

COMPOSITIONS AND METHODS FOR TREATMENT OF ANDROGENETIC ALOPECIA

REFERENCE TO RELATED APPLICATION

[0001] The application claims benefit of US Provisional Serial No. 63/457,928 filed April 7, 2023, the contents of which are incorporated by reference.

BACKGROUND OF THE INVENTION

[0002] Hair loss often has a negative social and psychological impact on the individual suffering therefrom. Many factors are believed to contribute to hair loss, including genetics, hormones, environmental exposure, medications, psychological stress, and nutrition. One known treatment is hair transplantation, which requires anesthesia, is costly, time-consuming, and sometimes painful. Other approaches include massage and acupuncture, but these have not been shown to be effective. Hormones and other drugs have been used to treat hair loss, however these treatments frequently cause undesirable side effects, such as hair growth in unwanted areas.

[0003] Accordingly, there is a need for an effective therapy for stimulating hair growth.

BRIEF SUMMARY OF THE INVENTION

[0004] Provided herein are methods of treating androgenetic alopecia (AGA) in a patient in need thereof. In some embodiments, the methods can include administering the compositions described herein to a skin of the patient. In some embodiments, the methods can include administering the compositions of the disclosure to a skin of the patient via an intradermal injection. In some embodiments, the compositions can include up to about 1 wt% of hyaluronic acid. For example, the compositions can include about 0.2 wt % to about 0.4 wt % hyaluronic acid. In some embodiments, the compositions can be administered at least two times a week to the subject. In some embodiments, the compositions can be administered for about 3 times a week. In some embodiments, the composition can include hyaluronic acid that is not cross-linked. In some embodiments, the average molecular weight of the hyaluronic acid can be up to about 100 kDa.

[0005] In some embodiments, the methods of treating AGA can include administering the composition to the patient on consecutive days in the week. In some embodiments, the compositions can be administered on three consecutive days in the week. In some embodiments, the compositions can be injected at a depth of about 0.1 mm or more into the skin. In some

embodiments, the composition can be injected about 0.6 mm to about 0.8 mm deep into the skin. In some embodiments, the injection area can be about 4 cm² or more. In some embodiments, the compositions can be administered at or proximal to a stem cell area of a follicle in the scalp of the subject.

[0006] In some embodiments, the compositions can be administered to the skin at one or more of a frontotemporal region of a scalp of the patient and a vertex region of a scalp of the patient.

[0007] In some embodiments, treatment with the composition can improve or increase target area hair count (TAHC); target area hair width (TAHW); and/or hair darkness.

[0008] In some embodiments, the compositions are administered to a patient who has experienced an onset of hair loss for about three years to five years prior to administering the composition. In some embodiments, the compositions are administered to a patient who has experienced an onset of hair loss for about ten years prior to administering the composition. In some embodiments, the patient has previously received a hair transplantation. In some embodiments, the patient has received the hair transplantation about one month to about two months prior to administering the composition. In some embodiments, the patient is a male patient.

[0009] In some embodiments, the compositions of the disclosure can be used to treat mild AGA or moderate AGA. In some embodiments, the compositions of the disclosure can be used to treat a patient who has received a Modified Norwood Hamilton Scale score of III, or a Modified Norwood Hamilton Scale score of IV. In some embodiments, the improvement or increase in TAHC, TAHW and/or hair darkness is measured from about 10 days to about 160 days after administering the composition.

[0010] In some embodiments, the patient has previously experienced hair loss.

[0011] In some embodiments, the compositions of the disclosure can stimulate hair growth in the frontotemporal region of the scalp of the patient and/or the vertex region of the scalp of the patient.

[0012] Also provided herein are methods of stimulating hair growth in a skin of a patient. The methods can include administering the compositions of the disclosure to the skin of the patient. In some embodiments, the compositions can be administered to the patient via an intradermal injection. In some embodiments, the compositions of the disclosure can include up to 1wt % hyaluronic acid, such as about 0.2 wt % to about 0.4 wt % hyaluronic acid. In some embodiments, the compositions of the disclosure can be administered at least two times a week. For example, the

compositions can be administered for about 3 times a week. In some embodiments, the composition can include hyaluronic acid that is not cross-linked. In some embodiments, the average molecular weight of the hyaluronic acid may be up to about 100 kDa.

[0013] The present disclosure provides method of administering a composition for hair growth to a patient in need thereof. The methods can include administering the compositions of the disclosure to a skin of the patient. In some embodiments, the compositions can be administered via an intradermal injection. In some embodiments, the compositions can include up to about 1 wt% hyaluronic acid, such as, about 0.2 wt % to about 0.4 wt % hyaluronic acid. The composition can be administered at least two times a week, for example, for about 3 times a week. In some embodiments, the composition can include hyaluronic acid that is not cross-linked. In some embodiments, the average molecular weight of the hyaluronic acid can be up to about 100 kDa.

[0014] In some embodiments, the methods for hair growth can include administering the composition to the patient on consecutive days. In one embodiment, the compositions can be administered on three consecutive days in the week. In some embodiments, the composition can be injected about 0.1 mm deep or more, for example from about 0.6 mm to about 0.8 mm deep into the skin. In some embodiments, the injection area can be about 4 cm² or more. In some embodiments, the compositions of the disclosure can be administered at or proximal to a stem cell area of a follicle.

[0015] In some embodiments, the compositions for hair growth can be administered to the skin at one or more of a frontotemporal region of a scalp of the patient and a vertex region of a scalp of the patient.

[0016] In some embodiments, treatment with the composition can improve or increases target area hair count (TAHC); target area hair width (TAHW); and/or hair darkness.

[0017] In some embodiments, the compositions are administered to a patient who has experienced an onset of hair loss for about three years to five years prior to administering the composition. In some embodiments, the compositions are administered to a patient who has experienced an onset of hair loss for about ten years prior to administering the composition. In some embodiments, the patient has previously received a hair transplantation. In some embodiments, the patient has received the hair transplantation about one month to about two months prior to administering the composition. In some embodiments, the patient is a male patient.

[0018] In some embodiments, the compositions can be used for hair growth in a patient who has AGA. The AGA can be mild AGA or moderate AGA. In some embodiments, the compositions of the disclosure can be used to treat hair loss in a patient who has received a Modified Norwood Hamilton Scale score of III, or a Modified Norwood Hamilton Scale score of IV. In some embodiments, the improvement or increase in TAHC, TAHW and/or hair darkness is measured from about 10 days to about 160 days after administering the composition.

BRIEF DESCRIPTION OF THE SEVERAL VIEWS OF THE DRAWINGS

[0019] The following detailed description of embodiments of the compositions and methods for stimulating hair growth will be better understood when read in conjunction with the appended drawings. It should be understood, however, that the invention is not limited to the precise arrangements shown.

In the drawings:

[0020] The figure is a drawing showing the characteristics associated with each Modified Norwood Hamilton Scale score.

DETAILED DESCRIPTION OF THE INVENTION

I. Compositions

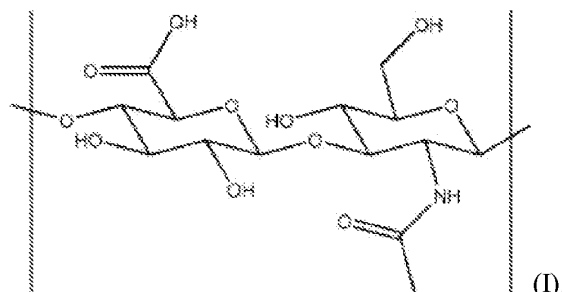
[0021] In some embodiments a hair growth stimulating composition includes hyaluronic acid. In some embodiments, the compositions described in U.S. Patent 11,337,993 can be utilized in the present disclosure (the contents of which are herein incorporated by reference in its entirety).

1. Hyaluronic Acid (HA)

[0022] HA is an endogenous, naturally occurring glycosaminoglycan. HA is found in the extracellular matrix and is widely distributed throughout the body, most abundant in the skin (~50%). HA is primarily produced by mesenchymal cells and its function in the body is to retain water; is responsible for hydration and viscoelasticity of skin; facilitate transport of ion solute and nutrients; and protects skin from free radical damage (Erickson & Stern, 2012).

[0023] In some embodiments a composition useful for stimulating hair growth includes hyaluronic acid. Hyaluronic acid is a natural ligand for CD44, and it has now been found to be pro-inflammatory and stimulate hair growth. Hyaluronic acid is a natural linear polymer containing

repeated units of a disaccharide of β -1,4-D-glucuronic acid and β -1,3-N-acetyl-D-glucosamine, as



shown in Formula (I):

(I).

[0024] The units link together to form long, linear molecules, which form into random coils as it gets longer. At concentrations higher than 0.1%, the chains of HA form a continuous network. HA can be chemically enhanced to create crosslinks between HA molecules with the purpose to adjust the physical properties of the product.

[0025] HA has been studied in a variety of medical applications, including aesthetic (i.e., dermal filler), ophthalmic (viscoelastic), and osteoarthritis applications. Multiple commercial HA products are available in the US, including dermal fillers such as Juvéderm and Restylane; viscoelastic products such as Healon and NuVisc; and osteoarthritis products such as Hyalgan, and Orthovisc. HA-based mesotherapy (intra dermal injection of small aliquots) has been well documented in the literature as a safe treatment for skin rejuvenation. Reported adverse events associated with HA were mild and transient and included injection-site pain, pruritus, stinging, erythema, edema, petechiae, purpura, bruising, swelling, hematoma, dark eye circle, ecchymosis, skin scratch, and pinpoint bleeding, allergic reactions, urticaria, and papule formation. Risks associated with HA dermal fillers are generally mild and transient, but rare and serious complications have occurred due to vascular occlusion including infection, embolism, and tissue necrosis. These events are associated with deep injection of cross-linked HA products. The present invention provides hyaluronic acid in non-crosslinked format, in phosphate buffered saline (PBS) for use in the methods described herein.

[0026] In some embodiments the hyaluronic acid has a low average molecular weight. In some embodiments, “low average molecular weight” as used herein refers to ranges from about 15,000 Da to about 40,000 Da. In some embodiments the hyaluronic acid has an intermediate average molecular weight. In some embodiments, “intermediate average molecular weight,” as used herein refers to ranges from about 75,000 Da to about 350,000 Da. In some embodiments the hyaluronic

acid has a high average molecular weight. In some embodiments, “high average molecular weight,” as used herein, refers to about 950,000 Da and greater.

[0027] In some embodiments the hyaluronic acid has an average molecular weight ranging from about 4,000 Da or less to about 10,000 Da. In some embodiments the hyaluronic acid has an average molecular weight ranging from about 10,000 Da to about 100,000 Da. In some embodiments the hyaluronic acid has an average molecular weight ranging from about 100,000 Da to about 1,500,000 Da or greater. In some embodiments, the hyaluronic acid has an average molecular weight can be about 40 kDa to about 100 kDa. In one embodiment, the hyaluronic acid has an average molecular weight of about 60 kDa.

