

TOPICAL COMPOSITION COMPRISING DUTASTERIDE AND LATANOPROST FOR ALOPECIA

RELATED APPLICATION

5 This application claims the benefit of Indian Provisional Application No. 202321086744 filed on December 19, 2023; which is hereby incorporated by reference in its entirety.

FIELD OF THE INVENTION

10 The present invention relates to the use of combination of 5 α -reductase inhibitors and prostaglandin analogues for preventing hair loss and/or stimulating hair growth. The present invention also relates to topical composition containing 5 α -reductase inhibitors and prostaglandin analogues for preventing hair loss and/or stimulating hair growth on the scalp. The present invention also relates to composition and methods for treating certain hair loss
15 disorders such as androgenetic alopecia.

BACKGROUND

 Hair loss is a natural phenomenon. Hair growth follows a cycle which involves the birth and development of the follicle, a stationary phase, and a final phase during which the hair is
20 expelled. This alternation between the phases of growth (the anagenic phase), regression (the catagenic phase), and the rest (the telogenic phase) is due to the specific secretion of the hair follicle which acts as a gland, and progressively produces a mass of keratin which it eliminates and replaces after a resting period.

 The cycle begins with the development of the hair follicle that rises up from the dermis
25 which contains large numbers of mesenchymatous cells, resulting in the formation of a dermal papilla. In the final stage (the anagenic phase) the cells surrounding the dermal papilla divide actively every 12 hours in order to produce cells which line up, grow longer, and begin to keratinize. This is hair growth. During the catagenic phase mitosis no longer occurs and the bulb detaches itself from the papilla and rises towards the surface. In the telogenic phase the
30 hair is fully keratinized and is ready to be expelled. After three to four months, another mitotic cycle begins in the germination zone of the hair and another hair follicle is formed.

 Male pattern alopecia is dependent on male hormones and is thus directly related to the amount of male hormones. Therefore, extensive research aimed at preventing and treating hair loss by inhibiting the activity of male hormones has recently been reported. The mechanism of

hair loss related to male hormones is briefly described below. The testosterone, which is one of the male hormones, is converted into dihydrotestosterone, which is an active male hormone, by a 5 α -reductase, and the active male hormone binds to a specific receptor to produce a protein that triggers hair loss, thus causing hair loss. Also, this mechanism produces excessive sebum, which causes acne or seborrheic dermatitis, eventually causing hair loss accompanied by inflammation in the scalp. As a result, the cause of male pattern alopecia is the synthesis of excessive dihydrotestosterone and thus it is possible to effectively prevent and treat male pattern alopecia by competitive inhibition with the androgen dihydrotestosterone from binding to androgen receptors in the sebaceous gland and hair follicles.

Treatments for the various forms of hair loss have limited success. Three medications have evidence to support their use in male pattern hair loss: oral finasteride (PROPECIA®, Merck), oral dutasteride and topical minoxidil (ROGAINE®, Pfizer/Johnson & Johnson). These treatments require prolonged usage of the drug and if treatment is stopped any benefits gained will be lost and the hair thickness will regress to levels as if no treatment was undertaken. Reversible side effects associated with the use of these androgen inhibitors have been reported such as decreased libido, erectile dysfunction and dermatologic discomfort.

US 10993934B2 discloses a topical application of dutasteride for preventing hair loss, androgenic alopecia and stimulating hair growth.

US 2022362382A1 discloses topical composition of a prostaglandin analogue for treating androgenetic alopecia.

Androgenetic alopecia is a common form of hair loss in both men and women. In men, this condition is also known as male-pattern baldness. Some of the current challenges in AGA include:

Understanding the underlying causes: Despite significant progress in the understanding of the genetics and biology of AGA, there is still much that is not fully understood about the condition. Researchers are still working to identify the precise genetic and environmental factors that contribute to AGA.

Developing effective treatments: Although there are several treatments available for AGA, including medications and hair transplant surgery, there is still no cure for the condition. Current treatments are often expensive, time-consuming, and may have side effects.

Addressing psychological impact: AGA can have a significant psychological impact on those affected, causing anxiety, depression, and low self-esteem. More research is

needed to better understand the psychological aspects of AGA and develop effective interventions to address these issues.

Preventing hair loss: While there are treatments available to slow down or even reverse hair loss in some cases, preventing hair loss altogether remains a challenge. Lifestyle changes, such as reducing stress and eating a healthy diet, may be beneficial, but more research is needed to determine the most effective ways to prevent hair loss.

Overall, the challenges in AGA highlight the need for continued research and development of new and more effective treatments, as well as increased focus on the psychological impact of the condition.

The combination of actives described herein constitute a major improvement to the currently available therapies of alopecia, and specifically AGA, and would allow the physicians to have an effective, valuable and safe treatment of alopecia, and in particular AGA.

The use of combination of 5 α -reductase inhibitor and prostaglandin analogue for preventing hair loss and stimulating hair growth provides an equal or superior hair loss prevention and hair growth stimulating effects compared to existing treatment options currently available in the marketplace.

SUMMARY OF THE INVENTION

The invention relates to the method for preventing hair loss and/or stimulating hair growth comprising: a. a pharmaceutically effective amount of a 5 α -reductase inhibitors, b. a pharmaceutically effective amount of a pharmaceutically effective amount of prostaglandin analogues, and c. pharmaceutically acceptable vehicle.

The invention relates to composition comprising: a. a pharmaceutically effective amount of a 5 α -reductase inhibitor, b. a pharmaceutically effective amount of a prostaglandin analogues and c. pharmaceutically acceptable vehicle.

The invention relates to the method for preventing hair loss and/or stimulating hair growth comprising: a. a pharmaceutically effective amount of dutasteride, b. a pharmaceutically effective amount of a prostaglandin, and c. pharmaceutically acceptable vehicle.

The invention relates to composition comprising: a. a pharmaceutically effective amount of a dutasteride, b. a pharmaceutically effective amount of a latanoprost; and c. pharmaceutically acceptable vehicle.

Inventors of the present invention have surprisingly found that the combined use of dutasteride and latanoprost, is an effective approach for treating androgenetic alopecia (AGA).

When used in combination, dutasteride, and latanoprost, target different aspects of the hair loss process, potentially providing more comprehensive and effective treatment for AGA.

The invention relates to the composition comprising: a. dutasteride, b. latanoprost; and c. pharmaceutically acceptable vehicle, wherein at least one of the active is partially solubilized.

5 In another embodiment, the invention relates to a composition comprising: a. dutasteride, b. latanoprost; and c. pharmaceutically acceptable vehicle, wherein dutasteride is partially solubilized or supersaturated or suspended.

10 In another embodiment, the invention relates to a composition comprising: a. dutasteride, b. latanoprost; and c. pharmaceutically acceptable vehicle, wherein latanoprost is partially solubilized or supersaturated or suspended.

In another embodiment, the invention relates to a composition comprising: a. dutasteride, b. latanoprost; and c. pharmaceutically acceptable vehicle, wherein dutasteride and latanoprost are fully solubilized.

15 In another embodiment, the invention relates to a stable composition comprising: a. dutasteride, b. latanoprost; and c. pharmaceutically acceptable vehicle.

