METHODS OF TREATING CONDITIONS RELATED TO THE $S1P_1$ RECEPTOR

Provided are methods useful in the treatment of alopecia areata.

Alopecia areata is the most common cause of inflammation-induced hair loss. In the United States, alopecia areata affects approximately 4.5 million people and the incidence rate is estimated to 0.1%-0.2%. The clinical presentation of hair loss is variable. The most common presentation is alopecia areata (90%) with one or more bald circumscribed patches on the scalp. Typically, the affected skin has no sign of inflammation. Short fragile hairs (so-called exclamation point) are often seen in the periphery of lesions. Approximately 7% of patients may progress to alopecia totalis with a total loss of scalp hair or alopecia universalis with hair loss on the scalp and body. A few patients experience a diffuse type of alopecia areata or preferential loss of pigmented hair. Nail changes, including trachonychia, pitted nail, or longitudinal ridges, are seen in 20% of patients. Spontaneous regrowth of hair may occur in 50% of patients within one year and particularly in mild cases.

Alopecia areata has an unpredictable course and there is currently no approved therapy specifically for the disease. Current evidence-based therapy is limited to topical (including injection) or systemic corticosteroids and sensitizing agents such as diphenylcyclopropenone and dinitrochlorobenzene. However, this treatment is only feasible or small areas, and long-term use is often unacceptable and with disappointing efficacy. There is no evidence of efficacy for systemic immunosuppressants such as methotrexate, mycophenolate mofitile, cyclosporine A, or azathioprine. Nor is there robust evidence for topical tacrolimus, cryotherapy, or ultraviolet light A combined with oral psoralens (PUVA).

Alopecia areata has a significant negative impact on quality of life and self-esteem and there is a large unmet medical need for new effective treatment options, as current therapies often provide only transient or marginal symptomatic relief. The present disclosure satisfies this need and provides related advantages as well.

Citation of any reference throughout this application is not to be construed as an admission that such reference is prior art to the present application.

SUMMARY

Provided is a method of treating alopecia areata in an individual in need thereof comprising: administering to the individual in need thereof a pharmaceutical dosage form comprising a therapeutically effective amount of (*R*)-2-(7-(4-cyclopentyl-3-

(trifluoromethyl)benzyloxy)-1,2,3,4-tetrahydrocyclopenta[*b*]indol-3-yl)acetic acid (Compound 1), or a pharmaceutically acceptable salt thereof. In one aspect, the present disclosure refers to use of a pharmaceutical dosage form comprising a therapeutically effective amount of (*R*)-2-(7-(4-cyclopentyl-3-(trifluoromethyl)benzyloxy)-1,2,3,4-tetrahydrocyclopenta[*b*]indol-3-yl)acetic acid (Compound 1), or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for treating alopecia areata (AA) in an individual in need thereof. In another aspect, the present disclosure refers to a compound that is (R)-2-(7-(4-cyclopentyl-3-(trifluoromethyl)benzyloxy)-1,2,3,4-tetrahydrocyclopenta[b]indol-3-yl)acetic acid (Compound 1), or a pharmaceutically acceptable salt thereof, for use in the treatment of alopecia areata in an individual. In some ~~embodiment~~examples, the individual has severe alopecia areata. In some ~~embodiment~~examples, the individual has moderate alopecia areata. In some ~~embodiment~~examples, the individual is administered a therapeutically effective amount of Compound 1, or a pharmaceutically acceptable salt thereof, that is equivalent to about 0.5 to about 5.0 mg of Compound 1. In some ~~embodiment~~examples, the individual is administered a therapeutically effective amount of Compound 1, or a pharmaceutically acceptable salt thereof, that is equivalent to 2 mg of Compound 1. In other ~~embodiment~~examples, the individual is administered a therapeutically effective amount of Compound 1, or a pharmaceutically acceptable salt thereof, that is equivalent to 3 mg of Compound 1. In some ~~embodiment~~examples, the Compound 1, or a pharmaceutically acceptable salt thereof, is administered orally. According to some ~~embodiment~~examples, the therapeutically effective amount of Compound 1, or a pharmaceutically acceptable salt thereof, is administered at a frequency of once per day. According to some ~~embodiment~~examples, the administering results in no serious adverse events. In some ~~embodiment~~examples, the Compound 1, or a pharmaceutically acceptable salt thereof, is administered without substantially inducing an acute heart rate reduction or heart block in the individual. In some ~~embodiment~~examples, the individual has greater than or equal to 50% scalp hair loss. In some ~~embodiment~~examples, the method is therapeutically effective to achieve at least a 50% improvement from the individual's baseline Severity of Alopecia Tool (SALT) score. In some ~~embodiment~~examples, the method is therapeutically effective to achieve at least a 50% improvement from the individual's baseline SALT score in a period of time of at least about 24 weeks.

