone (CB0301) was custom synthesized for Cosmo Pharmaceuticals (Lainate, Italy). Dihydrotestosterone (DHT) was obtained from Millipore-Sigma (Saint Louis, MO) and Minoxidil was obtained from VWR (San Diego, CA). All compounds were dissolved in 100% DMSO and then diluted in the HFDPC Basal Media + 5% DCC-FBS for cell culture experiments. Final DMSO concentrations in each well were 0.1%

[0213] Quantitation of IL-6 protein expression by ELISA

[0214] Various concentrations of DHT, clascoterone and minoxidil were used to treat the dermal papilla cells. Compounds were added simultaneously (no preincubation) in the wells. After 24 hours of culture, the medium in each well was collected and used immediately for determination of secreted IL-6. The Human IL-6 ELISA detection kit was from Invitrogen (San Diego, CA) and used as per the manufacturer's instructions. The absorbance was quantified on a ClarioStar microplate reader (Ortenberg, Germany) and the data analyzed in Prism software version 10.1.1 (GraphPad, La Jolla, CA).

[0215] **Results**

[0216] Figure 1 shows that the incubation of HFDPC with 100 nM DHT for 24 hours resulted in significantly increased secretion of IL-6 compared to 0.1% DMSO used as control (47.5 pg/mL vs. 39.2 pg/mL; $p < 0.004$). Minoxidil at a concentration of 1 μ M in the presence of DHT only slightly decreased IL-6 secretion by 7% (47.5 pg/mL to 44.3 pg/mL).

[0217] Clascoterone in the presence of 100 nM DHT dose-dependently inhibited IL-6 secretion at 24 hours. Importantly, the combination of 1 μ M Minoxidil with either 15 nM or 30 nM doses of clascoterone showed an unexpected synergism resulting in significantly greater inhibition of IL-6 secretion compared to clascoterone treatment alone. The 60 nM clascoterone group also showed synergism, but without statistical significance.

[0218] All clascoterone treatment groups showed statistically significant inhibition of IL-6 secretion relative to 100 nM DHT. Table 8 lists the concentrations of IL-6 and relative inhibition by the compounds in each treatment condition.

[0219] Table 8. Mean and standard deviation of IL-6 concentrations and relative inhibition by the compounds in each experimental treatment group.

Condition	Mean IL-6 (pg/mL)	Std. Deviation (pg/mL)	% Inhibition Relative to 100 nM DHT
DMSO	39.0	5.8	
100nm DHT	47.5	6.1	
1um MNX only	42.2	5.6	
1um MNX + DHT	44.3	4.1	7%
15nm CB0301 + 100nm DHT	39.7	2.8	16%
30nm CB0301 + 100nm DHT	38.4	6.4	19%
60nm CB0301 + 100nm DHT	31.3	3.0	34%
15nm CB0301 / 1um MNX / DHT	31.4	2.6	34%
30nm CB0301 / 1um MNX / DHT	30.3	3.2	36%
60nm CB0301 / 1um MNX / DHT	27.1	1.7	43%

[0220] As shown in Figure 2, when comparing the effects of clascoterone + DHT vs. clascoterone + DHT + minoxidil, the treatment groups with clascoterone that contained 1 uM minoxidil showed more than additive effect. That is, there was a synergistic inhibition of IL-6 in HFDPC for all clascoterone concentrations when combined with 1 uM minoxidil.

[0221] The predictive additive efficacy for combining clascoterone and minoxidil vs. the actual observed combination efficacy is listed in Table 9. This also includes the p values from ANOVA statistical analysis comparing the means of the clascoterone + DHT groups vs the clascoterone + DHT + minoxidil groups.

[0222] Table 9. Predicted additive effect of (clascoterone + DHT) + (minoxidil + DHT) vs. observed combination effect and statistical p value analysis of the mean of clascoterone vs mean clascoterone + minoxidil treatment groups.