In another embodiment, the invention relates to a composition for treating hair loss and/or stimulating hair growth comprising: a. dutasteride, b. latanoprost; and c. pharmaceutically acceptable vehicle, wherein dutasteride is partially solubilized; and latanoprost is solubilized.

20 In another embodiment, the invention relates to a composition for treating hair loss and/or stimulating hair growth comprising: a. dutasteride, b. latanoprost; and c. pharmaceutically acceptable vehicle, wherein dutasteride is solubilized; and latanoprost is partially solubilized.

25 In another embodiment, the invention is based on sol-gel technology, in sol-gel *in situ* gel-forming formulations, which undergo phase transition from liquid to gel upon exposure to physiological environments. This technology combines advantages of being convenient for administration to patients and prolonging drug delivery.

30 In another embodiment, the invention relates to a stable composition comprising: a. dutasteride, b. latanoprost; and d. pharmaceutically acceptable vehicle, wherein the composition is stable at least for a period of about 1 month at room temperature.

In another embodiment, the invention relates to a stable composition for treating hair loss and/or stimulating hair growth comprising: a. dutasteride, b. latanoprost; and d. pharmaceutically acceptable vehicle, wherein the composition is stable at least for a period of about 2 months at room temperature.

In another embodiment, the invention relates to a stable composition for treating hair loss and/or stimulating hair growth comprising: a. dutasteride, b. latanoprost; and c. pharmaceutically acceptable vehicle, wherein the composition is stable at least for a period of about 3 months at room temperature.

5 In another aspect, the invention relates to a topical composition comprising a. about 0.001% w/w to about 1% w/w of the dutasteride or a pharmaceutically acceptable salt thereof, b. about 0.001% w/w to about 1% w/w of the latanoprost or a pharmaceutically acceptable salt thereof; and c. a pharmaceutically acceptable vehicle.

In another aspect, the invention relates to a topical composition comprising a. about
10 0.01% w/w to about 0.1% w/w of the dutasteride or a pharmaceutically acceptable salt thereof, b. about 0.01% w/w to about 0.1% w/w of the latanoprost or a pharmaceutically acceptable salt thereof; and c. a pharmaceutically acceptable vehicle.

In another aspect, the invention relates to a topical composition comprising a. about
15 0.02% w/w to about 0.08% of the dutasteride or a pharmaceutically acceptable salt thereof, b. about 0.02% w/w to about 0.08% w/w of the latanoprost or a pharmaceutically acceptable salt thereof.; and c. a pharmaceutically acceptable vehicle.

In another aspect, the invention relates to a topical composition comprising a. about
20 0.04% w/w to about 0.06% of the dutasteride or a pharmaceutically acceptable salt thereof, b. about 0.02% w/w to about 0.06% w/w of the latanoprost or a pharmaceutically acceptable salt thereof.; and c. a pharmaceutically acceptable vehicle.

In another aspect, the invention relates to a topical composition comprising a. about
0.05% w/w of the dutasteride or a pharmaceutically acceptable salt thereof, b. about 0.03% w/w of the latanoprost or a pharmaceutically acceptable salt thereof.; and c. a pharmaceutically acceptable vehicle.

25 In another aspect, the invention relates to a topical composition comprising a. about 0.1% w/w of the dutasteride or a pharmaceutically acceptable salt thereof, b. about 0.03% w/w of the latanoprost or a pharmaceutically acceptable salt thereof.; and c. a pharmaceutically acceptable vehicle.

In another aspect, the invention relates method of treating hair loss and/or stimulating
30 hair growth in a subject in need thereof applying a formulation to a desired area of scalp in the form of the composition for external application, which formulation can be either hair tonic, solution, dispersion, suspension, emulsion, microemulsion, colloidal solution, cream, ointment, lotion, hair dye, shampoo, rinse, gel, patch, hair serum, foam, or spray.

In another aspect, the invention relates to composition for external application, - including but not limited to hair tonic, solution, dispersion, suspension, emulsion, microemulsion, colloidal solution, cream, ointment, lotion, hair dye, shampoo, rinse, gel, patch, hair serum, foam, and spray.

5 In another aspect, the invention relates to method of treating hair loss and/or stimulating hair growth in a subject in need thereof applying a formulation to a desired area of scalp in the form of the composition for external application, which formulation can be either hair tonic, solution, dispersion, suspension, emulsion, microemulsion, colloidal solution, cream, ointment, lotion, hair dye, shampoo, rinse, gel, patch, hair serum, foam, or spray.

10 A pharmaceutical composition comprising dutasteride, latanoprost and one or more pharmaceutically acceptable vehicle.

A pharmaceutical composition comprising effective amount of dutasteride, latanoprost and one or more pharmaceutically acceptable vehicle, wherein one or more pharmaceutically acceptable vehicle comprises one or more solvent.

15 A topical composition comprising dutasteride, latanoprost and pharmaceutical acceptable vehicle.

A stable topical composition comprising dutasteride, latanoprost and pharmaceutical acceptable vehicle.

A topical composition comprising 0.001% w/w to about 1% w/w of latanoprost and
20 0.001% w/w to about 1% w/w of dutasteride and one or more pharmaceutically acceptable vehicle, wherein one or more pharmaceutically acceptable vehicle comprises one or more solvent.

A topical composition comprising 0.02-0.05% w/w latanoprost and 0.03-0.07% w/w dutasteride and one or more pharmaceutically acceptable vehicle, wherein one or more
25 pharmaceutically acceptable vehicle comprises one or more solvent.

A topical composition comprising about 0.03-0.04% w/w latanoprost and about 0.05% w/w dutasteride and one or more pharmaceutically acceptable vehicle, wherein one or more pharmaceutically acceptable vehicle comprises one or more solvent.

A topical composition comprising of about 0.03% w/w latanoprost and about 0.05%
30 w/w dutasteride and one or more pharmaceutically acceptable vehicle, wherein one or more pharmaceutically acceptable vehicle comprises one or more solvent.

A topical composition comprising of about 0.03% w/w latanoprost and about 0.1% w/w dutasteride and one or more pharmaceutically acceptable vehicle, wherein one or more pharmaceutically acceptable vehicle comprises one or more solvent.

A topical composition for preventing hair loss and/or stimulating hair growth comprising about 0.03% w/w latanoprost and about 0.05% w/w dutasteride and one or more pharmaceutically acceptable vehicle, wherein one or more pharmaceutically acceptable vehicle comprises one or more solvent.

- 5 A topical composition for preventing hair loss and/or stimulating hair growth comprising about 0.03% w/w latanoprost and about 0.1% w/w dutasteride and one or more pharmaceutically acceptable vehicle, wherein one or more pharmaceutically acceptable vehicle comprises one or more solvent.

- 10 A method of preventing hair loss and/or stimulating hair growth in a patient suffering therefrom comprising applying a topical composition to an affected area of hair loss about 0.03% w/w latanoprost and about 0.05% w/w dutasteride and one or more pharmaceutically acceptable vehicle.

- 15 A method of preventing hair loss and/or stimulating hair growth in a patient suffering therefrom comprising applying a topical composition to an affected area of hair loss comprising about 0.03% w/w latanoprost and about 0.05% w/w dutasteride and one or more pharmaceutically acceptable vehicle, wherein one or more pharmaceutically acceptable vehicle comprises one or more solvent.