[0028] In some embodiments hyaluronic acid has an average molecular weight between about 1 kDa and about 10 kDa, between about 10 kDa and about 50 kDa, between about 50 kDa and about 100 kDa, between about 100 kDa and about 150 kDa, between about 200 kDa and about 250 kDa, between about 300 kDa and about 350 kDa, between about 400 kDa and about 450 kDa, between about 500 kDa and about 550 kDa, between about 600 kDa and about 650 kDa, between about 700 kDa and about 750 kDa, between about 800 kDa and about 850 kDa, between about 900 kDa and about 1000 kDa, between about 1000 kDa and about 1100 kDa, between about 1100 kDa and about 1200 kDa, between about 1200 kDa and about 1300 kDa, between about 1300 kDa and about 1400 kDa, between about 1400 kDa and about 1500 kDa, between about 1 kDa and about 100 kDa, between about 100 kDa and about 250 kDa, between about 250 kDa and about 500 kDa, between about 500 kDa and about 750 kDa, between about 750 kDa and about 1000 kDa, between about 1000 kDa and about 1250 kDa, between about 1250 kDa and about 1500 kDa, between about 1 kDa and about 250 kDa, between about 1 kDa and about 500 kDa, between about 100 kDa and about 500 kDa, between about 250 kDa and about 750 kDa, between about 500 kDa and about 1000 kDa, between about 750 kDa and about 1250 kDa, or between about 1000 kDa and about 1500 kDa.

[0029] In some embodiments, the average molecular weight of the hyaluronic acid may be up to about 100 kDa. For example the average molecular weight of the hyaluronic acid may be between about 1 kDa and about 10 kDa, between about 5 kDa and about 15 kDa, between about 10 kDa and about 20 kDa, between about 15 kDa and about 25 kDa, between about 20 kDa and about 30 kDa, between about 25 kDa and about 35 kDa, between about 30 kDa and about 40 kDa, between about 35 kDa and about 45 kDa, between about 40 kDa and about 50 kDa, between about

45 kDa and about 55 kDa, between about 50 kDa and about 60 kDa, between about 55 kDa and about 65 kDa, between about 60 kDa and about 70 kDa, between about 65 kDa and about 75 kDa, between about 70 kDa and about 80 kDa, between about 75 kDa and about 85 kDa, between about 80 kDa and about 90 kDa, between about 85 kDa and about 95 kDa, between about 90 kDa and about 100 kDa, between about 95 kDa and about 105 kDa, between about 100 kDa and about 200 kDa, between about 150 kDa and about 250 kDa, between about 200 kDa and about 300 kDa, between about 250 kDa and about 350 kDa, between about 300 kDa and about 400 kDa, between about 350 kDa and about 450 kDa, between about 400 kDa and about 500 kDa, between about 450 kDa and about 550 kDa, between about 500 kDa and about 600 kDa, between about 550 kDa and about 650 kDa, between about 600 kDa and about 700 kDa, between about 650 kDa and about 750 kDa, between about 700 kDa and about 800 kDa, between about 750 kDa and about 850 kDa, between about 800 kDa and about 900 kDa, between about 850 kDa and about 950 kDa, between about 900 kDa and about 1000 kDa, between about 950 kDa and about 1000 kDa or more.

[0030] In some embodiments, the hyaluronic acid is not cross-linked. In some embodiments, the hyaluronic acid is substantially free of cross-linking. In some embodiments, the composition includes free hyaluronic acid, that is, non-cross-linked hyaluronic acid. Generally, free hyaluronic acid is not exposed to cross-linking conditions. In some embodiments the compositions can have free hyaluronic acid, and the free hyaluronic acid may be present in the concentrations between 5 to 95 weight percent of total hyaluronic acid.

[0031] In some embodiments the hyaluronic acid is cross-linked. Cross-linking may improve the lifetime of the hyaluronic acid and in some embodiments, some degree of cross-linking can be desirable. In some embodiments the hyaluronic acid has sufficient cross-linking to last for about a week. However, without being bound by a mechanism of action, it is believed that hyaluronic acid is effective in stimulating hair growth by interacting with CD44 receptors. Accordingly, in some embodiments, it is desirable that the hyaluronic acid is not cross-linked so extensively that the cross-linking interferes with the ability of the hyaluronic acid to interact with a CD44 receptor.

[0032] The hydroxyl (--OH), carboxylic (--COOH), and/or amide (--NHCOCH_2) functional groups of hyaluronic acid can cross link via an ether bond (R--O--R), ester linkage (R--COO--R), or carbodiimide, respectively. In some embodiments hyaluronic acid is cross-linked with 1-ethyl-3-(3-dimethylaminopropyl) carbodiimide (EDC), glutaraldehyde (GTA), poly

(ethylene glycol) diglycidil ether (PEGDE), ethylene glycol diglycidil ether (EGDE), divinyl sulfonate (DVS), or pentaerythritol tetra-acrylate (PT).

[0033] The hyaluronic acid may have a cross-link density of about 1×10^{-7} mol/cm³ or greater, about 2×10^{-7} mol/cm³ or greater, about 3×10^{-7} mol/cm³ or greater, about 4×10^{-7} mol/cm³ or greater, about 5×10^{-7} mol/cm³ or greater, about 6×10^{-7} mol/cm³ or greater, about 7×10^{-7} mol/cm³ or greater, about 8×10^{-7} mol/cm³ or greater, about 9×10^{-7} mol/cm³ or greater, about 1×10^{-6} mol/cm³ or greater, about 2×10^{-6} mol/cm³ or greater, about 3×10^{-6} mol/cm³ or greater, about 4×10^{-6} mol/cm³ or greater, about 5×10^{-6} mol/cm³ or greater, about 6×10^{-6} mol/cm³ or greater, about 7×10^{-6} mol/cm³ or greater, about 8×10^{-6} mol/cm³ or greater, about 9×10^{-6} mol/cm³ or greater, or about 1×10^{-5} mol/cm³ or greater. In some embodiments the hyaluronic acid may have a cross-link density between about 1×10^{-7} mol/cm³ and about 1×10^{-5} mol/cm³, between about 1×10^{-7} mol/cm³ and about 1×10^{-6} mol/cm³, between about 1×10^{-7} mol/cm³ and about 5×10^{-7} mol/cm³, between about 5×10^{-7} mol/cm³ and about 1×10^{-6} mol/cm³, between about 1×10^{-6} mol/cm³ and about 1×10^{-5} mol/cm³, between about 1×10^{-6} mol/cm³ and about 2×10^{-6} mol/cm³, between about 2×10^{-6} mol/cm³ and about 4×10^{-6} mol/cm³, between about 4×10^{-6} mol/cm³ and about 6×10^{-6} mol/cm³, between about 6×10^{-6} mol/cm³ and about 8×10^{-6} mol/cm³, or between about 8×10^{-6} mol/cm³ and about 1×10^{-5} mol/cm³, between about 1×10^{-5} mol/cm³ and about 1×10^{-6} mol/cm³, between about 1×10^{-6} mol/cm³ and about 5×10^{-6} mol/cm³, between about 5×10^{-6} mol/cm³ and about 1×10^{-5} mol/cm³, between about 1×10^{-6} mol/cm³ and about 2×10^{-6} mol/cm³, between about 2×10^{-6} mol/cm³ and about 4×10^{-6} mol/cm³, between about 4×10^{-6} mol/cm³ and about 6×10^{-6} mol/cm³, between about 6×10^{-6} mol/cm³ and about 8×10^{-6} mol/cm³, between about 8×10^{-6} mol/cm³ and about 1×10^{-5} mol/cm³ or between about 5×10^{-7} mol/cm³ and about 5×10^{-6} mol/cm³.

[0034] Compositions of the invention may include an amount of hyaluronic acid sufficient to provide a therapeutic effect, for example stimulating hair growth in a patient in need thereof and/or to treat Androgenetic Alopecia (AGA). In some embodiments, higher concentrations of hyaluronic acid can result in undesirable inflammation. In some embodiments compositions of the invention include an amount of hyaluronic acid sufficient to provide a therapeutic effect, for example stimulating hair growth or treat AGA in a patient in need thereof, and insufficient to provide an unacceptable or undesirable inflammatory response.

[0035] In some embodiments a composition comprises about 0.001 wt % or greater hyaluronic acid, about 0.0025 wt % or greater hyaluronic acid, about 0.0050 wt % or greater hyaluronic acid, about 0.0075 wt % or greater hyaluronic acid, about 0.01 wt % or greater hyaluronic acid, about

0.025 wt % or greater hyaluronic acid, about 0.05 wt % or greater hyaluronic acid, about 0.075 wt % or greater hyaluronic acid, about 0.1 wt % or greater hyaluronic acid, about 0.25 wt % or greater hyaluronic acid, about 0.5 wt % or greater hyaluronic acid, about 0.75 wt % or greater hyaluronic acid, or about 1 wt % or greater hyaluronic acid. In some embodiments a composition comprises between about 0.001 wt % and about 0.0025 wt % hyaluronic acid, between about 0.0025 wt % and about 0.005 wt % hyaluronic acid, between about 0.0025 wt % and about 0.0075 wt % hyaluronic acid, between about 0.0025 wt % and about 0.01 wt % hyaluronic acid, between about 0.001 wt % and about 0.01 wt % hyaluronic acid, between about 0.005 wt % and about 0.0075 wt % hyaluronic acid, between about 0.005 wt % and about 0.01 wt % hyaluronic acid, between about 0.0075 wt % and about 0.01 wt % hyaluronic acid, between about 0.01 wt % and about 0.02 wt % hyaluronic acid, between about 0.01 wt % and about 0.05 wt % hyaluronic acid, between about 0.02 wt % and about 0.04 wt % hyaluronic acid, between about 0.05 wt % and about 0.1 wt % hyaluronic acid, between about 0.04 wt % and about 0.06 wt % hyaluronic acid, between about 0.06 and about 0.08 wt % hyaluronic acid, between about 0.08 wt % and about 0.1 wt % hyaluronic acid, between about 0.1 wt % and about 0.2 wt % hyaluronic acid, between about 0.2 wt % and about 0.3 wt % hyaluronic acid, between about 0.1 wt % and about 0.5 wt % hyaluronic acid, between about 0.2 wt % and about 0.4 wt % hyaluronic acid, between about 0.5 wt % and about 1 wt % hyaluronic acid, between about 0.3 wt % and about 0.4 wt % hyaluronic acid, between about 0.4 wt % and about 0.5 wt % hyaluronic acid, between about 0.5 wt % and about 0.6 wt % hyaluronic acid, between about 0.4 wt % and about 0.6 wt % hyaluronic acid, between about 0.6 wt % and about 0.7 wt % hyaluronic acid, between about 0.7 wt % and about 0.8 wt % hyaluronic acid, between about 0.6 and about 0.8 wt % hyaluronic acid, between about 0.8 wt % and about 0.9 wt % hyaluronic acid or between about 0.8 wt % and about 1 wt % hyaluronic acid. In some embodiments a composition comprises about 0.1 wt %, about 0.11 wt %, about 0.12 wt %, about 0.13 wt %, about 0.14 wt %, about 0.15 wt %, about 0.16 wt %, about 0.17 wt %, about 0.18 wt %, about 0.19 wt %, about 0.2 wt %, about 0.21 wt %, about 0.22 wt %, about 0.23 wt %, about 0.24 wt %, about 0.25 wt %, about 0.26 wt %, about 0.27 wt %, about 0.28 wt %, about 0.29 wt %, about 0.3 wt %, about 0.31 wt %, about 0.32 wt %, about 0.33 wt %, about 0.34 wt %, about 0.35 wt %, about 0.36 wt %, about 0.37 wt %, about 0.38 wt %, about 0.39 wt %, about 0.4 wt %, about 0.41 wt %, about 0.42 wt %, about 0.43 wt %, about 0.44 wt %, about 0.45 wt %, about 0.46 wt %, about 0.47 wt %, about 0.48 wt %, about 0.49 wt %, about 0.5 wt %, about 0.51 wt %, about 0.52 wt %, about 0.53 wt %, about 0.54 wt %, about