Clascoterone Concentration (nM)	Predicted Additive Effect (%)	Observed Combination Effect (%)	P value
15	23%	34%	p<0.009
30	26%	36%	p<0.003
60	41%	43%	p<0.7

[0223] The 15 nM clascoterone + DHT group showed 16% inhibition relative to DHT alone and the 1 μ M minoxidil + DHT group showed 7% inhibition relative to DHT alone. Therefore, an additive effect should provide 23% (16% +7%) inhibition. However, the observed 34% inhibition for the combination of clascoterone + DHT + minoxidil is greater than 23%, which indicates a synergistic inhibition between clascoterone and minoxidil when used in combination. The combination treatment was significantly different compared to clascoterone + DHT (p < 0.009).

[0224] The 30 nM clascoterone group showed 19% inhibition relative to DHT alone and the 1 μ M minoxidil group showed 7% inhibition relative to DHT alone. Therefore, an additive effect should provide 26% (19%+7%) inhibition. However, the observed 36% inhibition for the combination is greater, which indicates synergistic inhibition between clascoterone and minoxidil when used in combination. The combination treatment (clascoterone + DHT + minoxidil) was significantly different compared to clascoterone + DHT (p < 0.003).

[0225] The 60 nM clascoterone group showed 34% inhibition relative to DHT alone and the 1 μ M minoxidil group showed 7% inhibition relative to DHT alone. Therefore, an additive effect should provide 41% (34%+7%) inhibition. The observed 43% inhibition for the combination is greater, which may indicate synergistic inhibition. However, this difference was not significant (p < 0.7).

[0226] Conclusion

[0227] Human dermal papilla cells respond to DHT to activate the androgen receptor. IL-6 is a key negative regulator of hair growth and has been shown to be elevated in balding scalp hair follicles relative to non-balding scalp hair follicles. Clascoterone is a potent anti-androgen that clinically demonstrates efficacy in androgenetic alopecia patients to increase hair growth. Previously it has been demonstrated that clascoterone inhibits DHT-induced IL-6 secretion from human dermal papilla cells. Therefore, IL-6 is a HFDPC biomarker that correlates to hair growth.

[0228] Minoxidil is also approved for the treatment of androgenetic alopecia but there is no information in the literature regarding its effects on IL-6 secretion from dermal papilla cells. In the presented experimental data Minoxidil demonstrated a mild, non-significant inhibition of IL-6 secretion from HFDPC. Clascoterone at all tested concentrations demonstrated statistically significant inhibition of IL-6 vs DHT treated HFDPC. Comparison of clascoterone + DHT vs. clascoterone + DHT + minoxidil showed that the combination was more than additive. In fact, the combination of clascoterone with minoxidil displayed synergistic efficacy to inhibit IL-6 secretion from HFDPC.

[0229] As such, it is evident that androgenetic alopecia patients should dramatically benefit from the combination treatment of clascoterone plus minoxidil.

[0230] The phraseology or terminology herein is for the purpose of description and not of limitation. As such, the terminology and/or phraseology of the present specification should be interpreted by the skilled artisan in light of the teachings and guidance herein.

[0231] The breadth and scope of the present invention should not be limited by any of the above-described exemplary embodiments but should be defined only in accordance with the following claims and their equivalents.

[0232] All patents, patent applications, and other references noted or referenced in this application are hereby incorporated by reference in their entirety.

[0233] **References**

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WHAT IS CLAIMED IS:

1. A method of treating hair loss in a subject in need thereof, comprising topically co-administering to the subject an effective amount of cortexolone-17 α -propionate and an effective amount of minoxidil.
2. The method of claim 1, wherein cortexolone-17 α -propionate is co-administered in an amount from at least 1 wt% to about 20 wt%.
3. The method of claim 1, wherein minoxidil is co-administered in an amount from about 0.1 wt% to about 20 wt%.
4. The method of any one of claims 1-3, wherein the cortexolone-17 α -propionate and minoxidil are co-administered sequentially.
5. The method of claim 4, wherein the cortexolone-17 α -propionate and minoxidil are in separate pharmaceutical formulations.
6. The method of any one of claims 1-3, wherein the cortexolone-17 α -propionate and minoxidil are co-administered simultaneously.
7. The method of claim 6, wherein the cortexolone-17 α -propionate and minoxidil are in the same pharmaceutical formulation.
8. The method of claim 7, wherein the pharmaceutical formulation is a liquid or semi-solid formulation.
9. The method of claim 7 or 8, wherein the pharmaceutical formulation is a solution, a suspension, an emulsion, a microemulsion, a cream, a paste, a gel, an ointment, or a foam.
10. The method of any one of claims 7-9, wherein the pharmaceutical formulation is a solution.
11. The method of claim 10, wherein the solution comprises water, saline, a buffered saline solution, a polyol, a polyol ether, a C₁-C₇ alcohol, or a combination thereof.