In one embodiment solvent can be ethanol.

In one embodiment solvent can be polyol ether.

- 20 A topical composition for preventing hair loss and/or stimulating hair growth in a patient suffering therefrom comprising applying a topical composition to an affected area of hair loss, wherein the composition comprises latanoprost and dutasteride.

The topical composition comprises 0.01-0.06% w/w latanoprost and 0.01-0.2% w/w dutasteride.

- 25 The topical composition comprises 0.02-0.05% w/w latanoprost and 0.03-0.08% w/w dutasteride.

The topical composition is required to be applied to the human skin area affected with hair loss.

- 30 The topical composition when applied to the area affected with hair loss shows hair growth to an extent greater than a composition with the same amount and concentration of latanoprost.

The topical composition when applied to the area affected with hair loss shows hair growth to an extent greater than a composition with the same amount and concentration of dutasteride.

The topical composition is applied to the affected area which is scalp.

The method according to present invention, wherein the composition is applied at least once a day to the scalp.

A method of treating androgenetic alopecia in a patient suffering therefrom comprising
5 applying a composition to an area experiencing hair loss wherein the active agents of the composition comprises latanoprost and dutasteride.

The method according to present invention, wherein the active agent comprises 0.02-0.04% w/w latanoprost and 0.03-0.06% w/w dutasteride.

The method according to present invention, wherein the patient experiences more hair
10 growth in the area experiencing hair loss when the composition is applied as compared to if the patient had not applied the formulation to the area experiencing hair loss.

The method according to present invention, wherein new hair growth results in the area experiencing hair loss where the formulation is applied in which the individual hairs are thicker in diameter as compared to hair growth in areas where the patient did not apply the formulation.

15 The method according to present invention, wherein the application of the topical composition to the area affected with hair loss shows hair growth to an extent greater than a composition with the same amount and concentration of dutasteride.

The method according to present invention, wherein the application of the topical composition to the area affected with hair loss shows hair growth to an extent greater than a
20 composition with the same amount and concentration of latanoprost.

The method according to present invention, wherein the application of the formulation to the scalp results in a faster onset of new hair growth as compared to the patient not applying the formulation.

A method of preventing hair loss in a patient suffering from a hair loss disorder
25 comprising applying a formulation wherein the active agent comprises 0.02%-0.04% w/w latanoprost and dutasteride.

A method of preventing hair loss in a patient suffering from a hair loss disorder comprising applying a formulation wherein the active agent comprises latanoprost and dutasteride of 0.04%-0.06% w/w.

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BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1A: Effect of hair growth formulations on hair coverage: line graph showing daywise hair coverage score.

Figure 1B: Effect of hair growth formulations on hair coverage: bar graph showing terminal hair coverage score.

Figure 2. Effect of hair growth formulations on anagen phase onset: line graph showing daywise number of mice in anagen phase.

5 Figure 3: Terminal macroscopic photos of mice: topical placebo.

Figure 4: Terminal macroscopic photos of mice: topical dutasteride 0.05%.

Figure 5: Terminal macroscopic photos of mice: topical latanoprost 0.03%.

Figure 6: Terminal macroscopic photos of mice: topical dutasteride 0.05% + topical latanoprost 0.03%.

10 Figure 7: Representative skin histopathology of mice skin treated with placebo showing normal morphology of epidermis, dermis and hair follicles in resting/inactive (telogen) phase.

Figure 8: Representative image if skin histopathology of mice skin treated with dutasteride 0.05% showing increased thickness of dermis (lines), hair follicles in active (anagen) phase and increased number of hair follicles (numbers).

15 Figure 9: Representative image if skin histopathology of mice skin treated with latanoprost 0.03% showing increased thickness of dermis (lines), hair follicles in active (anagen) phase and increased number of hair follicles (numbers).

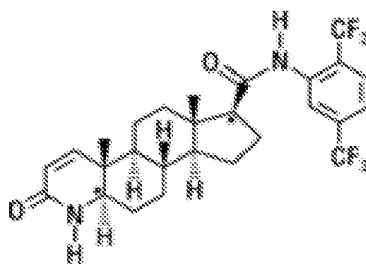
Figure 10: Representative skin histopathology of mice skin treated with dutasteride 0.05% and latanoprost 0.03% combination composition showing increased thickness of dermis
20 (lines), hair follicles in active (anagen) phase and increased number of hair follicles (numbers).

DETAILED DESCRIPTION

Disclosed herein are detailed descriptions of specific aspects of the invention of a topical composition in the form of a cream, ointment, gel, lotion, hair tonic, patch, hair serum, emulgel,
25 emulsion, aerosol foam, solution, spray, suspension, swab, sponge, powder or paste. It will be understood that the disclosed embodiments are merely examples of the way in which certain aspects of the application can be implemented and do not represent an exhaustive list of all of the ways the application may be embodied.

A. Dutasteride

30 Dutasteride has a chemical name (5 α ,17 β)-N-{2,5-bis(trifluoromethyl)phenyl}-3-oxo-4-azaandrost-1-ene-17-carboxamide. It has the structural formula shown as Formula I.



Formula I

Dutasteride is a synthetic 4-azasteroid compound that is a selective inhibitor of both type I and type II isoforms of steroid 5 α -reductase (5AR), an intracellular enzyme that converts testosterone to 5 α -dihydrotestosterone (DHT), and is indicated for the treatment of symptomatic benign prostatic hyperplasia (BPH) in men. A pharmaceutical product containing dutasteride as the active ingredient is commercially available as AVODART® from GlaxoSmithKline, in the form of soft gelatin capsules for oral administration and containing 0.5 mg of the active ingredient.

R. Clerk et al., Journal of Clinical Endocrinology and Metabolism, Vol. 89, pages 2179-2184, 2004, demonstrated approximately 3 times higher potency of dutasteride at inhibiting type II 5 α -reductase and more than 100 times higher potency at inhibiting the type I isoform, as compared with finasteride.

While type I 5 α -reductase has been reported to be located predominantly in the skin, both in hair follicles and sebaceous glands, as well as in the liver, prostate, and kidney, type II 5 α -reductase is found in the male genitalia, prostate and hair follicles. Due to the distribution of both isoforms of 5 α -reductase in skin, it has been hypothesized that dutasteride, being a dual inhibitor, would be more useful for treatment of AA when compared to the selective type II inhibitor such as finasteride. (S. Marihart et. al., Reviews in Urology, Vol. 7, pages 203-210, 2005).

Dutasteride (0.5 mg/day) is approved for treatment of androgenic alopecia in South Korea, Japan, and Taiwan. However, efficacy and safety data for dutasteride is largely derived from short-term clinical trials and post-marketing surveillance studies. Long-term, real-world evidence for the effectiveness of dutasteride in androgenic alopecia is limited.

Dutasteride when used topically can provide the local effective concentrations and minimal systemic concentration. When applied topically, it works by stopping DHT conversion in the hair follicles, the site of action.