Also provided is a method of inducing hair regrowth in an individual diagnosed with alopecia areata comprising: administering to the individual in need thereof a pharmaceutical dosage form comprising a therapeutically effective amount of (*R*)-2-(7-(4-cyclopentyl-3-(trifluoromethyl)benzyloxy)-1,2,3,4-tetrahydrocyclopenta[*b*]indol-3-yl)acetic acid (Compound 1), or a pharmaceutically acceptable salt thereof. In some ~~embodiment~~examples, the individual has severe alopecia areata. In some ~~embodiment~~examples, the individual has moderate alopecia areata. In some ~~embodiment~~examples, the individual is administered a therapeutically effective amount of Compound 1, or a pharmaceutically acceptable salt thereof, that is equivalent to about 0.5 to about 5.0 mg of Compound 1. In some ~~embodiment~~examples, the individual is administered a therapeutically effective amount of Compound 1, or a pharmaceutically acceptable salt thereof, that is equivalent to 2 mg of Compound 1. In other ~~embodiment~~examples, the individual is administered a therapeutically effective amount of Compound 1, or a pharmaceutically acceptable salt thereof, that is equivalent to 3 mg of Compound 1. In some ~~embodiment~~examples, the Compound 1, or a pharmaceutically acceptable salt

thereof, is administered orally. According to some ~~embodiment~~examples, the therapeutically effective amount of Compound 1, or a pharmaceutically acceptable salt thereof, is administered at a frequency of once per day. According to some ~~embodiment~~examples, the administering results in no serious adverse events.

These and other ~~aspect~~examples of the ~~invention~~disclosure disclosed herein will be set forth in greater detail as the patent disclosure proceeds.

BRIEF DESCRIPTION OF DRAWINGS

Figure 1: Normal hair cycle is shown in panel A. The hair cycle in alopecia areata is shown in panel B. See Gilhar et al. *NEJM* 2012; 366:1515-25.

Figure 2: Examples of severity of alopecia areata: (**a**) >50% hair loss, (**b**) <50% hair loss, and (**c**) subject with alopecia totalis.

Figure 3: The SALT I aid for determining scalp surface area is shown.

Figure 4: The SALT II aid for determining scalp surface area is shown.

Figure 5: Comparative images of hair follicle epithelium and S1P expression data in an AA patient sample versus a healthy patient sample are illustrated according to Example 3.

Figure 6: Images of $S1P_1^+$ $CD8^+$ cells increase in AA patients are illustrated and shown through data according to Example 3.

Figure 7: Illustrates the effect of Compound 1 on hair cycle staging and hair cycle score as compared to vehicle according to Example 3.

Figure 8a: Demonstrates the effect of Compound 1 on MHC class I in the dermal cup, germinative hair matrix, and outer root sheath in anagen and catagen hair follicles as described in Example 3.

Figure 8b: Demonstrates the effect of Compound 1 on MHC class I in the dermal cup, germinative hair matrix, and outer root sheath in anagen hair follicles as described in Example 3.

Figure 9a: Shows the effect of Compound 1 on MICA in the dermal cup, germinative hair matrix, and outer root sheath in anagen and catagen hair follicles as described in Example 3.

Figure 9b: Demonstrates the effect of Compound 1 on MICA in the dermal cup, germinative hair matrix, and outer root sheath in anagen hair follicles as described in Example 3.

Figure 10: Illustrates the effect of Compound 1 on hair cycle staging and hair cycle score according to Example 3.

Figure 11: Shows the effect of Compound 1 on MHC I in the dermal cup as described in Example 3.

CLAIMS

What is claimed is:

1. ~~A method of treating alopecia areata (AA) in an individual in need thereof comprising: administering to the individual in need thereof~~Use of a pharmaceutical dosage form comprising a therapeutically effective amount of (*R*)-2-(7-(4-cyclopentyl-3-(trifluoromethyl)benzyloxy)-1,2,3,4-tetrahydrocyclopenta[*b*]indol-3-yl)acetic acid (Compound 1), or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for treating alopecia areata (AA) in an individual in need thereof.

2. The use~~method~~ of claim 1, further comprising detecting in the individual an AA-associated biomarker.

~~3. The method of claim 2, wherein the AA-associated biomarker is indicative of severity of alopecia areata.~~

~~4. The method of claim 2, wherein the AA-associated biomarker is indicative of the propensity of the individual to respond to treatment with Compound 1, or a pharmaceutically acceptable salt thereof.~~

~~5.~~3. The use~~method~~ of any one of the above claims, wherein prior to ~~administering~~ administration of Compound 1, or a pharmaceutically acceptable salt thereof, to the individual, the use~~method~~ further comprises selecting the individual based on a level of an AA-associated biomarker.

~~6.~~4. The use~~method~~ of any one of the preceding claims, wherein the administration of Compound 1, or a pharmaceutically acceptable salt thereof, results in a change in a level of an AA-associated biomarker in the individual.

~~7.~~5. The use~~method~~ of any one of the preceding claims, wherein the individual has severe alopecia areata, moderate alopecia areata, diffuse alopecia areata, alopecia areata

monolocularis, alopecia areata multilocularis, ophiasis, alopecia areata barbae, alopecia areata totalis, or alopecia areata universalis.