12. The method of any one of claims 7-11, wherein the pharmaceutical formulation further comprises at least one additive selected from an acid, a buffer, an antioxidant, an emulsifier, a penetration enhancer, a moisturizer, a preservative, a chelating agent, and combinations thereof.
13. The method of any one of claims 1-12, wherein the cortexolone-17 α -propionate is co-administered in a pharmaceutical formulation comprising less than about 5 wt% water.
14. The method of any one of claims 1-13, wherein the pharmaceutical formulation is co-administered topically once or twice daily.
15. The method of any one of claims 1-14, wherein the hair loss is alopecia.
16. The method of claim 15, wherein the alopecia is androgenetic alopecia, alopecia areata telogen effluvium, anagen effluvium, traction alopecia, or a combination of any of the foregoing.
17. The method of claim 16, wherein the alopecia areata is selected from the group consisting of diffuse alopecia areata, alopecia areata monolocularis, alopecia areata multilocularis, ophiasis, alopecia totalis, and alopecia universalis.
18. The method of claim 16, wherein the alopecia is androgenetic alopecia.
19. A topical pharmaceutical formulation comprising cortexolone-17 α -propionate, minoxidil, and one or more pharmaceutically acceptable carriers.
20. The topical pharmaceutical formulation of claim 19, wherein the cortexolone-17 α -propionate is fully solubilized in the pharmaceutical formulation.
21. The topical pharmaceutical formulation of claim 19 or 20, wherein the pharmaceutical formulation comprises cortexolone-17 α -propionate at a concentration from about 1 wt% to about 20 wt%.

22. The topical pharmaceutical formulation of any one of claims 19-21, wherein the pharmaceutical formulation comprises minoxidil at a concentration from about 0.1 wt% to about 20 wt%.
23. The topical pharmaceutical formulation of any one of claims 19-22, wherein the pharmaceutical formulation is a liquid or semi-solid formulation.
24. The topical pharmaceutical formulation of claim 23, wherein the liquid or semi-solid formulation is a solution, a suspension, an emulsion, a microemulsion, a cream, a paste, a gel, an ointment, or a foam.
25. The topical pharmaceutical formulation of claim 24, wherein the pharmaceutical formulation is a solution.
26. The topical pharmaceutical formulation of claim 24 or 25, wherein the solution comprises water, saline, a buffered saline solution, or a combination thereof.
27. The topical pharmaceutical formulation of any one of claims 19-26, wherein the pharmaceutical formulation comprises less than about 5 percent water by weight.
28. The topical pharmaceutical formulation of any one of claims 19-27, wherein the one or more pharmaceutically acceptable carriers are selected from the group consisting of a polyol, a polyol ether, and a C₁-C₇ alcohol.
29. The topical pharmaceutical formulation of claim 28, wherein the C₁-C₇ alcohol is ethanol, isopropanol, methanol, or a combination thereof.
30. The topical pharmaceutical formulation of claim 29, wherein the C₁-C₇ alcohol is ethanol.
31. The topical pharmaceutical formulation of any one of claims 28-30, wherein the polyol is selected from the group consisting of ethylene glycol, propylene glycol, glycerol, hexanetriol, and combinations thereof.
32. The topical pharmaceutical formulation of claim 31, wherein the polyol is propylene glycol.