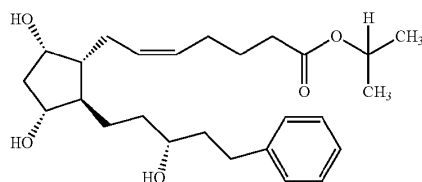
The therapeutically effective amount of dutasteride is from about 0.001% w/w to 1% w/w or from about at least 0.01% w/w to about 0.5% w/w, or preferably from about at least

0.01% w/w to about 0.07% w/w b, or preferably of about 0.1% w/w, or preferably of about 0.03% w/w, most preferably about 0.05% w/w based on the total weight of the composition.

In a specific aspect, the concentration of dutasteride in the composition is selected from about 0.001% w/w, 0.002% w/w, 0.003% w/w, 0.004% w/w, 0.005% w/w, 0.006% w/w, 0.007% w/w, 0.008% w/w, 0.009% w/w, 0.01% w/w, 0.02% w/w, 0.03% w/w, 0.04% w/w, 0.05% w/w, 0.06% w/w, 0.07% w/w, 0.08% w/w, 0.09% w/w, 0.1% w/w, 0.11% w/w, 0.12% w/w, 0.13% w/w, 0.14% w/w, 0.15% w/w; 0.16% w/w, 0.17% w/w, 0.18% w/w, 0.19% w/w, 0.2% w/w, 0.21% w/w, 0.22% w/w, 0.23% w/w, 0.24% w/w, 0.25% w/w, 0.26% w/w, 0.27% w/w, 0.28% w/w, 0.29% w/w, 0.3% w/w, 0.31% w/w, 0.32% w/w, 0.33% w/w, 0.34% w/w, 0.35% w/w, 0.36% w/w, 0.37% w/w, 0.38% w/w, 0.39% w/w, 0.4% w/w, 0.41% w/w, 0.42% w/w, 0.43% w/w, 0.44% w/w, 0.45% w/w, 0.46% w/w, 0.47% w/w, 0.48% w/w, 0.49% w/w, 0.5% w/w, 0.51% w/w, 0.52% w/w, 0.53% w/w, 0.54% w/w, 0.55% w/w, 0.56% w/w, 0.57% w/w, 0.58% w/w, 0.59% w/w, 0.6% w/w, 0.61% w/w, 0.62% w/w, 0.63% w/w, 0.64% w/w, 0.65% w/w, 0.66% w/w, 0.67% w/w, 0.68% w/w, 0.69% w/w, 0.7% w/w, 0.71% w/w, 0.72% w/w, 0.73% w/w, 0.74% w/w, 0.75% w/w, 0.76% w/w, 0.77% w/w, 0.78% w/w, 0.79% w/w, 0.80% w/w, 0.80% w/w, 0.80% w/w, 0.81% w/w, 0.82% w/w, 0.83% w/w, 0.84% w/w, 0.85% w/w, 0.86% w/w, 0.87% w/w, 0.88% w/w, 0.89% w/w, 0.9% w/w, 0.91% w/w, 0.92% w/w, 0.93% w/w, 0.94% w/w, 0.95% w/w, 0.96% w/w, 0.97% w/w, 0.98% w/w, 0.99% w/w or 1% w/w.

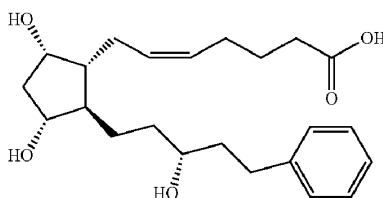
B. Latanoprost

Latanoprost has the following structure:



Formula II

Latanoprost is a prostaglandin analogue and is in fact a prodrug with its acid form (Latanoprost acid) being biologically active:



Formula III

Latanoprost is an isopropyl ester, and is a prodrug which converts to latanoprost free acid by r[(3R)-3-hydroxy-5-phenylpentyl] cyclopentyl]hept-5-enoic acid. The free acid form of latanoprost is two-hundred times more potent than latanoprost as an FP receptor ligand for the human recombinant FP receptor. Latanoprost free acid is a potent FP receptor agonist with an EC50 of 3.6 nM for human FP receptors, which is twice the potency of PGF2 α . The efficacy of PG analog esters for the treatment of glaucoma or elevated IOP correlates closely with the FP receptor binding affinity of the free acid. Other forms of latanoprost which may be used in the invention include 15-keto latanoprost, 15(S)-latanoprost, 5-trans latanoprost, latanoprost-d4, latanoprost lactol and latanoprost ethyl amide-d4.

Latanoprost is poorly soluble in water but is generally fat soluble. The solubility of latanoprost in PBS (pH 7.2) is approximately 50 μ g/mL. For maximum solubility in aqueous buffers, latanoprost should first be dissolved in ethanol or propylene glycol and then diluted with the aqueous buffer of choice. Latanoprost has a solubility of 400 μ g/mL in a 1:4 solution of ethanol: PBS (pH 7.2) using this method.

In acidic or basic aqueous solutions, latanoprost is stable for no more than 48 hours and in neutral aqueous solutions it has shown to be stable for up to one month at room temperature. Latanoprost is the isopropyl ester of 17-phenyl-13,14-dihydro prostaglandin F2a (17-phenyl-13,14-dihydro PGF2a).

The therapeutically effective amount of latanoprost is from about 0.001% w/w to 1% w/w, or from about at least 0.01% w/w to about 0.1% w/w, or preferably from about at least 0.02% w/w to about 0.08% w/w b, or preferably of about 0.025% w/w to about 0.06% w/w, or most preferably about 0.03% w/w based on the total weight of the composition. In a specific aspect, the concentration of Latanoprost in the composition is selected from about 0.001% w/w, 0.002% w/w, 0.003% w/w, 0.004% w/w, 0.005% w/w, 0.006% w/w, 0.007% w/w, 0.008% w/w, 0.009% w/w, 0.01% w/w, 0.02% w/w, 0.03% w/w, 0.04% w/w, 0.05% w/w, 0.06% w/w, 0.07% w/w, 0.08% w/w, 0.09% w/w, 0.1% w/w, 0.11% w/w, 0.12% w/w, 0.13% w/w, 0.14% w/w, 0.15% w/w, 0.16% w/w, 0.17% w/w, 0.18% w/w, 0.19% w/w, 0.2% w/w, 0.21% w/w, 0.22% w/w, 0.23% w/w, 0.24% w/w, 0.25% w/w, 0.26% w/w, 0.27% w/w, 0.28% w/w, 0.29% w/w, 0.3% w/w, 0.31% w/w, 0.32% w/w, 0.33% w/w, 0.34% w/w, 0.35% w/w, 0.36% w/w, 0.37% w/w, 0.38% w/w, 0.39% w/w, 0.4% w/w, 0.41% w/w, 0.42% w/w, 0.43% w/w, 0.44% w/w, 0.45% w/w, 0.46% w/w, 0.47% w/w, 0.48% w/w, 0.49% w/w, 0.5% w/w, 0.51% w/w, 0.52% w/w, 0.53% w/w, 0.54% w/w, 0.55% w/w, 0.56% w/w, 0.57% w/w, 0.58% w/w, 0.59% w/w, 0.6% w/w, 0.61% w/w, 0.62% w/w, 0.63% w/w, 0.64% w/w 0.65%, 0.66% w/w, 0.67% w/w, 0.68% w/w, 0.69% w/w, 0.7% w/w, 0.71% w/w, 0.72% w/w, 0.73% w/w, 0.74% w/w,

0.75% w/w, 0.76% w/w, 0.77% w/w, 0.78% w/w, 0.79% w/w, 0.80% w/w, 0.80% w/w, 0.80% w/w, 0.81% w/w, 0.82% w/w, 0.83% w/w, 0.84% w/w, 0.85% w/w, 0.86% w/w, 0.87% w/w, 0.88% w/w, 0.89% w/w, 0.9% w/w, 0.91% w/w, 0.92% w/w, 0.93% w/w, 0.94% w/w, 0.95% w/w, 0.96% w/w, 0.97% w/w, 0.98% w/w, 0.99% w/w or 1% w/w.