0.55 wt %, about 0.56 wt %, about 0.57 wt %, about 0.58 wt %, about 0.59 wt %, about 0.6 wt %, about 0.61 wt %, about 0.62 wt %, about 0.63 wt %, about 0.64 wt %, about 0.65 wt %, about 0.66 wt %, about 0.67 wt %, about 0.68 wt %, about 0.69 wt %, about 0.7 wt %, about 0.71 wt %, about 0.72 wt %, about 0.73 wt %, about 0.74 wt %, about 0.75 wt %, about 0.76 wt %, about 0.77 wt %, about 0.78 wt %, about 0.79 wt %, about 0.8 wt %, about 0.81 wt %, about 0.82 wt %, about 0.83 wt %, about 0.84 wt %, about 0.85 wt %, about 0.86 wt %, about 0.87 wt %, about 0.88 wt %, about 0.89 wt %, about 0.9 wt %, about 0.91 wt %, about 0.92 wt %, about 0.93 wt %, about 0.94 wt %, about 0.95 wt %, about 0.96 wt %, about 0.97 wt %, about 0.98 wt %, about 0.99 wt %, about 1 wt %. or greater hyaluronic acid.

[0036] As used throughout this description, both mcg/mL and ug/mL refer to micrograms per milliliter. In some embodiments hyaluronic acid is present in an amount of about 10 mcg/mL of composition or greater, about 15 mcg/mL of composition or greater, about 20 mcg/mL of composition or greater, about 25 mcg/mL of composition or greater, about 30 mcg/mL of composition or greater, about 35 mcg/mL of composition or greater, about 40 mcg/mL of composition or greater, about 45 mcg/mL of composition or greater, about 50 mcg/mL of composition or greater, about 55 mcg/mL of composition or greater, about 60 mcg/mL of composition or greater, about 65 mcg/mL of composition or greater, about 70 mcg/mL of composition or greater, about 75 mcg/mL of composition or greater, about 80 mcg/mL of composition or greater, about 85 mcg/mL of composition or greater, about 90 mcg/mL of composition or greater, about 95 mcg/mL of composition or greater, about 100 mcg/mL composition or greater, about 110 mcg/mL composition or greater, about 120 mcg/mL composition or greater, about 130 mcg/mL composition or greater, about 140 mcg/mL composition or greater, about 150 mcg/mL composition or greater, about 160 mcg/mL composition or greater, about 170 mcg/mL composition or greater, about 180 mcg/mL composition or greater, about 190 mcg/mL composition or greater, about 200 mcg/mL composition or greater, about 210 mcg/mL composition or greater, about 220 mcg/mL composition or greater, about 230 mcg/mL composition or greater, about 240 mcg/mL composition or greater, about 250 mcg/mL composition or greater, about 260 mcg/mL composition or greater, about 270 mcg/mL composition or greater, about 280 mcg/mL composition or greater, about 290 mcg/mL composition or greater, about 300 mcg/mL composition or greater, about 310 mcg/mL composition or greater, about 320 mcg/mL

[illegible]

composition or greater, about 960 mcg/mL composition or greater, about 970 mcg/mL composition, about 980 mcg/mL composition or greater,.

[0037] In some embodiments hyaluronic acid is present in an amount in a range of about 1 mcg/mL of composition to about 250 mcg/mL of composition, about 10 mcg/mL of composition to about 250 mcg/mL of composition, about 10 mcg/mL of composition to about 200 mcg/mL of composition, 10 mcg/mL of composition to about 150 mcg/mL of composition, 10 mcg/mL of composition to about 100 mcg/mL of composition, about 25 mcg/mL of composition to about 250 mcg/mL of composition, about 25 mcg/mL of composition to about 200 mcg/mL of composition, about 25 mcg/mL of composition to about 150 mcg/mL of composition, about 25 mcg/mL of composition to about 100 mcg/mL of composition, about 50 mcg/mL of composition to about 250 mcg/mL of composition, about 50 mcg/mL of composition to about 200 mcg/mL of composition, about 50 mcg/mL of composition to about 150 mcg/mL of composition, about 50 mcg/mL of composition to about 100 mcg/mL of composition, about 75 mcg/mL of composition to about 250 mcg/mL of composition, about 75 mcg/mL of composition to about 200 mcg/mL of composition, about 75 mcg/mL of composition to about 150 mcg/mL of composition, about 75 mcg/mL of composition to about 100 mcg/mL of composition, about 100 mcg/mL of composition to about 250 mcg/mL of composition, about 100 mcg/mL of composition to about 200 mcg/mL of composition, about 100 mcg/mL of composition to about 150 mcg/mL of composition, about 150 mcg/mL of composition to about 250 mcg/mL of composition, about 200 mcg/mL of composition to about 250 mcg/mL of composition, about 60 mcg/mL of composition to about 80 mcg/mL of composition, about 50 mcg/mL of composition to about 75 mcg/mL of composition, about 25 mcg/mL of composition to about 75 mcg/mL of composition, about 10 mcg/mL of composition to about 50 mcg/mL of composition, or about 10 mcg/mL of composition to about 25 mcg/mL of composition.

[0038] In some embodiments hyaluronic acid is present in an amount in a range of about 1 mcg/mL of composition to about 500 mcg/mL of composition, about 10 mcg/mL of composition to about 500 mcg/mL of composition, about 10 mcg/mL of composition to about 450 mcg/mL of composition, about 10 mcg/mL of composition to about 400 mcg/mL of composition, about 10 mcg/mL of composition to about 350 mcg/mL of composition, about 10 mcg/mL of composition to about 300 mcg/mL of composition, about 25 mcg/mL of composition to about 500 mcg/mL of composition, about 25 mcg/mL of composition to about 450 mcg/mL of composition, about 25

mcg/mL of composition to about 400 mcg/mL of composition, about 25 mcg/mL of composition to about 350 mcg/mL of composition, about 25 mcg/mL of composition to about 300 mcg/mL of composition, about 50 mcg/mL of composition to about 500 mcg/mL of composition, about 50 mcg/mL of composition to about 450 mcg/mL of composition, about 50 mcg/mL of composition to about 400 mcg/mL of composition, about 50 mcg/mL of composition to about 350 mcg/mL of composition, about 50 mcg/mL of composition to about 300 mcg/mL of composition, about 75 mcg/mL of composition to about 500 mcg/mL of composition, about 75 mcg/mL of composition to about 450 mcg/mL of composition, about 75 mcg/mL of composition to about 400 mcg/mL of composition, about 75 mcg/mL of composition to about 350 mcg/mL of composition, about 75 mcg/mL of composition to about 300 mcg/mL of composition, about 100 mcg/mL of composition to about 500 mcg/mL of composition, about 100 mcg/mL of composition to about 450 mcg/mL of composition, about 100 mcg/mL of composition to about 400 mcg/mL of composition, about 100 mcg/mL of composition to about 350 mcg/mL of composition, about 100 mcg/mL of composition to about 300 mcg/mL of composition, about 150 mcg/mL of composition to about 500 mcg/mL of composition, about 150 mcg/mL of composition to about 450 mcg/mL of composition, about 150 mcg/mL of composition to about 400 mcg/mL of composition, about 150 mcg/mL of composition to about 350 mcg/mL of composition, about 150 mcg/mL of composition to about 300 mcg/mL of composition, about 200 mcg/mL of composition to about 500 mcg/mL of composition, about 200 mcg/mL of composition to about 450 mcg/mL of composition, about 200 mcg/mL of composition to about 400 mcg/mL of composition, about 200 mcg/mL of composition to about 350 mcg/mL of composition, about 200 mcg/mL of composition to about 300 mcg/mL of composition, or about 200 mcg/mL of composition to about 250 mcg/mL of composition.

[0039] In some embodiments hyaluronic acid is present in an amount in a range of about 1 mcg/mL of composition to about 750 mcg/mL of composition, about 10 mcg/mL of composition to about 750 mcg/mL of composition, about 10 mcg/mL of composition to about 700 mcg/mL of composition, about 10 mcg/mL of composition to about 650 mcg/mL of composition, about 10 mcg/mL of composition to about 600 mcg/mL of composition, about 10 mcg/mL of composition to about 550 mcg/mL of composition, about 25 mcg/mL of composition to about 750 mcg/mL of composition, about 25 mcg/mL of composition to about 700 mcg/mL of composition, about 25 mcg/mL of composition to about 650 mcg/mL of composition, about 25 mcg/mL of composition to about 600 mcg/mL of composition, about 25 mcg/mL of composition to about 550 mcg/mL of

[illegible]

mcg/mL of composition to about 700 mcg/mL of composition, about 600 mcg/mL of composition to about 650 mcg/mL of composition, or about 700 mcg/mL of composition to about 750 mcg/mL of composition.

[0040] In some embodiments, the hyaluronic acid is present in an amount of about 100 mcg/ml, about 200 mcg/ml, about 300 mcg/ml, about 400 mcg/ml, about 500 mcg/ml, about 600 mcg/ml, about 700 mcg/ml, about 800 mcg/ml, about 900 mcg/ml, about 1000 mcg/ml, or more.