33. The topical pharmaceutical formulation of any one of claims 28-32, wherein the polyol ether is selected from the group consisting of polypropylene glycol, polyethylene glycol, polyethylene-polypropylene triblock copolymers, dipropylene glycol, diethylene glycol monoethyl ether, and combinations thereof.
34. The topical pharmaceutical formulation of claim 33, wherein the polyol ether is diethylene glycol monoethyl ether.
35. The topical pharmaceutical formulation of claim any one of claims 28-34, wherein the polyol is propylene glycol, the polyol ether is diethylene glycol monoethyl ether, and the C₁-C₇ alcohol is ethanol.
36. The topical pharmaceutical formulation of any one of claims 19-35, wherein the pharmaceutical formulation further comprises at least one additive selected from an acid, a buffer, an antioxidant, an emulsifier, a penetration enhancer, a moisturizer, a preservative, a chelating agent, and combinations thereof.
37. The topical pharmaceutical formulation of claim 36, wherein the antioxidant is selected from the group consisting of butylated hydroxytoluene (BHT), butylated hydroxyanisole (BHA), ascorbyl palmitate, ascorbic acid, alpha tocopherol, propyl gallate, 2,4,5-trihydroxybutyrophenone, 4-hydroxymethyl-2,6-di-tert-butylphenol, erythorbic acid, gum guaiac, thiodipropionic acid, dilauryl thiodipropionate, tert-butylhydroquinone, pharmaceutically acceptable salts or esters thereof, and combinations thereof.
38. The topical pharmaceutical formulation of claim 37, wherein the antioxidant is BHT, ascorbyl palmitate, or a combination of BHT and ascorbyl palmitate.
39. The topical pharmaceutical formulation of any one of claims 36-38, wherein the emulsifier is selected from the group consisting of PEG-15 hydroxystearate (polyoxyl-15-hydroxystearate), PEG-30 stearate, PEG-40 laurate, PEG-40 oleate, polysorbate 20, polysorbate 60, polysorbate 80, PEG-20 cetostearyl ether, polyoxyl 25 cetostearyl, cetomacrogol 1000, sorbitan monolaurate, sorbitan monopalmitate, sorbitan monooleate propylene glycol esters of fatty acids, polyglycerol esters of fatty acids, polyoxyl 5 castor

oil, polyoxyl 15 castor oil, polyoxyl 35 castor oil, polyoxyl 40 hydrogenated castor oil, caprylocapryl polyoxyl-8 glycerides, caprylocaproyl polyoxylglycerides, lauroyl polyoxylglycerides, oleoyl polyoxylglycerides, and combinations thereof.

40. The topical pharmaceutical formulation of claim 39, wherein the emulsifier is polysorbate 60, polysorbate 80, or a combination of polysorbate 60 and polysorbate 80.
41. The topical pharmaceutical formulation of any one of claims 36-40, wherein the penetration enhancer is selected from the group consisting of a diol, a polyol, a fatty acid, a fatty alcohol, a fatty acid ester, a surfactant, a pyrrolidone, and combinations thereof.
42. The topical pharmaceutical formulation of any one of claims 36-41, wherein the moisturizer is selected from the group consisting of a fatty alcohol, a fatty acid, a fatty acid ester, an oil, a polyethylene glycol, glycerin, an alpha hydroxy acid, and combinations thereof.
43. The topical pharmaceutical formulation of claim 42, wherein the moisturizer is cetyl alcohol, cetaryl alcohol, stearyl alcohol, stearic acid, isopropyl myristate, isopropyl palmitate, cocoa butter, lanolin, liquid paraffin, shea butter, a silicone oil, castor oil, a polyethylene glycol, glycerin, lactic acid, glycolic acid, malic acid, citric acid, tartaric acid, or a combination thereof.
44. The topical pharmaceutical formulation of any one of claims 36-43, wherein the buffer is a phosphate buffer, citrate buffer, lactate buffer, or a combination thereof.
45. A method of treating alopecia, the method comprising topically administering to a subject in need thereof the topical pharmaceutical formulation of any one of claims 19-44, wherein the topical administration of the pharmaceutical formulation for at least six months achieves a weighted average Hair Growth Assessment (HGA) score of about 0.30 in comparison with vehicle.
46. A method of treating alopecia, the method comprising topically administering to a subject in need thereof the topical pharmaceutical formulation of any one of claims 19-44, wherein the topical administration of the pharmaceutical formulation for at least six months

achieves a weighted average Investigator's Global Assessment (IGA) score of about 0.43 in comparison with vehicle.