- 5 In specific aspect, the active agents of inventive combination comprise dutasteride and latanoprost.

Definitions:

- 10 The terms “active” and “active agent” as used herein refers to therapeutically active agent used in the treatment of a disease or disorder. For example, therapeutically active agent used herein is useful for the treatment, alleviation or prevention of hair loss, and/or the stimulation of hair growth. Exemplary agents are a hair growth stimulant, and/or hair growth stimulating agent and/or hair density increasing agent and/or hair loss prevention agent.

For example, an active agent may be dutasteride or latanoprost or combination thereof.

- 15 The term “effective amount” refers to an amount that is sufficient to achieve the desired modification of a physical property of the composition or material. For example, an “effective amount” of a therapeutic agent refers to an amount that is sufficient to achieve the desired improvement in clinical condition modulated by the formulation component, e.g. achieving the desired level of hair growth or mitigation of hair loss. Therapeutic agents should be understood to include the neutral forms of the drug and pharmaceutically acceptable forms thereof.
- 20 “Pharmaceutically acceptable” refers to those compounds, materials, compositions, salts and/or dosage forms which, are suitable for administration to patients without excessive toxicity, irritation, allergic response, or other problems or complications commensurate with a reasonable benefit/risk ratio, when used in the compositions of the invention, including when the compositions are applied topically according to methods described herein.

- 25 By “pharmaceutically acceptable forms” thereof is meant any pharmaceutically acceptable derivative or variation, including stereoisomers, stereoisomer mixtures, enantiomers, solvates, hydrates, isomorphs, polymorphs, pseudomorphs, salt forms and prodrugs. Preferably in some aspects, the pharmaceutically acceptable forms include salt forms. In other preferable aspects the pharmaceutically acceptable forms include, any stereoisomer or
- 30 stereoisomeric mixture of the therapeutic agent. The specific level in terms of % w/w in a composition required as an effective amount will depend upon a variety of factors including the amount and type of therapeutic agent and formulation type, e.g., solution, emulsion, suspension, spray, ointment, cream, gel, and the like.

The term “comprising” is to be interpreted as specifying the presence of the stated features, integers, steps, or components as referred to, but does not preclude the presence or addition of one or more features, integers, steps, or components, or groups thereof. Moreover, each of the terms “by”, “comprising,” “comprises”, “comprised of,” “including,” “includes,” “included,” “involving,” “involves,” “involved,” and “such as” are used in their open, non-limiting sense and may be used interchangeably. Further, the term “comprising” is intended to include examples and aspects encompassed by the terms “consisting essentially of” and “consisting of.” Similarly, the term “consisting essentially of” is intended to include examples encompassed by the term “consisting of”.

10 The term “safe and effective amount” as used herein means an amount of a compound or composition sufficient to significantly induce a positive benefit, for example, hair growth, but low enough to avoid serious side effects, i.e., to provide a reasonable benefit to risk ratio, within the scope of sound judgment of the skilled artisan.

The term “hair growth,” “regulating hair growth,” “hair growth regulation,” and “regulating the growth of hair,” are meant to include: stimulating hair growth; stimulating hair thickening; preventing, reducing, arresting and/or retarding the loss of hair; preventing, reducing, arresting and/or retarding the thinning of hair; increasing the rate of hair growth; inducing the formation of a greater number of hair strands; increasing the diameter of the hair strand; lengthening the hair strand; changing the hair follicle from a vellus or miniaturized follicle to a large terminal follicle; inducing the formation of vellus and terminal follicles.

20 The term “alopecia” as used herein refers to, collectively, or individually as specified, androgenetic alopecia (AGA), alopecia areata (including diffuse alopecia areata, alopecia areata monolocularis, alopecia areata multilocularis, ophiasis, alopecia totalis, and alopecia universalis), telogen effluvium, anagen effluvium, and traction alopecia.

25 As used herein, the terms “about,” “approximate,” “at or about,” and “substantially” mean that the amount or value in question can be the exact value or a value that provides equivalent results or effects as recited in the claims or taught herein. That is, it is understood that amounts, sizes, formulations, parameters, and other quantities and characteristics are not and need not be exact, but may be approximate and/or larger or smaller, as desired, reflecting tolerances, conversion factors, rounding off, measurement error and the like, and other factors known to those of skill in the art such that equivalent results or effects are obtained. In some circumstances, the value that provides equivalent results or effects cannot be reasonably determined. In such cases, it is generally understood, as used herein, that “about” and “at or about” mean the nominal value indicated $\pm 20\%$ variation unless otherwise indicated or inferred.

In general, an amount, size, formulation, parameter or other quantity or characteristic is “about,” “approximate,” or “at or about” whether or not expressly stated to be such. It is understood that where “about,” “approximate,” or “at or about” is used before a quantitative value, the parameter also includes the specific quantitative value itself, unless specifically stated otherwise.

As used herein, the terms “optional” or “optionally” means that the subsequently described event or circumstance can or cannot occur, and that the description includes instances where said event or circumstance occurs and instances where it does not.

As used herein, the term “administration” refers to the act of administering a drug, prodrug, or other active agent, or therapeutic treatment (e.g., compositions of the invention) to a subject. Exemplary routes of administration to the human body can be on the skin, e.g., on the scalp. Administration may be in one or more administrations, applications or dosages, and is not intended to be limited to a particular time period. “Administered” and “applied” are used to describe the act of “administration” and are used synonymously.

The term “substantially solubilized,” as used herein, means that the therapeutic agent is dissolved in the compositions and is at a concentration which is less than about its solubility limit in the compositions.

The term “partially solubilized,” as used herein, means that the therapeutic agent is insoluble in the compositions and is at a concentration which is less than about its solubility limit in the compositions.

The term “topical” or “topically” in reference to administration or application of a composition or a product refers to epicutaneous administration or application, or administration onto the surface of the skin. The term “topically active agent” as used herein refers to a compound that is effective in a treatment of a skin condition when administered topically. The term “topical,” when used in reference to a composition, formulation or a product refers to a composition or a product formulated for topical application. “Formulation” and “composition” can be interchangeable.