[0041] In some embodiments, hyaluronic acid is present in an amount in a range of about 1 mcg/mL of composition to about 950 mcg/mL of composition, about 10 mcg/mL of composition to about 950 mcg/mL of composition, about 10 mcg/mL of composition to about 900 mcg/mL of composition, 10 mcg/mL of composition to about 850 mcg/mL of composition, 10 mcg/mL of composition to about 800 mcg/mL of composition, about 25 mcg/mL of composition to about 950 mcg/mL of composition, about 25 mcg/mL of composition to about 900 mcg/mL of composition, about 25 mcg/mL of composition to about 850 mcg/mL of composition, about 25 mcg/mL of composition to about 800 mcg/mL of composition, about 50 mcg/mL of composition to about 950 mcg/mL of composition, about 50 mcg/mL of composition to about 900 mcg/mL of composition, about 50 mcg/mL of composition to about 850 mcg/mL of composition, about 50 mcg/mL of composition to about 800 mcg/mL of composition, about 75 mcg/mL of composition to about 950 mcg/mL of composition, about 75 mcg/mL of composition to about 900 mcg/mL of composition, about 75 mcg/mL of composition to about 850 mcg/mL of composition, about 75 mcg/mL of composition to about 800 mcg/mL of composition, about 100 mcg/mL of composition to about 950 mcg/mL of composition, about 100 mcg/mL of composition to about 900 mcg/mL of composition, about 100 mcg/mL of composition to about 850 mcg/mL of composition, about 100 mcg/mL of composition to about 800 mcg/mL of composition, about 150 mcg/mL of composition to about 950 mcg/mL of composition, about 150 mcg/mL of composition to about 900 mcg/mL of composition, about 150 mcg/mL of composition to about 850 mcg/mL of composition, about 150 mcg/mL of composition to about 800 mcg/mL of composition, about 200 mcg/mL of composition to about 950 mcg/mL of composition, about 200 mcg/mL of composition to about 900 mcg/mL of composition, about 200 mcg/mL of composition to about 850 mcg/mL of composition, about 200 mcg/mL of composition to about 800 mcg/mL of composition, about 300 mcg/mL of composition to about 950 mcg/mL of composition, about 300 mcg/mL of composition to about 900 mcg/mL of composition, about 300 mcg/mL of composition to about 850 mcg/mL of composition, about 300 mcg/mL of

composition to about 800 mcg/mL of composition, about 400 mcg/mL of composition to about 950 mcg/mL of composition, about 400 mcg/mL of composition to about 900 mcg/mL of composition, about 400 mcg/mL of composition to about 950 mcg/mL of composition, about 400 mcg/mL of composition to about 900 mcg/mL of composition, about 400 mcg/mL of composition to about 850 mcg/mL of composition, about 400 mcg/mL of composition to about 800 mcg/mL of composition, about 500 mcg/mL of composition to about 950 mcg/mL of composition, about 500 mcg/mL of composition to about 900 mcg/mL of composition, about 500 mcg/mL of composition to about 850 mcg/mL of composition, about 500 mcg/mL of composition to about 800 mcg/mL of composition, about 600 mcg/mL of composition to about 950 mcg/mL of composition, about 600 mcg/mL of composition to about 900 mcg/mL of composition, about 600 mcg/mL of composition to about 850 mcg/mL of composition, about 600 mcg/mL of composition to about 800 mcg/mL of composition, about 700 mcg/mL of composition to about 950 mcg/mL of composition, about 700 mcg/mL of composition to about 900 mcg/mL of composition, about 700 mcg/mL of composition to about 850 mcg/mL of composition, about 700 mcg/mL of composition to about 800 mcg/mL of composition, about 800 mcg/mL of composition to about 950 mcg/mL of composition, about 800 mcg/mL of composition to about 900 mcg/mL of composition, about 800 mcg/mL of composition to about 850, about 900 mcg/mL of composition to about 950 mcg/mL of composition, about 1000mcg/ml.

[0042] In some embodiments, the hyaluronic acid is present in an amount in a range of about 1 mg/mL of composition to about 10 mg/mL of composition. For example, the hyaluronic acid is present in an amount of about 1.0 mg/ml, about 1.1 mg/ml, about 1.2 mg/ml, about 1.3 mg/ml, about 1.4 mg/ml, about 1.5 mg/ml, about 1.6 mg/ml, about 1.7 mg/ml, about 1.8 mg/ml, about 1.9 mg/ml, about 2 mg/ml, about 2.1 mg/ml, about 2.2 mg/ml, about 2.3 mg/ml, about 2.4 mg/ml, about 2.5 mg/ml, about 2.6 mg/ml, about 2.7 mg/ml, about 2.8 mg/ml, about 2.9 mg/ml, about 3 mg/ml, about 3.1 mg/ml, about 3.2 mg/ml, about 3.3 mg/ml, about 3.4 mg/ml, about 3.5 mg/ml, about 3.6 mg/ml, about 3.7 mg/ml, about 3.8 mg/ml, about 3.9 mg/ml, about 4 mg/ml, about 4.1 mg/ml, about 4.2 mg/ml, about 4.3 mg/ml, about 4.4 mg/ml, about 4.5 mg/ml, about 4.6 mg/ml, about 4.7 mg/ml, about 4.8 mg/ml, about 4.9 mg/ml, about 5 mg/ml, about 5.5 mg/ml, about 6 mg/ml, about 6.5 mg/ml, about 7 mg/ml, about 7.5 mg/ml, about 8 mg/ml, about 8.5 mg/ml, about 9 mg/ml, about 9.5 mg/ml, about 10 mg/ml or more.

[0043] In some embodiments, a composition according to an embodiment of the invention comprises a commercially available hyaluronic acid composition. For example, suitable

commercially available hyaluronic acid compositions include, but are not limited to, hyaluronic acids sold under the trademarks JUVEDERM™, RESTYLANE-L™, CAPTIQUE™, BELOTERO BALANCE™, PREVELLE SILK™, ELEVESS™, HYLAFORM™, EUFLEXXA™, GEL-ONE™, HYALGAN™, ORTHOVISC™, MONOVISC™, SUPARTZ™, SYNVISIC™ and SYNVISIC-ONE™.

a. Polydispersity index (PDI) of hyaluronic acid

[0044] The term "polydispersity index (PD) as used herein characterizes in the art the width of the molecular weight distribution curve in terms of the ratio of the weight average molecular weight M_w , (which is the total weight of all polymer (hyaluronic acid) molecules in the sample divided by the total number of molecules), to the number average molecular weight M_n (which is the weight average molecular weight of each molecule multiplied by its corresponding molecular weight, i.e., the weight statistically averaged molecular weight). In general, a smaller PDI value indicates a narrower molecular weight distribution range.

[0045] In some embodiments, analysis of hyaluronic acid can be conducted by size exclusion chromatography (SEC). In some embodiments, SEC can include separating samples, monitoring the output with a concentration detector such as a refractometer or a UV absorbance detector and comparing the elution time to molar mass. In some embodiments, analysis of hyaluronic acid can include using multiangle light scattering (MALS) devices in series with concentration detectors. In some embodiments, MALS instrument, a differential refractometer, and a differential viscometer with SEC, can be used to study material characteristics of hyaluronic acid. A combination of these methods can be used to determine the absolute hyaluronic acid molecular weight, molecular weight distribution, and radius information.

2. Carrier and Other Additives

[0046] In some embodiments a composition includes a carrier medium. Such carrier medium may be a biocompatible fluid suitable for injection into a mammalian skin. In some embodiments the carrier medium comprises a saline solution. In some embodiments hyaluronic acid serves as the carrier medium as well as an active ingredient

[0047] In some embodiments a composition includes one or more additives. Such additives may include a preservative or a biocide.

[0048] In some embodiments a composition includes a micro emulsifier, a nano emulsifier, a solid lipid nanoparticle, a nanostructured lipid carrier, a liposome, or a vesicle.

[0049] In some embodiments a composition may comprise a fatty acid (e.g., oleic acid), ester of a fatty acid and alcohol (e.g., isopropyl myristate, isopropyl palmitate, ethyl oleate), medium chain triglycerides, triacetin, or a terpene (e.g., limonene, methol, cineole). In some embodiments a composition may comprise a surfactant. For example, suitable surfactants include, but are not limited to, TWEENTM (polysorbates), CREMOPHORTM (mixture of macrogol glycerol hydroxystearate, PEG-40 castor oil, polyoxyl 40 hydrogenated castor oil), TRANSCUTOLTM P (diethylene glycol monoethyl ether), PLUROL OLEIQUETM (polyglyceryl-3-oleate), PLUROL ISOSTEARIQUETM (isostearic acid ester of poly-glycerols and higher oligomers) and LABRASOLTM (mixture of mono-, di- and triglycerides of C8 and C10 fatty acids, and mono- and di-esters of PEG), and lecithin. In some embodiments a composition may comprise a cosurfactant. For example, suitable cosurfactants include, but are not limited to short and medium chain alcohols and polyglyceryl derivatives, including ethanol, isopropanol, isopropyl myristate and propylene glycol.

[0050] In some embodiments a composition comprises one or more of soybean oil, jojoba oil, aloe vera oil, soybean phosphatidylcholine, water, polysorbate 80, ethanol, benzyl alcohol, isopropyl alcohol, glycerine, glyceryl monostearate, propylene glycol.

II. Methods

[0051] The present disclosure provides methods of treatment, and administration as well as methods of preparing the compositions. In some embodiments, the methods described in U.S. Patent 11,337,993 can be utilized in the present disclosure (the contents of which are herein incorporated by reference in its entirety).

1. Methods of Treatment

[0052] The present disclosure provides a method of treatment using the compositions described herein. As used herein, the terms "treat," "treatment," or "treating" refer to therapeutic treatments, wherein the object is to reverse, alleviate, ameliorate, inhibit, slow down or stop the progression or severity of a disease or condition, e.g., androgenetic alopecia or other form of alopecia. The term "treating" includes reducing or alleviating at least one adverse effect or symptom of a disease or condition, e.g., androgenetic alopecia or other form of alopecia. Treatment can be considered effective if one or more symptoms are reduced, e.g., rate of hair loss is reduced. Alternatively, treatment can be considered effective if the progression of a disease is reduced or halted. That is, the term "treatment" includes not just the improvement of symptoms, but also a

cessation of, or at least slowing of, progress or worsening of symptoms compared to what would be expected in the absence of treatment. Beneficial or desired clinical results include, but are not limited to, alleviation of one or more symptom(s), diminishment of extent of disease, stabilized (i.e., not worsening) state of disease, delay or slowing of disease progression, amelioration, or palliation of the disease state, and/or remission (whether partial or total). For example, treatment is considered effective if the extent or amount of hair loss is reduced, the progression of hair loss is slowed or halted, or hair re-growth is induced.

[0053] In some embodiments, the compositions of the disclosure can be used to treat androgenetic alopecia (AGA). In some embodiments, the compositions of the disclosure can improve one or more metrics associated with AGA. In some embodiments, the compositions of the disclosure can be used to treat hair loss in a patient with AGA. In some embodiments, the compositions stimulate hair growth in a patient with AGA.