47. A method of treating alopecia, the method comprising topically administering to a subject in need thereof the topical pharmaceutical formulation of any one of claims 19-44, wherein the topical administration of the pharmaceutical formulation for at least six months is free from systemic antiandrogenic side-effects.
48. A method of treating alopecia, the method comprising topically administering to a subject in need thereof the topical pharmaceutical formulation of any one of claims 19-44, wherein the topical administration of the pharmaceutical formulation provides
- a) a mean change from baseline in Target Area Hair Count equal to or higher than 9 hairs/cm² after 6 months of daily or BID application; or
 - b) a mean change from baseline in Target Area Hair Count equal to or higher than 10 hairs/cm² after 6 months of daily or BID application; or
 - c) a mean change from baseline in Target Area Hair Count equal to or higher than 11 hairs/cm² after 6 months of daily or BID application; or
 - d) a mean change from baseline in Target Area Hair Count equal to or higher than 12 hairs/cm² after 6 months of daily or BID application; or
 - e) a weighted average HGA score equal to or higher than 0.20 after 6 months of daily or BID application; or
 - f) a weighted average HGA score equal to or higher than 0.30 after 6 months of daily or BID application; or
 - g) a weighted average HGA score equal to or higher than 0.40 after 6 months of daily or BID application; or
 - h) a weighted average IGA score equal to or higher than 0.10 after 6 months of daily or BID application; or

- i) a weighted average IGA score equal to or higher than 0.20 after 6 months of daily or BID application; or
 - j) a weighted average IGA score equal to or higher than 0.30 after 6 months of daily or BID application; or
 - k) a favorable (positive) HGA score in at least about 10 % of subjects after 6 months of daily or BID application; or
 - l) a favorable (positive) HGA score in at least about 20 % of subjects after 6 months of daily or BID application; or
 - m) a favorable (positive) HGA score in at least about 30 % of subjects after 6 months of daily or BID application; or
 - n) a favorable (positive) IGA score in at least about 10 % of subjects after 6 months of daily or BID application; or
 - o) a favorable (positive) IGA score in at least about 20 % of subjects after 6 months of daily or BID application; or
 - p) a favorable (positive) IGA score in at least about 30 % of subjects after 6 months of daily or BID application; or
 - q) a favorable (positive) IGA score in at least about 40 % of subjects after 6 months of daily or BID application.
49. Cortisolone-17 α -propionate and minoxidil for use in the treatment of hair loss in a subject in need thereof, characterized in that they are co-administered topically to the subject.
50. Cortisolone-17 α -propionate and minoxidil for use according to claim 49, wherein cortisolone-17 α -propionate is co-administered in an amount from at least 1 wt% to about 20 wt%.

51. Cortisolone-17 α -propionate and minoxidil for use according to claim 49, wherein minoxidil is co-administered in an amount from about 0.1 wt% to about 20 wt%.
52. Cortisolone-17 α -propionate and minoxidil for use according to any one of claims 49-51, wherein the cortisolone-17 α -propionate and minoxidil are co-administered sequentially, preferably the cortisolone-17 α -propionate and minoxidil are in separate pharmaceutical formulations.
53. Cortisolone-17 α -propionate and minoxidil for use according to any one of claims 49-51, wherein the cortisolone-17 α -propionate and minoxidil are co-administered simultaneously, preferably the cortisolone-17 α -propionate and minoxidil are in the same pharmaceutical formulation.
54. Cortisolone-17 α -propionate and minoxidil for use according to claim 53, wherein the pharmaceutical formulation is a liquid or semi-solid formulation, preferably the pharmaceutical formulation is a solution, a suspension, an emulsion, a microemulsion, a cream, a paste, a gel, an ointment, or a foam, more preferably the pharmaceutical formulation is a solution.
55. Cortisolone-17 α -propionate and minoxidil for use according to claim 54, wherein the solution comprises water, saline, a buffered saline solution, a polyol, a polyol ether, a C₁-C₇ alcohol, or a combination thereof.
56. Cortisolone-17 α -propionate and minoxidil for use according to any one of claims 54-55, wherein the pharmaceutical formulation further comprises at least one additive selected from an acid, a buffer, an antioxidant, an emulsifier, a penetration enhancer, a moisturizer, a preservative, a chelating agent, and combinations thereof.
57. Cortisolone-17 α -propionate and minoxidil for use according to any one of claims 49-56, wherein the cortisolone-17 α -propionate is co-administered in a pharmaceutical formulation comprising less than about 5 wt% water.
58. Cortisolone-17 α -propionate and minoxidil for use according to any one of claims 49-57, wherein the pharmaceutical formulation is co-administered topically once or twice daily.