The term “pharmaceutical composition” as used herein refers to compositions comprising 5 α -reductase inhibitors and prostaglandin analogues together with one or more pharmaceutically acceptable excipients as required to prepare a dosage form for the effective delivery of the active agent. Such pharmaceutical compositions can be in the form of solutions, ointments, creams, gels, lotions, suspensions, sprays, foams, microspheres, microemulsions, nanoemulsions, nanoparticles, nanosuspensions, dermal sticks, roll-ons, pumps, patches, tapes, and the like.

“Scalp” according to the present invention means the skin covering the head and is bordered by the face anteriorly and the neck to the sides and posteriorly.

The term “treatment duration” as used herein, means that the composition prescribed or used or administered for said period of time for example one month, two months, six months,
5 1 year or two year).

The term “solvent” as used herein refers to a substance that solubilizes active agent or one or more excipient and provides uniform distribution of active agent or one or more excipient throughout the composition. As used herein “solvent” and “solubilizer” can be interchangeable. Solvent can be ethanol, polyol ether.

10 The term “subject” as used herein refers to human subject or an animal including mammals (such as monkeys, guinea pig, domestic pets, for instance cats and dogs).

In embodiments, topical pharmaceutical compositions according to the present invention provide improved local delivery of an active agent, i.e., a 5 α -reductase inhibitor, such as dutasteride, that results in enhanced bioavailability and is substantially comparable effect to
15 an oral formulation of the 5 α -reductase inhibitor.

In one of the aspect, invention relates to a synergistic composition for preventing hair loss and/or stimulating hair growth in a patient in need thereof comprising about 0.01% w/w to 0.1% w/w of dutasteride, about 0.01% w/w to about 0.1% w/w of latanoprost and pharmaceutically acceptable vehicle.

20 In one of the aspect, invention provides a method of preventing hair loss and/or stimulating hair growth in a patient in need thereof, comprising topically administering to the subject a pharmaceutical formulation comprising about 0.01% w/w of dutasteride, about 0.03% w/w of latanoprost and a pharmaceutically acceptable vehicle.

In one of the aspect, invention provides a method of preventing hair loss and/or
25 stimulating hair growth in a patient in need thereof, comprising topically administering to the subject a pharmaceutical formulation comprising about 0.02% w/w of dutasteride, about 0.03% w/w of latanoprost and a pharmaceutically acceptable vehicle.

In one of the aspect, invention provides a method of preventing hair loss and/or stimulating hair growth in a patient in need thereof, comprising topically administering to the
30 subject a pharmaceutical formulation comprising about 0.05% w/w of dutasteride, about 0.03% w/w of latanoprost and a pharmaceutically acceptable vehicle.

In one of the aspect, invention provides a method of preventing hair loss and/or stimulating hair growth in a patient in need thereof, comprising topically administering to the

subject a pharmaceutical formulation comprising about 0.1% w/w of dutasteride, about 0.03% w/w of latanoprost and a pharmaceutically acceptable vehicle.

In an aspect, the invention relates to a composition comprising a. dutasteride b. latanoprost; and c. a pharmaceutically acceptable vehicle comprising one or more solvent.

5 In one embodiment solvent can be ethanol.

In one embodiment solvent can be polyol ether.

10 In one of the embodiment composition according to invention relates to a topical composition comprising active ingredients consisting of: a. dutasteride, at a concentration of about 0.05% w/w of the composition; b. latanoprost at a concentration of about 0.03% w/w by weight of the composition and c. a pharmaceutically acceptable vehicle, wherein solution comprises a solvent; and wherein the composition comprising the dutasteride and latanoprost at said concentrations is capable of providing synergistic efficacy.

EXAMPLES

15 Example-1

Ingredients	% w/w
Dutasteride	0.01 - 0.2
Latanoprost	0.01 - 0.2
Solvent	2.0 – 98.0
Purified water	q.s

Brief Manufacturing Process:

Dutasteride and latanoprost were added to mixture of one or more solvents and purified water in SS vessel; mixed under stirring, to obtain clear phase.

20

The stability study results of Example-1 at 25 °C/60% RH & 40 °C/75% RH is shown in Table 1.

Table-1:

Storage condition	Period	Description	% Assay of Dutasteride	% Assay of latanoprost	Specific gravity	Viscosity	pH
Stability specification		Clear colorless to pale yellow solution	90-110%	90-110%	0.8-1.2	1-20cP	3.0-7.0
-	Initial		97	100.5	0.94	7.22	5.32
	1M		99.6	102.4	0.94	7.16	5.32

Storage condition	Period	Description	% Assay of Dutasteride	% Assay of latanoprost	Specific gravity	Viscosity	pH
25 °C/60% RH	2M	Clear colorless to pale yellow solution	98.3	100.1	0.94	7.20	5.41
	3M		99.2	100.0	0.94	7.20	5.36
	6M		99.6	100.2	0.94	7.50	5.32
40 °C/75% RH	1M		100.1	102.8	0.94	7.48	5.29
	2M		98.4	100.4	0.94	7.22	5.36
	3M		98.7	99.7	0.94	7.14	5.36
	6M		97.4	97.6	0.94	7.34	5.31

The stability study results impurity profile of Example-1 – latanoprost component at 25 °C/60% RH & 40 °C/75% RH is shown in Table-2.

Table-2:

Related substances of Latanoprost								
		Orlistat Related compound C	Latanoprost witting Impurity	Latanoprost Impurity B	Latanoprost Impurity A	Latanoprost Impurity E	Single max impurity	Total impurities
Specification		-	-	-	-	-	Not more than 1%	Not more than 3%
25 °C/60% RH	Initial	ND	ND	ND	ND	ND	ND	ND
	1M	ND	ND	ND	ND	ND	ND	ND
	2M	ND	ND	ND	BLQ (<0.05)	ND	0.19	0.19
	3M	ND	ND	ND	BLQ (<0.05)	0.13	0.16	0.28
	6M	ND	ND	ND	ND	0.12	0.16	0.40
40 °C/75% RH	1M	ND	ND	ND	ND	0.12	ND	0.12
	2M	ND	ND	ND	ND	0.06	0.19	0.25
	3M	ND	ND	ND	BLQ (<0.05)	0.25	0.18	0.43
	6M	ND	ND	ND	ND	0.39	0.16	0.55

5

ND: Not detected

BLQ: below limit of quantification

The stability study results impurity profile of Example-1 Dutasteride at 25 °C/60% RH & 40 °C/75% RH is shown in Table-3.

10 Table-3:

Related substances of Dutasteride														
		Impurity A	Impurity B	Impurity C	Impurity D	Impurity E	Impurity F	Impurity G	B-Isomer	Impurity H	Impurity I	Dihydro dutasteride	Highest individual unspecified impurity	Total impurities
Specification		-	-	-	-	-	-	-	-	-	-	-	Not more than 1%	Not more than 3%

Related substances of Dutasteride														
		Impurity A	Impurity B	Impurity C	Impurity D	Impurity E	Impurity F	Impurity G	B- Isomer	Impurity H	Impurity I	Dihydro dutasteride	Highest individual unspecified impurity	Total impurities
Initial	-	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND
25 °C/60% RH	1M	ND	ND	0.04	ND	ND	ND	ND	ND	ND	ND	ND	ND	0.04
	2M	ND	ND	0.06	ND	ND	ND	ND	ND	ND	ND	0.03	0.05	0.18
	3M	ND	ND	0.03	ND	ND	ND	ND	ND	ND	ND	0.03	ND	0.06
	6M	ND	ND	0.04	ND	ND	ND	ND	ND	ND	ND	0.03	ND	0.07
40 °C/75% RH	1M	ND	ND	0.04	ND	ND	ND	ND	ND	ND	ND	ND	ND	0.04
	2M	ND	ND	0.06	ND	ND	ND	ND	ND	ND	ND	0.02	0.06	0.18
	3M	ND	ND	0.04	ND	ND	ND	ND	ND	ND	ND	0.03	ND	0.07
	6M	ND	ND	0.05	ND	ND	ND	ND	ND	ND	ND	0.03	ND	0.07

ND: Not detected.