[0054] Androgenetic alopecia (AGA) is a genetically predetermined disorder due to an excessive response to androgens is characterized by progressive loss of terminal hair of the scalp any time after puberty and affects up to 50 percent of males and females. Elevated levels of androgens, including dihydrotestosterone (DHT) present cause increased activation of androgen receptors on the hair follicles, which cause a shortening of the anagen (growth) phase in the normal hair growth cycle. Excessive activation leads to follicular miniaturization through progressively shorter anagen phase, resulting in thinner, and shorter hair follicles. In males, hair loss is prominent in the vertex and frontotemporal regions; in women, hair loss typically occurs in the vertex region.

[0055] A method of stimulating hair growth in a patient in need thereof includes administering a composition according to an embodiment of the present invention to the surface of or into the patient's skin. Also provided herein is a method of administering a composition for hair growth.

[0056] In some embodiments, the compositions of the disclosure may be administered to the skin of the patient. In some embodiments the composition is administered topically by applying the composition to the surface of the patient's skin. In some embodiments the composition is administered into the dermis or hypodermis of the patient's skin, for example, by injection as described herein. In one embodiment, the compositions may be administered to the skin of the patient by an intradermal injection.

[0057] The assessment of hair growth in a patient can be based on patient self-assessment, physician assessment using a standardized scale, global photography assessment, target area hair

count (TAHC), target area hair width (TAHW; also referred to herein as hair diameter measurement), average hair length measurement, average hair diameter measurement, and/or hair weight measurements. In one embodiment, the composition can improve or increase target area hair count (TAHC), TAHW, average hair length, average hair diameter, hair darkness, and/or hair weight. As used herein, target area hair count refers to the number of hairs per cm² on a patient's head. In some embodiments, higher values of TAHC can represent better outcomes. In some embodiments, Target Area Hair Width (TAHW) can refer to the cumulative width of hair in the area of the head of the patient that is being treated with the compositions of the disclosure (the target area). Higher values of TAHW can represent better outcomes.

[0058] In some aspects, the composition can improve or increase target area hair count (TAHC), TAHW, average hair length, average hair diameter, hair darkness, and/or hair weight by about 5 %, 10 %, 15 %, 20 %, 25 %, 30 %, 35 %, 40 %, 45 %, 50 %, 55 %, 60 %, 65 %, 70 %, 75 %, 80 %, 85 %, 90 %, 95 %, 100%, about 1-10%, 15-25%, 20-30%, 25-35%, 30-40%, 35-45%, 40-50%, 45-55%, 50-60%, 55-65%, 60-70%, 65-75%, 70-80%, 75-85%, 80-90%, 85-95% or more. In some aspects, the composition can improve or increase target area hair count (TAHC), TAHW, average hair length, average hair diameter, hair darkness, and/or hair weight by about 2-fold, 3-fold, 4-fold, 5-fold, 6-fold, 7-fold, 8-fold, 9-fold, 10 -fold, 15 -fold, 20-fold or more.

[0059] Improvement or increase in target area hair count (TAHC), TAHW, average hair length, average hair diameter, hair darkness, and/or hair weight can be measured any time after treatment with the compositions of the disclosure. For example, after administering the compositions, the improvement can be measured from about 10 days to about 160 days after administering the compound. In some embodiments, the improvement can be measured after about 10 days, about 20 days, about 30 days, about 40 days, about 50 days, about 60 days, about 70 days, about 80 days, about 90 days, about 100 days, about 110 days, about 120 days, about 130 days, about 140 days, about 150 days, about 160 days, about 170 days, about 180 days, or more.

[0060] In some embodiments, prior to treatment with the compositions of the disclosure, the patient has experienced hair loss for about 1 month, 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 1 year, about 2 years, about 3 years, about years, about 5 years, about 6 years, about 7 years, about 8 years, about 9 years, about 10 years, about or more. In some

embodiments, the patient has experienced hair loss for about three to about five years prior to administering the composition of the disclosure.

[0061] In some embodiments, the patient has received a prior hair transplantation procedure. In some embodiments, the patient has received a hair transplantation about 1 month to about 2 months, about 2 months to about 3 months, about 3 months to about 4 months, about 4 months to about 5 months, about 5 months to about 6 months, about 6 months to about 7 months, about 7 months to about 8 months, about 8 months to about 9 months, about 9 months to about 10 months, about 10 months to about 11 months, about 11 months to about 12 months or more.

[0062] In some embodiments, the patient is a male patient or a female patient.

[0063] In some embodiments, the patient has mild AGA or moderate AGA.

[0064] In some embodiments, the patient has received a Modified Norwood Hamilton Scale score of I, II, IIa, III, III vertex, IIIa, IV, V, Iva, VI, VII, or Va. Characteristics associated with each Modified Norwood Hamilton Scale score are presented in the figure. In some aspects, the patient has received a Modified Norwood Hamilton Scale score of III, or a Modified Norwood Hamilton Scale score of IV.

[0065] In some embodiments, a method of stimulating hair growth in a patient in need thereof includes administering a composition according to an embodiment of the present invention to the surface of or into the patient's skin. In some embodiments the composition is administered topically by applying the composition to the surface of the patient's skin. In some embodiments the composition is administered into the dermis or hypodermis of the patient's skin, for example, by injection as described herein.

[0066] In some embodiments, a composition according to an embodiment of the invention is administered to a patient's skin once a day for one day, once a day for one week, once a day for one month, once a day for one year, twice a day for one day, twice a day for one week, twice a day for one month, twice a day for one year, once a week for one week, once a week for one month, once a week for one year, twice a week for one week, twice a week for one month, twice a week for one year, once a month for one month, once a month for two months, once a month for six months, once a month for one year, twice a month for one month, twice a month for two months, twice a month for six months, twice a month for one year, once every two months for two months, once every two months for four months, once every two months for six months, once every two months for one year, once every three months for three months, once every three months for six

months, once every three months for nine months, once every three months for one year, once every four months for four months, once every four months for eight months, once every four months for one year, once every six months for six months, once every six months for one year, or as needed.

[0067] In some embodiments, the composition is administered for about at least once per week, at least about two times per week, at least about three times per week, at least about four times per week, at least about five times per week, at least about six times per week, at least about seven times per week or more. In some embodiments, the composition is administered on consecutive days of the week. In some embodiments, the compositions are administered on about two consecutive days, on about three consecutive days, on about 4 consecutive days, on about 5 consecutive days, on about 6 consecutive days, on about 7 days or more. In some embodiments, the composition is administered on alternate days of the week. As a non-limiting example, the compositions can be administered three times a week on three consecutive days.

[0068] As a non-limiting example, the methods of the disclosure include administration of up to 1 % hyaluronic acid, 3 times a week. As a non-limiting example, the methods of the disclosure can include administration of up to 1% hyaluronic acid to the skin of the subject for at least 2 times a week. As a non-limiting example, the methods of the disclosure can include administration of up to 1% hyaluronic acid to the skin of the subject for at least 3 times a week. As a non-limiting example, the methods of the disclosure can include administration of up to 1% hyaluronic acid to the skin of the subject for at least 4 times a week. As a non-limiting example, the methods of the disclosure can include administration of up to 1% hyaluronic acid to the skin of the subject for at least 5 times a week. As a non-limiting example, the methods of the disclosure can include administration of up to 1% hyaluronic acid to the skin of the subject for at least 6 times a week. As a non-limiting example, the methods of the disclosure can include administration of up to 1% hyaluronic acid to the skin of the subject for at least 7 times a week.

[0069] As a non-limiting example, the methods of the disclosure include administration of up to 1 % hyaluronic acid, 3 times a week on 3 consecutive days. As a non-limiting example, the methods of the disclosure can include administration of up to 1% hyaluronic acid to the skin of the subject for at least 2 times a week on two consecutive days. As a non-limiting example, the methods of the disclosure can include administration of up to 1% hyaluronic acid to the skin of the subject for at least 4 times a week on 4 consecutive days. As a non-limiting example, the methods

of the disclosure can include administration of up to 1% hyaluronic acid to the skin of the subject for at least 5 times a week on 5 consecutive days. As a non-limiting example, the methods of the disclosure can include administration of up to 1% hyaluronic acid to the skin of the subject for at least 6 times a week on 6 consecutive days. As a non-limiting example, the methods of the disclosure can include administration of up to 1% hyaluronic acid to the skin of the subject for at least 7 times a week on 7 consecutive days.

[0070] As a non-limiting example, the methods of the disclosure can utilize 0.3 % hyaluronic acid for intradermal injection, 3 times a week. As a non-limiting example, the methods of the disclosure can utilize 0.4 % hyaluronic acid for intradermal injection, 3 times a week. As a non-limiting example, the methods of the disclosure can utilize 0.2 % hyaluronic acid for intradermal injection, 3 times a week. As a non-limiting example, the methods of the disclosure can utilize 0.3 % hyaluronic acid for intradermal injection, 3 times a week on three consecutive days. As a non-limiting example, the methods of the disclosure can utilize 0.4 % hyaluronic acid for intradermal injection, 3 times a week on three consecutive days. As a non-limiting example, the methods of the disclosure can utilize 0.2 % hyaluronic acid for intradermal injection, 3 times a week on three consecutive days.

2. Administration

[0071] A method of administering a composition according to an embodiment of the invention comprises delivery of a composition according to an embodiment of the invention to a hair follicle. In some embodiments the delivery is by topical administration, that is, application of the composition to the surface of the skin and allowing the composition to permeate the skin. In some embodiments a method of administration includes a step to enhance permeation prior to topical administration of a composition. In some embodiments the delivery is by injection into the skin.

[0072] A method for administering a composition according to an embodiment of the invention comprises injecting a therapeutic amount of composition in the skin of a patient in need of treatment. In some embodiments a composition according to an embodiment of the invention is administered as a bolus, which, as used herein refers to the dosage being delivered in a time of less than ten minutes. In some embodiments a composition according to an embodiment of the invention is administered as an infusion, which, as used herein refers to the dosage being delivered in a time of about ten minutes or greater.

[0073] Such injection may be made via a single needle, microneedle, or similar device, or an array of needles, microneedles, or similar devices. In some embodiments a composition according to an embodiment of the invention is delivered via a conventional syringe. In some embodiments, subdermal delivery is performed via a hollow microneedle injector. In some embodiments, subdermal delivery is performed a microneedle patch that has been coated with a composition according to an embodiment of the invention, for example that has been coated with a composition according to an embodiment of the invention by 3D printing. In some embodiments the composition is delivered via jet injector. The term "needle" as used herein refers to any such device for piercing the skin and injecting a composition according to an embodiment of the invention.

[0074] Preferably the composition is administered near the hair follicle of the patient. Accordingly, in some embodiments the composition is administered by injecting a therapeutic amount of composition in the dermis (intradermal injection) of the patient.