59. Cortexolone-17 α -propionate and minoxidil for use according to any one of claims 49-58, wherein the hair loss is alopecia, preferably the alopecia is androgenetic alopecia, alopecia areata telogen effluvium, anagen effluvium, traction alopecia, or a combination of any of the foregoing, more preferably the alopecia is androgenic alopecia.
60. Cortexolone-17 α -propionate and minoxidil for use according to claim 59, wherein the alopecia areata is selected from the group consisting of diffuse alopecia areata, alopecia areata monolocularis, alopecia areata multilocularis, ophiasis, alopecia totalis, and alopecia universalis.
61. The topical pharmaceutical formulation according to any one of claims 19- 44, wherein the formulation is for use in the treatment of hair loss in a subject in need thereof.
62. The topical pharmaceutical formulation for use according to claim 61, wherein the hair loss is alopecia.
63. The topical pharmaceutical formulation for use according to claim 62, wherein alopecia is androgenetic alopecia, alopecia areata telogen effluvium, anagen effluvium, traction alopecia, or a combination of any of the foregoing.
64. The topical pharmaceutical formulation for use according to claim 63, wherein the alopecia areata is selected from the group consisting of diffuse alopecia areata, alopecia areata monolocularis, alopecia areata multilocularis, ophiasis, alopecia totalis, and alopecia universalis.
65. The topical pharmaceutical formulation for use according to claim 62, wherein alopecia is androgenic alopecia.
66. The topical pharmaceutical formulation for use according to any one of claims 61-65, wherein the topical administration of the pharmaceutical formulation for at least six months

achieves a weighted average Hair Growth Assessment (HGA) score of about 0.30 in comparison with vehicle.

67. The topical pharmaceutical formulation for use according to any one of claims 61-65, wherein the topical administration of the pharmaceutical formulation for at least six months achieves a weighted average Investigator's Global Assessment (IGA) score of about 0.43 in comparison with vehicle.
68. The topical pharmaceutical formulation for use according to any one of claims 61-67, wherein the topical administration of the pharmaceutical formulation for at least six months is free from systemic antiandrogenic side-effects.
69. The topical pharmaceutical formulation for use according to any one of claims 61-67, wherein the topical administration of the pharmaceutical formulation provides
 - a) a mean change from baseline in Target Area Hair Count equal to or higher than 9 hairs/cm² after 6 months of daily or BID application; or
 - b) a mean change from baseline in Target Area Hair Count equal to or higher than 10 hairs/cm² after 6 months of daily or BID application; or
 - c) a mean change from baseline in Target Area Hair Count equal to or higher than 11 hairs/cm² after 6 months of daily or BID application; or
 - d) a mean change from baseline in Target Area Hair Count equal to or higher than 12 hairs/cm² after 6 months of daily or BID application; or
 - e) a weighted average HGA score equal to or higher than 0.20 after 6 months of daily or BID application; or
 - f) a weighted average HGA score equal to or higher than 0.30 after 6 months of daily or BID application; or

- g) a weighted average HGA score equal to or higher than 0.40 after 6 months of daily or BID application; or
- h) a weighted average IGA score equal to or higher than 0.10 after 6 months of daily or BID application; or
- i) a weighted average IGA score equal to or higher than 0.20 after 6 months of daily or BID application; or
- j) a weighted average IGA score equal to or higher than 0.30 after 6 months of daily or BID application; or
- k) a favorable (positive) HGA score in at least about 10 % of subjects after 6 months of daily or BID application; or
- l) a favorable (positive) HGA score in at least about 20 % of subjects after 6 months of daily or BID application; or
- m) a favorable (positive) HGA score in at least about 30 % of subjects after 6 months of daily or BID application; or
- n) a favorable (positive) IGA score in at least about 10 % of subjects after 6 months of daily or BID application; or
- o) a favorable (positive) IGA score in at least about 20 % of subjects after 6 months of daily or BID application; or
- p) a favorable (positive) IGA score in at least about 30 % of subjects after 6 months of daily or BID application; or
- q) a favorable (positive) IGA score in at least about 40 % of subjects after 6 months of daily or BID application.