Example-2

Pre-Clinical Trials for Evaluation of Hair Growth

- 5 The hair growth measurement to be conducted in C3H mice (6 – 7 weeks old). C3H mice divided into four groups, each group having about 7 animals as provided in Table 4. The study on the C3H mice is planned for sufficient number of days.

Formulations:

- 1) Placebo Vehicle
 10 2) Dutasteride 0.05%
 3) Latanoprost 0.03%
 4) Topical Dutasteride 0.05% + Latanoprost 0.03%

Table-4:

Group	Treatment Formulation	Number of animals
A	Placebo vehicle	7
B	Topical Dutasteride 0.05%	7
C	Topical Latanoprost 0.03%	7
D	Topical Dutasteride 0.05% + Topical Latanoprost 0.03%	7

- 15 Procedure:

Mice were housed in approximately sized cages in an environmentally controlled room with a 12-hour light-12-hour dark photoperiod and supplied with food and water ad libitum. Animal care was based on the “Guide for the Care and Use of Laboratory Animals”, NIH Publication No. 85-23. Once all mice entered their prolonged telogen/resting phase of the hair

cycle, they were clipped over the dorsal area (Wahl Clippers KM10 series, Blade # 40). Ten female mice per group were clipped while sedated with isoflurane anesthesia.

Determination of Accelerated Onset of Anagen Phase:

The mice were shaved with short hair clipper to hairless on their back as determined by visual inspection at the start of the study. The test articles were applied daily to the shaved areas of the mice daily at 0.2 ml per dose. Both the hair anagen phase and the hair coverage were observed by visual inspection and recorded 5 days a week for each mouse's hair condition (Telogen phase: resting phase in hair growth cycle-shaved skin shown no dark hair bulbs/roots; Anagen phase: anagen follicles, i.e. follicles in the growth state of the hair growth cycle-shaved skin shows dark hair bulbs/roots). A study log (or, Anagen Phase Log) documenting day-to-day observations of mice entering anagen (grey skin, the first visual clue to a new hair growth) were recorded. Treatments continued for 8 weeks.

The groups were ranked in order of highest degree of terminal hair coverage to lowest degree of terminal hair coverage according to the following hair coverage scoring system.

Hair Coverage Scoring System	
Grading	Description
0	No hair at all
1	A few patches of hair growth, less than 1/4 of the dorsal area
2	Hair growth covering about 1/4 of the dorsal area
3	Hair growth covering about 1/2 of the dorsal area
4	Hair growth covering more than 1/2 of the dorsal area
5	Hair growth completely covering treatment area

Histological Analysis:

At the end of experiment, skin was surgically removed from the mice after euthanizing using CO₂ asphyxiation to examine the histological features at the end of the treatment period. The skin samples were fixed in phosphate-buffered 10% formalin for 24 h. The samples were embedded in paraffin blocks. Paraffin section were processed for histological analysis. General histology was examined by hematoxylin and eosin staining. The number of hair follicles were counted and subcutis thickness was measured.

Statistical Analysis:

All statistical analyses were carried out using Prism 8 software (GraphPad Software, San Diego, CA, USA). The hair growth area was evaluated by two-way repeated measures ANOVA followed by Tukey's multiple comparison post hoc test.

5 Results:

i) Hair coverage score

Healthy six to seven weeks old female C3H mice were taken. Mice were shaved on the back to hairless. Next day mice were randomized on the basis of body weight. Hair coverage scoring and application composition of example 1 was initiated. Composition of example 1 was applied for 48 days and scoring was also done all along the study. As depicted in figure 1A, topical application of composition of example 1 containing dutasteride 0.05% w/w & latanoprost 0.03% w/w showed faster hair growth as compared to mono treatment groups & placebo. As depicted in figure 1B, topical application of composition of example 1 containing dutasteride 0.05% w/w & latanoprost 0.03% w/w showed significantly increased hair coverage score terminally as compared to mono treatment groups & placebo (Table 5 – Mean hair coverage score).

Table-5:

Day/Treatment	Placebo	Dutasteride 0.05%	Latanoprost 0.03%	Dutasteride 0.05%+ Latanoprost 0.03%
1	0.0	0.0	0.0	0.0
2	0.0	0.0	0.0	0.0
3	0.0	0.0	0.7	1.1
4	0.0	0.0	0.7	1.1
5	0.0	0.0	0.9	1.3
6	0.0	0.0	0.9	1.7
7	0.0	0.0	0.9	1.7
8	0.0	0.0	0.9	1.9
9	0.0	0.0	0.9	1.9
10	0.0	0.0	0.9	1.9
13	0.0	0.0	0.9	1.9
14	0.0	0.0	0.9	1.9
15	0.0	0.0	0.9	2.1
16	0.0	0.0	0.9	2.1

Day/Treatment	Placebo	Dutasteride 0.05%	Latanoprost 0.03%	Dutasteride 0.05%+ Latanoprost 0.03%
17	0.0	0.0	1.0	2.3
20	0.0	0.0	1.0	2.3
21	0.0	0.0	1.0	2.3
22	0.0	0.0	1.0	2.3
23	0.0	0.0	1.0	2.3
24	0.0	0.0	1.0	2.3
27	0.0	0.0	1.0	2.3
28	0.0	0.0	1.0	2.3
29	0.0	0.0	1.0	2.3
30	0.0	0.0	1.0	2.3
31	0.0	0.0	1.0	2.3
34	0.0	0.0	1.0	2.3
35	0.0	0.0	1.0	2.4
36	0.0	0.0	1.0	2.4
37	0.0	0.0	1.1	2.4
38	0.0	0.0	1.1	2.4
41	0.0	0.0	1.3	2.4
42	0.0	0.0	1.3	2.4
43	0.0	0.0	1.4	2.4
44	0.1	0.0	1.4	2.4
45	0.3	0.0	1.6	2.7
48	0.3	0.0	1.6	2.7
49	0.4	0.3	1.7	2.7

ii) Anagen phase onset log

- After hair growth formulations application initiation, number of mice showing growth phase (anagen phase) from resting phase (telogen phase) were recorded in anagen phase log.
- 5 On day 3 of treatment application, significantly more number of mice showed anagen phase in combination group as compared to mono treatments and placebo vehicle (Figure 2, Table 6).