[0075] In some embodiments the composition is administered by injecting a therapeutic amount of composition in the hypodermis of the patient. In some embodiments the composition is administered about 0.4 mm to about 2 mm into the patient's skin (i.e., about 0.4 mm to about 3 mm from the surface of the skin). In some embodiments the composition is administered about 0.1mm, 0.2 mm, 0.3mm, 0.4 mm, about 0.5 mm, about 0.6 mm, about 0.7 mm, about 0.8 mm, about 0.9 mm, about 1 mm, about 1.1 mm, about 1.2 mm, about 1.3 mm, about 1.4 mm, about 1.5 mm, about 1.6 mm, about 1.7 mm, about 1.8 mm, about 1.9 mm, about 2 mm, about 2.1 mm, about 2.2 mm, about 2.3 mm, about 2.4 mm, about 2.5 mm, about 2.6 mm, about 2.7 mm, about 2.8 mm, about 2.9 mm, or about 3 mm into the patient's skin. In some embodiments the composition is administered between, about 0.1 mm to about 0.5 mm, about 0.1mm to about 1mm, about 0.5 mm to about 1 mm, between about 1 mm to about 1.5 mm, between about 1.5 mm to about 2 mm, between about 2 mm to about 2.5 mm, between about 2.5 mm to about 3 mm, between about 1 mm to about 3 mm, between about 1.5 mm to about 3 mm, between about 0.4 mm to about 0.6 mm, between about 0.4 mm to about 0.8 mm, between about 0.4 mm to about 1 mm, between about 0.4 mm to about 1.2 mm, between about 0.4 mm to about 1.4 mm, between about 0.4 mm to about 1.6 mm, between about 0.4 mm to about 1.8 mm, between about 0.4 mm to about 2 mm, between about 0.4 mm to about 2.2 mm, between about 0.4 mm to about 2.4 mm, between about 0.4 mm to about 2.6 mm, between about 0.4 mm to about 2.8 mm, between about 0.4 mm to about 3 mm, between about 0.6 mm to about 0.8 mm, between about 0.6 mm to about 1 mm, about 0.6 mm to about 1.2 mm, between about 0.6 mm to

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mm, or between about 2.8 mm to about 3 mm into the patient's skin. In some embodiments, the compositions of the disclosure are injected above the skull.

[0076] In one aspect, the depth of the injection can vary by the thickness of the scalp in different regions of the scalp. Different regions of the scalp can have different thickness. For example, the average dermal thickness of the posterior scalp can be about 1443.86 μm , the thickness of the temporal scalp can be about 1349.52 μm , and/or the thickness of the anterior scalp can be about 1146.13 μm . In some embodiments, the depth of the injection can be from about 0.7mm to about 2 mm.

[0077] In one embodiment, the compositions are administered at, adjacent to or proximal to a stem cell area of the hair follicles.

[0078] In some embodiments, the injection area can be about 1 cm^2 , about 2 cm^2 , about 3 cm^2 , about 4 cm^2 , about 5 cm^2 , about 6 cm^2 , about 7 cm^2 , about 8 cm^2 , about 9 cm^2 , about 10 cm^2 , about 15 cm^2 , about 20 cm^2 , about 25 cm^2 , about 30 cm^2 , about 35 cm^2 , about 40 cm^2 , about 45 cm^2 , about 50 cm^2 , about 55 cm^2 , about 60 cm^2 , about cm^2 , about 70 cm^2 , about 75 cm^2 , about 80 cm^2 , about 85 cm^2 , about 90 cm^2 , about 95 cm^2 , about 100 cm^2 , 200 cm^2 , 300 cm^2 , 400 cm^2 , 500 cm^2 , 600 cm^2 , 700 cm^2 or more. In one embodiment, the injection area can up the entire area of the scalp of the subject.

[0079] The compositions can be injected in a line about 0.2-0.3 cm apart. In some embodiments, the compositions can be injected in lines that are about 1 cm apart.

[0080] In some embodiments a composition according to an embodiment of the invention can be administered in a plurality of injections. In some embodiments a composition according to an embodiment of the invention is administered in via about 1 injection/ cm^2 skin to about 1000 injections/ cm^2 skin, about 200 injections/ cm^2 skin to about 800 injections/ cm^2 skin, or about 400 injections/ cm^2 skin to about 650 injections/ cm^2 skin. In some embodiments a composition is administered via about 200 injections/ cm^2 skin, about 250 injections/ cm^2 skin, about 300 injections/ cm^2 skin, about 350 injections/ cm^2 skin, about 400 injections/ cm^2 skin, about 450 injections/ cm^2 skin, about 500 injections/ cm^2 skin, about 550 injections/ cm^2 skin, about 600 injections/ cm^2 skin, or about 650 injections/ cm^2 skin. The contents of US Patent No. 11, 337,993 are hereby incorporated by reference.

[0081] The compositions of the disclosure can be administered to one or more areas of the scalp. For example, the compositions can be administered to the frontal region (or central

forelock), the mid scalp (or posterior mid scalp), temporal scalp (sides), vertex transition zone (or vertex transition point), and the crown (or vertex). In some embodiments, the frontal and the temporal region of the scalp can be collectively referred to as the frontotemporal region. In one embodiment, the compositions are administered to the frontotemporal regions of the scalp.

[0082] In some embodiments, topical delivery is performed following, or in conjunction with, application of iontophoresis. For example, iontophoreses may comprise application of a mild electric current (e.g., 0.1 to 1.0 mA/ cm²) to increase skin permeation of the composition. Without being bound by theory, it is believed iontophoresis may improve permeation of the skin by electromigration, electroosmosis, and/or enhanced passive diffusion.

[0083] In some embodiments, topical delivery is performed following, or in conjunction with, application of electroporation. For example, electroporation may comprise application of high intensity, high voltage (e.g., 50-1500 V) electric pulses of short duration (10 microseconds to 10 milliseconds) to form aqueous pores in the lipid bilayers of the stratum corneum of the skin.

[0084] In some embodiments, topical delivery is performed following, or in conjunction with, application of sonophoresis. For example, sonophoresis may comprise application of acoustic waves at high frequency (e.g., about 500 kHz to 1250 kHz) or low frequency (e.g., about 20 to about 100 kHz) or (beginning with one of high or low frequency and progressing to the other of high or low frequency).

[0085] In some embodiments, topical delivery is performed following, or in conjunction with, application of laser ablation. Laser ablation may comprise generation of a photomechanical wave by laser ablation of a target material (e.g., polymer) placed on the surface of the skin.

[0086] In some embodiments, topical delivery is performed following, or in conjunction with, magnetophoresis. Magnetophoresis may comprise application of a magnetic field, for example pulsed electromagnetic fields, to the skin.

[0087] In some embodiments, topical delivery is performed following application of radiofrequency thermal ablation. Thermal ablation may comprise application of extreme heat (e.g., about 300.degree. C. for microseconds) at the skin surface. Without being bound by theory, it is believed that thermal ablation may vaporize portions of the stratum corneum to create micron-scale channels. Thermal ablation may be accomplished with commercially available devices including VIADORTM (Syneron Medical Ltd, Israel) and PASSPORTTM (Nitto-Denko, Japan). In some embodiments thermal ablation may be accomplished with an erbium:yttrium-gallium-garnet

(Er:YAG) emitting at 2,790 nm or yttrium scandium gallium garnet (YSGG) laser emitting at 2,940 nm. In some embodiments fractional laser ablation may be applied to sub-mm regions to generate spots mimicking a microneedle array-type pattern (e.g., 40-300 μm with densities between 50-600 cm^{-2}). In some embodiments, topical delivery is performed following application of microneedle device.

3. Methods of Production

[0088] A process for the production of a composition according to an embodiment of the invention comprises preparing an effective amount of the hyaluronic acid. In some embodiments an effective amount of hyaluronic acid can further be mixed with an effective amount of osteopontin. In some embodiments, the hyaluronic acid has average molecular weight in a range of about 4,000 Da to 10,000 Da, in a range of about 10,000 Da to about 100,000 Da, in a range of about 15 kDa to about 50 kDa, in a range of about 75 kDa to about 350 kDa, or in a range of about 20 kDa to 1350 kDa. In some embodiments, hyaluronic acid has an average molecular weight greater than about 950 kDa. In some embodiments an effective amount of hyaluronic acid is mixed with an effective amount of CD44-binding ligand. Said processes may also include a step of preparing a physiologically acceptable carrier medium, to which the active agents are added. In some embodiments, the physiologically acceptable carrier medium is injectable.

[0089] In some embodiments a method of production includes a step of forming a microemulsion or a nano emulsion. A microemulsion or nano emulsion may comprise oil, water, surfactant and cosurfactant to form a colloidal dispersion of droplet sizes in a range of about 10 nm to about 100 nm. In some embodiments a microemulsion or nano emulsion may comprise a fatty acid (e.g., oleic acid), ester of a fatty acid and alcohol (e.g., isopropyl myristate, isopropyl palmitate, ethyl oleate), medium chain triglycerides, triacetin, or a terpene (e.g., limonene, menthol, cineole). In some embodiments a microemulsion or nano emulsion may comprise a surfactant. For example, suitable surfactants include, but are not limited to, TWEENTM (polysorbates), CREMOPHORTM (mixture of macrogol glycerol hydroxystearate, PEG-40 castor oil, polyoxyl 40 hydrogenated castor oil), TRANSCUTOLTM P (diethylene glycol monoethyl ether), PLUROL OLEIQUETM (polyglyceryl-3-oleate), PLUROL ISOSTEARIQUETM (isostearic acid ester of polyglycerols and higher oligomers) and LABRASOLTM (mixture of mono-, di-and triglycerides of C8 and C10 fatty acids, and mono- and di-esters of PEG), and lecithin. In some embodiments a microemulsion or nano emulsion may comprise a cosurfactant. For example, suitable cosurfactants include, but are not

limited to short and medium chain alcohols and polyglyceryl derivatives, including ethanol, isopropanol, isopropyl myristate and propylene glycol. In some embodiments formation of a microemulsion or nano emulsion includes use of a high-pressure homogenizer, microfluidizer and/or ultrasonicator.

[0090] In some embodiments a method of production includes a step of mixing a composition according to an embodiment of the invention with a solid nanoparticle. A solid nanoparticle may comprise an inorganic material such as a metal oxide (e.g., zinc oxide, titanium dioxide) or polymers that are solid at room temperature.

[0091] In some embodiments a method of production includes a step of mixing a composition according to an embodiment of the invention with a solid lipid nanoparticle. A solid lipid nanoparticle may comprise a lipid that is solid at room temperature with a surface covering of surfactant to stabilize them as droplets having a size of less than about 100 nm when dispersed in water.

[0092] In some embodiments a method of production includes a step of mixing a composition according to an embodiment of the invention with a nanostructured lipid carrier. A nanostructured lipid carrier may comprise a fluid lipid phase embedded into a solid lipid matrix or localized at the surface of solid platelets and the surfactant layer.

[0093] In some embodiments a method of production includes a step of mixing a composition according to an embodiment of the invention with a liposome. A liposome may comprise spherical vesicles composed of amphiphilic phospholipids and cholesterol, self-associated into multilamellar, large unilamellar and small unilamellar vesicles.

[0094] In some embodiments a method of production includes a step of mixing a composition according to an embodiment of the invention with a flexible vesicle. A flexible vesicle may comprise a material that will associate into bilayer structures as well as components that confer flexibility. In some embodiments a flexible vesicle comprises an ethosome (i.e., a phospholipid with a high proportion of ethanol), a niosome (i.e., non-ionic surfactant), an invasome (i.e., phospholipids, ethanol, and a mixture of terpene penetration enhancer), an SECosomes (i.e., surfactant, ethanol, and cholesterol), or a PEV (i.e., penetration enhancer vesicle). In some embodiments a PEV may comprise oleic acid, limonene, or propylene glycol.

[0095] In some embodiments a method of production includes a step of mixing a composition according to an embodiment of the invention with a polymeric micelle or polymeric dendrimer. A

polymeric micelle may be a colloidal carrier with a hydrophilic exterior shell and a hydrophobic interior core. A polymeric micelle may be nanosized. A polymeric dendrimer may comprise a branched polymer structure.

EXAMPLES

[0096] Example 1. Assessment of hyaluronic acid (AMP-303) compared to saline control in male subjects with androgenetic alopecia

Study Design Justification

[0097] Quantitative hair growth measures have become a standard in substantiating the efficacy of AGA hair growth products. To date dosage forms typically used to treat AGA are administered topically or orally. Intradermal injections may change skin surface topology/contours, hair orientation or other features that could interfere with hair imaging or accurate serial imaging over time. To measure the impact of this route of administration on the utility of standard hair counts and related measures was evaluated. The trial is focused on evaluating what differences between pre and post injection may arise due to AMP-303 compared to saline control over the study period. Local safety effects of intradermal injection of AMP-303 compared to saline control will be collected. In addition, the study will include three (3) different groups of patients with androgenetic alopecia to refine the study population for future studies in androgenetic alopecia.

Study product and formulation

[0098] The study compound is hyaluronic acid (also herein AMP-303) for intradermal injection at a concentration of 0.3% $\pm$ 0.1%.

[0099] AMP-303 for intradermal injection consists of a non-crosslinked hyaluronic acid and phosphate buffered saline.

[0100] The control, injectable sterile saline will be phosphate buffered saline.

[0101] Both AMP-303 vehicle and saline control will be supplied as injectable solutions. Identical 1 mL syringes will be used for AMP-303 and the control, with 0.1mL 0.5mL demarcations. AMP-303 and saline control will be provided as sterile products.

Study Objectives

[0102] The objective of the study was to evaluate the safety and tolerability of AMP-303 injected into the dermis of the scalp compared to saline control in male subjects with androgenetic

alopecia. The study will also evaluate the impact (if any) of AMP-303 compared to saline control on hair count assessment methodology in male subjects with androgenetic alopecia will be evaluated. Additionally, the study will be used to refine the intended use population.

Study Design

[0103] The study is a prospective, multicenter, randomized, saline control, non-significant risk (NSR), early feasibility study.

[0104] The dose regimen will include up to 2mL AMP-303 and saline control, to be injected intradermally; injection will occur on 3 consecutive days.

[0105] The study is randomized on day 0 at each investigational site. Subjects are randomly assigned to receive AMP-303 on either the right or left side, and saline control on the contralateral side. All subjects will receive intradermal injection of AMP-303 vehicle and saline control on days 0, 1 and 2 to the frontotemporal regions of the scalp. Subjects will receive AMP-303 on one side and saline control on the other side in the frontotemporal regions. The injection area will be approximately up to 4 cm² and the injection volume will be up to 2 mL for each injection area. Injection will be limited to the frontotemporal regions of the scalp. Each subject is expected to be in the study up to approximately 6 months (screening through exit).

[0106] The visit schedule is as follows:

Visit 1: Screening (Days -30 to -1)

Visit 2: Day 0 (Injection / Baseline)

Visit 3: Day 1 (Injection)

Visit 4: Day 2 (Injection)

Visit 5: Day 14 (± 3 days)

Visit 6: Day 30 (± 7 days)

Visit 7: Day 60 (± 7 days)

Visit 8: Day 90 (± 7 days)

Visit 9: Day 120 (± 7 days)

Visit 10: Day 150 (± 7 days)

[0107] Approximately 36 subjects (12 subjects per group) are enrolled into this study at up to 3 investigational sites.

[0108] Three (3) different groups will be enrolled into the study, with approximately 12 male subjects in each group: 1) recent onset of hair loss (defined as a history of hair loss of ~3 to 5

years); 2) established hair loss (defined as a history of hair loss > 10 years); and 3) post-transplant. Group 3 will enroll subjects who have completed a hair transplant procedure that includes the bilateral frontotemporal regions. Qualified subjects must (1) be 1 to 2 months post-transplantation, (2) have had an unremarkable post-transplant healing course, and (3) have no active adverse events or medical concerns in the designated post-transplant injection areas.

[0109] On day 0, eligible subjects will be randomized to receive AMP-303 on either the right or left frontotemporal region, and saline control on the contralateral side (“the Injection Sites”). AMP-303 and saline control will be administered by a physician investigator via intradermal injection per randomization at days 0, 1, and 2 visits. Physicians, study staff and subjects will be blinded to study product injected on each side. Subjects who are discontinued from the study will not be replaced.

Potential benefits and risks

[0110] Benefits of intradermal injection of AMP-303 Vehicle and this study include collection of safety and tolerability of a vehicle for future investigational product(s), determine the effect, if any, on hair count assessments due to the possible surface topology effects related to the intradermal injection of AMP-303 Vehicle and saline control, refine the intended population for future studies. Potential risks associated with needle injection into the skin, which include injection site pain, erythema, bruising, and edema. These events are expected as a result of intradermal injection of AMP-303 or saline control; however, if any particular reaction or effect is greater in severity or degree of incidence than anticipated, the occurrence can be considered an adverse event (AE).

Minimization of Anticipated Risks

[0111] Risks are minimized under this protocol by: 1) Limited injection area on the scalp, consisting of no more than a total area of 4 cm²; 2) low molecular weight, non-crosslinked hyaluronic acid; 3) limited to intradermal injection, at a depth of approximately 0.6mm to 0.8mm; careful consideration of the anatomical structures of the scalp; 4) AMP-303 and saline control will be provided as a sterile product in syringes to be used for injection; 5) the injectors will be physicians with experience with intradermal injections; 6) standard precautions with injectable materials will be followed ; and/or 7) only male subjects will be enrolled.

Inclusion Criteria

[0112] The following are criteria for entry into the study:

- [0113] 1. Male adults, 18 to 45 years at the time of consent.
- [0114] 2. Clinical diagnosis of mild to moderate androgenetic alopecia (AGA) in the temple and vertex region with a score of III, or IV on the Modified Norwood Hamilton Scale in subjects with approximately 3 to 5 years since onset of hair loss, or at least 10 years since onset of hair loss, or recent hair transplant in the bilateral frontotemporal area.
- [0115] 3. Willing to maintain the same hairstyle, hair length and hair color throughout the study.
- [0116] 4. Agrees to continue general hair care products and regimen for at least 2 weeks prior to Day 0 and throughout the study.
- [0117] 5. Willing to have hair clipped in the injection areas at screening and at each follow-up visit.
- [0118] 6. Willing to have photographs taken that could identify the subject.
- [0119] 7. Written informed consent prior to any study related procedures.
- [0120] 8. Written Authorization for Use and Release of Health and Study Research Information.
- [0121] 9. Ability to follow study instructions and complete study assessment tools without assistance, and likely to complete all required visits

Exclusion Criteria

- [0122] The following are criteria for exclusion from participating in the study:
- [0123] 1. Any uncontrolled systemic disease.
- [0124] 2. History of a positive result for human immunodeficiency virus (HIV) or active hepatitis B or C.
- [0125] 3. History or current evidence of drug or alcohol abuse within 12 months prior to the screening visit .
- [0126] 4. Visible inflammatory skin disease, injury, or condition of the scalp in the injection areas.
- [0127] 5. History of, known, or suspected malignancy (other than non-melanoma skin cancer); treatment with chemotherapy or cytotoxic agents; or radiation of the scalp.
- [0128] 6. Any dermatological disorders of the scalp on the regions that are bald and thinning with the possibility of interfering with the study injection or study assessments, such as fungal or

bacterial infections, seborrheic dermatitis, psoriasis, eczema, folliculitis, scars, skin carcinoma, tattoos, or scalp atrophy.

[0129] 7. History or active hair loss due to any condition other than AGA, such as, but not limited to, diffuse telogen effluvium, alopecia areata, scarring alopecia, trichotillomania, or other genetic disorders.

[0130] 8. History of severe dietary changes, weight changes, or eating disorder(s), in the opinion of the investigator, which has resulted in hair loss within the 6 months prior to the screening visit.

[0131] 9. History of scalp reduction, notable trauma with related scarring, previous hair transplants (groups 1 and 2), hair weaves, and/or platelet rich plasma (PRP) procedures on the scalp.

[0132] 10. Subject has used any other systemic therapy, which in the opinion of the investigator, may materially affect the subject's hair growth, including, but not limited to, vitamin or homeopathy supplement hair growth or hair health products or other steroid hormones (in any form), including anabolic steroids.

[0133] 11. Any of the following topical preparations or procedures on the scalp occurring within the specified period prior to day 0 (baseline)

[0134] 4 weeks: Topical scalp over the counter (OTC) or cosmetic treatments that may affect hair growth (e.g., brands such as Aminexil, Maxilene, Nioxin, Foltene); hair growth products with saw palmetto, copper, etc. including hair growth devices such as Cappilus, Revian, Theradome, etc.; and/or topical scalp treatments that may have ancillary effects on hair growth including, but not limited to, corticosteroids, pimecrolimus, tacrolimus, and retinoids.

[0135] 12 weeks: Topical scalp treatments for hair growth including minoxidil, hormone therapy, anti-androgen, or other agents known to affect hair growth.

[0136] 6 months: Laser, light-source or energy treatments, or micro-needling of the scalp; oral retinoids, isotretinoin.

[0137] 12. Any of the following systemic medications or procedures occurring within the specified period prior to day 0 (baseline).

[0138] 12 weeks: Beta blockers, cimetidine, diazoxide, or corticosteroids (including intramuscular and intralesional injections) within 12 weeks of Visit 2/Baseline. Inhaled, intranasal,

or ocular corticosteroids are allowed if use is stable. Stable is defined as doses and frequency unchanged for at least 4 weeks prior to Visit 2/Baseline.