Table-6:

Day / Treatment	Placebo	Dutasteride 0.05%	Latanoprost 0.03%	Dutasteride 0.05% + Latanoprost 0.03%
1	0	0	0	0
2	0	0	0	0
3	0	0	2	4
4	0	0	2	4
5	0	0	2	4
6	0	0	2	5
7	0	0	2	5
8	0	0	2	5
9	0	0	2	5
10	0	0	2	5
13	0	0	2	5
14	0	0	2	5
15	0	0	2	5
16	0	0	2	5
17	0	0	2	5
20	0	0	2	5
21	0	0	2	5
22	0	0	2	5
23	0	0	2	5
24	0	0	2	5
27	0	0	2	5
28	0	0	2	5
29	0	0	2	5
30	0	0	2	5
31	0	0	2	5
34	0	0	2	5
35	0	0	2	5
36	0	0	2	5
37	0	0	3	5
38	0	0	3	5
41	0	0	4	5

Day / Treatment	Placebo	Dutasteride 0.05%	Latanoprost 0.03%	Dutasteride 0.05% + Latanoprost 0.03%
42	0	0	4	5
43	0	0	4	5
44	1	0	4	5
45	2	0	4	5
48	2	0	4	5
49	2	2	5	5

iii) Histopathology Evaluation

Termination & Necropsy:

At the end of experiment on day-49, all mice were euthanized by CO₂ asphyxiation. skins were collected, preserved and processed for histopathology evaluation.

Histopathological assessment was performed by qualitative and quantitative (morphometric) evaluation for all 4 mice/group. The qualitative evaluation was performed for skin sectioned at 4µm and stained with hematoxylin and eosin (H&E) stain. The quantitative/morphometric evaluation was performed for same skin section by using Leica LAS software. The number of follicles and dermis thickness was measured for each animal. For each skin section, the number of follicles per 20x microscopic field were counted. A total of 10 different areas for each skin section at 20x microscopic field were evaluated and mean was calculated. For each skin section, the dermal thickness was measured at minimum of 6 different areas and mean was calculated.

15 Table-7:

Groups	G1	G2	G4	G6
Group ID	A	B	C	D
Treatment	Placebo control	Dutasteride (0.05%)	Latanoprost (0.03%)	Dutasteride (0.05%) + Latanoprost (0.03%)
Qualitative Microscopic Evaluation				
Organs with lesion	Incidence of finding			
Number of animals examined	7	7	7	7
Skin - increased number of hair follicles (anagen phase)	2	3	5	6

Groups	G1	G2	G4	G6
Group ID	A	B	C	D
~16 to 30 follicles/20x field	2	2	3	4
~46 to 60 follicles/20x field	0	0	0	1
Skin - increased thickness of dermis	2	4	5	6
~200 - 300 μ M	2	3	2	4
Quantitative / Morphometric Evaluation				
Skin - number of hair follicles per 20x microscopic field (mean of 10 different fields)	14	22	24	28
Skin - thickness of dermis (μ M), (mean of 6 different locations)	174	242	267	270

Figure-7 (placebo treated mice skin histopathology), Figure-8 (dutasteride 0.05% treated mice skin histopathology), Figure-9 (latanoprost 0.03% treated mice skin histopathology), Figure-10 (dutasteride 0.05% + latanoprost 0.03% combination composition treated mice skin histopathology) & Table-7 shows the effect of the topical combination formulation of dutasteride 0.05% and latanoprost 0.03% on the number of skin hair follicles and thickness of dermis in the mice.

As shown in Figure-7 to 10 and the results in Table-7, compared to the placebo group the number of hair follicles and thickness of dermis of mice in the latanoprost 0.03% solution group, dutasteride 0.05% solution group and dutasteride 0.05% + latanoprost 0.03% solution group were significantly increased.

Compared to the latanoprost 0.03% solution group the number of hair follicles and thickness of dermis of mice in dutasteride 0.05% + latanoprost 0.03% solution group is more.

Compared to the dutasteride 0.05% solution group the number of hair follicles and thickness of dermis of mice, in the dutasteride 0.05% + latanoprost 0.03% solution group, was found to be higher.

The results of the embodiment show that the combination formulation of latanoprost and dutasteride in the present invention has better efficacy than a composition of mono latanoprost composition or a dutasteride composition.

The results of the Example-1 show that compared with the mono latanoprost preparation or dutasteride preparation, the topical composition of latanoprost and dutasteride in the present invention has better efficacy; compared with the composition with only latanoprost or only dutasteride.

5 As such, it is evident that androgenetic alopecia patients should dramatically benefit from the combination treatment of dutasteride plus latanoprost.

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

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

15

20

We Claim:

1. A topical composition comprising about 0.01% w/w to about 0.06% w/w latanoprost and about 0.01% w/w to about 0.2% w/w dutasteride and pharmaceutically acceptable vehicle.
- 5 2. The topical composition of claim 1, wherein pharmaceutically acceptable vehicle comprises one or more solvent.
3. The topical composition of claim 2, wherein one or more solvent is of about 2% w/w to about 98% w/w.
4. The topical composition of claim 1, wherein pharmaceutically acceptable vehicle is
10 aqueous.
5. The topical composition of claim 1, wherein pharmaceutically acceptable vehicle is non-aqueous.
6. The topical composition of claim 1, wherein latanoprost is about 0.02% w/w to about 0.05% w/w and dutasteride is about 0.03 to about 0.07% w/w.
- 15 7. The topical composition of claim 1, wherein latanoprost about 0.02% w/w to about 0.05% w/w and dutasteride is about 0.03 to about 0.07% w/w.
8. The topical composition of claim 1, wherein latanoprost is about 0.03% w/w latanoprost and dutasteride is about 0.05% w/w.
9. A method for preventing hair loss and/or stimulating hair growth comprising
20 administering topical composition about 0.01% w/w to about 0.06% w/w latanoprost and about 0.01% w/w to about 0.2% w/w dutasteride and pharmaceutically acceptable vehicle.
10. The method for preventing hair loss and/or stimulating hair growth as claimed in claim 9, wherein the pharmaceutically acceptable vehicle comprises one or more solvent.
- 25 11. The method for preventing hair loss and/or stimulating hair growth as claimed in claim 10, wherein one or more solvent is of about 2% w/w to about 98% w/w.
12. The method for preventing hair loss and/or stimulating hair growth of claim 9, wherein the pharmaceutically acceptable vehicle is aqueous.
13. The method for preventing hair loss and/or stimulating hair growth of claim 9, wherein
30 the pharmaceutically acceptable vehicle is non-aqueous.
14. The method for preventing hair loss and/or stimulating hair growth as claimed in claim 9, wherein latanoprost is about 0.02% w/w to about 0.05% w/w and dutasteride is about 0.03 to about 0.07% w/w.

15. The method for preventing hair loss and/or stimulating hair growth of claim 9, wherein the pharmaceutical composition comprises latanoprost about 0.02% w/w to about 0.05% w/w and dutasteride is about 0.03 to about 0.07% w/w.
- 5 16. The method for preventing hair loss and/or stimulating hair growth of claim 9, wherein the pharmaceutical composition comprises latanoprost is about 0.03% w/w latanoprost and dutasteride is about 0.05% w/w.
17. The method of any one of claims 9-16, wherein the pharmaceutical formulation is administered topically once or twice daily.