[0139] 6 months: 5alpha reductase inhibitors, such as finasteride (e.g., Propecia®) or dutasteride; retinoids, isotretinoin, vitamin A intake about 10,000 IU per day, or cyclosporine therapy; and/or minoxidil.

[0140] 13. Known hypersensitivity to any component(s) of the study products (AMP-303 Vehicle or sterile saline).

[0141] 14. Subject is known to be noncompliant or is unlikely to comply with the requirements of the study protocol in the opinion of the investigator.

[0142] 15. Current enrollment in an investigational drug or device study or participation in such a study within 30 days of entry into this study.

[0143] 16. Patient who has a condition or is in a situation that, in the investigator's opinion, may put the patient at significant risk, confound study results, or may significantly interfere with the patient's participation in the study

Injection administration

[0144] Injection will be limited to the frontotemporal regions of the scalp. On Day 0, subjects who qualify for the study will be randomized to receive injection (either AMP-303 or saline control) to either the right or left treatment areas. Standard injection site preparation will be performed (e.g., cleansed and swabbed with alcohol). The same injection technique shall be used on each day for each subject (days 0, 1 and 2).

Response measures:

[0145] The response measures to be evaluated include adverse events (including injection adverse events), local skin reaction: severity (none, minimal, mild, moderate, severe) of erythema, edema, bruising will be assessed by the physician investigator and pain, itching and burning/stinging by the subject.

[0146] Vital signs such as blood pressure, pulse rate, respiration rate will also be measured.

[0147] Other response measures include digital image analysis of photographs of non-vellus hair; target area hair count (TAHC); target area hair width (TAHW); and/or hair darkness.

Standardized photography and Digital Image Analysis (DIA)

[0148] A qualified vendor will provide instructions for taking photographs and processing digital photographs. Macro hair imaging (1 cm² target area) of a representative area of thinning

will be obtained to document and measure scalp hair: length, width, growth rate (anagen/telogen ratios), follicular unit ratios, and color. Digital image analysis of photographs will be used to calculate Target Area Hair Count (TAHC), summation of Target Area Hair Widths (TAHW), and hair darkness.

[0149] The Modified Norwood Hamilton classification is used to classify the stages of male androgenetic alopecia (the figure) and will be used to determine eligibility.

Statistical Procedures

[0150] For all endpoints, descriptive statistics will be reported. Descriptive statistics will vary depending on variable type. In general, they will include continuous variables: descriptive statistics include number of observations, mean, median, standard deviation, minimum, maximum, and 95% confidence interval. Categorical variables will include descriptive statistics include the number in category, number of total observations, percentage of subjects in each category and 95% confidence interval.

Visits and Associated Procedures

[0151] Assessments are be performed by the same evaluator throughout the study whenever possible.

Visit 1: Screening (Day -30 to -1)

[0152] The screening visit can occur at any time 30 days to 1 day before the baseline visit. After informed consent has been obtained, procedures performed include inclusion/exclusion criteria; demographics; Fitzpatrick Skin Phototype; medical history/surgical history; androgenetic alopecia history; Modified Norwood Hamilton classification; concomitant medications and concurrent procedures; vital signs; standardized photography; review subject instructions.

Visit 2: Baseline and Injection (Day 0)

[0153] Screening and Day 0 may occur on the same date if no washout from prohibited medications is required . At any time during the visit, information on changes in health status, concomitant medications and concurrent procedures will be collected from patients. The order of events will include inclusion/exclusion criteria (confirm eligibility); vital signs; standardized photography (completed after above assessments); randomization; intradermal injection; local skin reaction (pre-injection and approximately 15 minutes post-injection); adverse events.

Visit 3: Day 1

[0154] At any time during the visit, information on adverse events, concomitant medications and concurrent procedures will be collected from patients. Vital signs are measured followed by intradermal injection; and local skin reaction (pre-injection and approximately 15 minutes post-injection) measurement.

Visit 4: Day 2

[0155] At any time during the visit, information on adverse events, concomitant medications and concurrent procedures will be collected from patients. Vital signs are measured followed by intradermal injection; local skin reaction (pre-injection and approximately 15 minutes post-injection) are measured.

Visit 5: Day 14 (± 3 days)

[0156] At any time during the visit, information on adverse events, concomitant medications and concurrent procedures will be collected from patients. Vital signs are measured followed by local skin reaction, and standardized photography.

Visit 6: Day 30 (± 7 days)

[0157] At any time during the visit, information on adverse events, concomitant medications and concurrent procedures will be collected from patients. Vital signs are measured followed by local skin reaction and standardized photography.

Visit 7: Day 60 (± 7 days)

[0158] At any time during the visit, information on adverse events, concomitant medications and concurrent procedures will be collected from patients.

[0159] Vital signs are measured followed by local skin reaction and standardized photography.

Visit 8: Day 90 (± 7 days)

[0160] At any time during the visit, information on adverse events, concomitant medications and concurrent procedures will be collected from patients. Vital signs are measured followed by local skin reaction and standardized photography.

Visit 9: Day 120 (± 7 days)

[0161] At any time during the visit, information on adverse events, concomitant medications and concurrent procedures will be collected from patients.

[0162] Vital signs are measured followed by local skin reaction and standardized photography.

Visit 10: Day 150 (± 7 days)

[0163] At any time during the visit, information on adverse events, concomitant medications and concurrent procedures will be collected from patients.

[0164] Vital signs are measured followed by local skin reaction and standardized photography. The subject is then exited from the study.

[0165] It will be appreciated by those skilled in the art that changes could be made to the exemplary embodiments shown and described above without departing from the broad inventive concepts thereof. It is understood, therefore, that this invention is not limited to the exemplary embodiments shown and described, but it is intended to cover modifications within the spirit and scope of the present invention as defined by the claims. For example, specific features of the exemplary embodiments may or may not be part of the claimed invention and various features of the disclosed embodiments may be combined. Unless specifically set forth herein, the terms "a", "an" and "the" are not limited to one element but instead should be read as meaning "at least one".

[0166] Further, to the extent that the methods of the present invention do not rely on the particular order of steps set forth herein, the particular order of the steps should not be construed as limitation on the claims. Any claims directed to the methods of the present invention should not be limited to the performance of their steps in the order written, and one skilled in the art can readily appreciate that the steps may be varied and still remain within the spirit and scope of the present invention.

What Is Claimed Is:

1. A method of treating androgenetic alopecia (AGA) in a patient in need thereof, comprising:
administering to a skin of the patient, a composition comprising up to about 1wt% hyaluronic acid for at least 2 times a week;
wherein the hyaluronic acid is not cross-linked; and
wherein the hyaluronic acid comprises an average molecular weight of up to about 100 kDa;
thereby treating AGA.
2. The method of claim 1, wherein the composition is administered to the patient on consecutive days in the week.
3. The method of claim 1, wherein the composition is administered via an intradermal injection.
4. The method of claim 3, wherein the composition is injected about 0.1 mm or more deep into the skin.
5. The method of claim 3, wherein the composition is administered at or proximal to a stem cell area of a follicle.
6. The method of claim 1, comprising an injection area is about 4 cm² or more.
7. The method of claim 1, wherein the composition is administered to the skin comprising one or more of a frontotemporal region of a scalp of the patient and a vertex region of a scalp of the patient.
8. The method of claim 1, wherein treatment with the composition improves or increases one or more of:
 - a) Target area hair count (TAHC);
 - b) Target area hair width (TAHW); and
 - c) Hair darkness.
9. The method of claim 1, wherein an onset of hair loss in the patient is about three to five years prior to administering the composition.
10. The method of claim 1, wherein an onset of hair loss in the patient is about ten years prior to administering the composition.

11. The method of claim 1, wherein the patient has previously received a hair transplantation.
12. The method of claim 11, wherein the patient has received the hair transplantation about one month to about two months prior to administering the composition.
13. The method of claim 1, wherein the AGA is mild AGA or moderate AGA.
14. The method of claim 1, wherein the patient has received a Modified Norwood Hamilton Scale score of III, or a Modified Norwood Hamilton Scale score of IV.
15. The method of claim 8, wherein said improvement or increase is measured from about 10 days to about 160 days after administering the composition.
16. The method of claim 1, wherein the patient has previously experienced hair loss.
17. The method of claim 7, wherein the hyaluronic acid stimulates hair growth in the frontotemporal region of the scalp of the patient and/or the vertex region of the scalp of the patient.
18. A method of stimulating hair growth in a skin of a patient in need thereof, comprising:
administering to the skin of the patient, a composition comprising up to about 1 wt % hyaluronic acid for about at least 2 times a week;
wherein the hyaluronic acid is not cross-linked; and
wherein the hyaluronic acid comprises an average molecular weight of up to about 100 kDa,
thereby stimulating hair growth in the skin of the patient.
19. A method of administering a composition for hair growth to a patient in need thereof:
administering to a skin of the patient, a composition comprising up to about 1 wt % hyaluronic acid for at least 2 times a week;
wherein the hyaluronic acid is not cross-linked; and
wherein the hyaluronic acid comprises an average molecular weight of up to about 100 kDa.
20. The method of claim 18 or claim 19, wherein the composition is administered to the patient on consecutive days in the week.
21. The method of claim 18 or claim 19, wherein the composition is administered via an intradermal injection.
22. The method of claim 21, wherein the composition is injected about 0.1 mm or more, deep into the skin.

23. The method of claim 21, wherein the composition is administered at or proximal to a stem cell area of a follicle.
24. The method of claim 18 or claim 19, comprising an injection area is about 4 cm² or more.
25. The method of claim 18 or claim 19, wherein the composition is administered to the skin comprising one or more of a frontotemporal region of a scalp of the patient and a vertex region of a scalp of the patient.
26. The method of claim 18 or claim 19, wherein the composition improves or increases one or more of:
 - a) Target area hair count (TAHC);
 - b) Target area hair width (TAHW); and
 - c) Hair darkness.
27. The method of claim 18 or claim 19, wherein an onset of hair loss in the patient is about three to five years prior to administering the composition.
28. The method of claim 18 or claim 19, wherein an onset of hair loss in the patient is about ten years prior to administering the composition.
29. The method of claim 18 or claim 19, wherein the patient has received previously received a hair transplantation.
30. The method of claim 29, wherein the patient has received the hair transplantation about one to two months prior to administering the composition.
31. The method of claim 18 or claim 19, wherein the patient suffers from androgenetic alopecia (AGA).
32. The method of claim 31, wherein the AGA is mild AGA to moderate AGA.
33. The method of claim 18 or claim 19, wherein the patient has received a Modified Norwood Hamilton Scale score of III, or a Modified Norwood Hamilton Scale score of IV.
34. The method of claim 26, wherein said improvement or increase is measured from about 10 days to about 160 days after administering the composition.