~~8. The method of any one of the preceding claims, wherein the individual has moderate alopecia areata.~~

~~9. The method of any one of claims 1 to 8, wherein the individual has diffuse alopecia areata.~~

~~10. The method of any one of claims 1 to 8, wherein the individual has alopecia areata monolocularis.~~

~~11. The method of any one of claims 1 to 8, wherein the individual has alopecia areata multilocularis.~~

~~12. The method of any one of claims 1 to 8, wherein the individual has ophiasis.~~

~~13. The method of any one of claims 1 to 8, wherein the individual has alopecia areata barbae.~~

~~14. The method of any one of claims 1 to 7, wherein the individual has alopecia areata totalis.~~

~~15. The method of any one of claims 1 to 7, wherein the individual has alopecia areata universalis.~~

~~16.~~6. The use~~method~~ of any one of the preceding claims, wherein the Compound 1, or a pharmaceutically acceptable salt thereof, is to be administered in combination with a second therapeutic agent or therapy.

~~17.~~7. The use~~method~~ of any one of the preceding claims, wherein the individual has demonstrated an inadequate response to, loss of response to, or intolerance of to at least one therapeutic agent or therapy.

~~18.~~8. The use~~method~~ of any one of the preceding claims, wherein the dosage form is to be administered under fasted conditions.

~~19.~~9. The use~~method~~ of any one of claims 1 to ~~17~~7, wherein the dosage form is to be administered under fed conditions.

~~20.~~10. The use~~method~~ of any one of the preceding claims, wherein the therapeutically effective amount is equivalent to about 0.5 to about 5.0 mg of Compound 1.

~~21. The method of claim 20, wherein the therapeutically effective amount is in an amount equivalent to 2 mg of Compound 1.~~

~~22. The method of claim 20, wherein the individual is administered an amount equivalent to 2 mg of Compound 1 for a first time period and subsequently an amount equivalent to 3 mg of Compound 1 for a second time period.~~

~~23. The method of claim 20, wherein the therapeutically effective amount is in an amount equivalent to 3 mg of Compound 1.~~

~~24.~~11. The use~~method~~ of any one of the preceding claims, wherein the dosage form is to be administered without titration.

~~25.~~12. The use~~method~~ of any one of the preceding claims, wherein the Compound 1, or a pharmaceutically acceptable salt thereof, is to be administered orally.

~~26.~~13. The use~~method~~ of any one of the preceding claims, wherein the Compound 1, or a pharmaceutically acceptable salt thereof, is formulated as a capsule or tablet suitable for oral administration.

~~27.~~14. The use~~method~~ of any one of the preceding claims, wherein the Compound 1, or a pharmaceutically acceptable salt thereof, is selected from:

Compound 1;

a calcium salt of Compound 1; and

an L-arginine salt of Compound 1.

~~28.~~15. The use~~method~~ of claim ~~27~~14, wherein the Compound 1, or a pharmaceutically acceptable salt thereof, is an L-arginine salt of Compound 1, an anhydrous, non-solvated crystalline form of an L-arginine salt of Compound 1, or an anhydrous, non-solvated crystalline form of Compound 1.

~~29. The method of claim 28, wherein the Compound 1, or a pharmaceutically acceptable salt thereof, is an anhydrous, non-solvated crystalline form of an L-arginine salt of Compound 1.~~

~~30. The method of claim 27, wherein the Compound 1, or a pharmaceutically acceptable salt thereof, is an anhydrous, non-solvated crystalline form of Compound 1.~~

~~31.~~16. The use~~method~~ of any one of the preceding claims, wherein the therapeutically effective amount of Compound 1, or a pharmaceutically acceptable salt thereof is to be administered once daily to the individual and/or wherein the use is non-gender specific.

~~32. The method of any one of the preceding claims, wherein the method is non-gender specific.~~

~~33.~~17. The use~~method~~ of any one of the preceding claims, wherein the individual was previously administered at least one therapeutic agent or therapy.

~~34. The method of claim 33, wherein the individual had an inadequate response with, lost response to, or was intolerant to the at least one therapeutic agent or therapy.~~

~~35.~~18. The use~~method~~ of any one of the preceding claims, wherein treating comprises inducing and/or maintaining clinical response and/or inducing and/or maintaining clinical remission.

~~36.~~19. The use~~method~~ of any one of the preceding claims, wherein said ~~administering~~ use results in no serious adverse events.

~~37.~~20. The use~~method~~ of any one of the preceding claims, wherein the Compound 1, or a pharmaceutically acceptable salt thereof, is to be administered without substantially inducing an acute heart rate reduction or heart block in the individual.

~~38.~~21. The use~~method~~ of any one of the preceding claims, further comprising monitoring for adverse events during the administration of the Compound 1, or a pharmaceutically acceptable salt thereof, and optionally, interrupting or terminating the administration of the Compound 1, or a pharmaceutically acceptable salt thereof.

~~39.~~22. The use~~method~~ of any one of Claims 2-~~38~~21, wherein the AA-associated biomarker is selected from at least one of IL-2, IL-10, IL-12, IL-13, IL-17, IL-17A, IL-22, and IFN-γ.

~~40.~~23. The use~~method~~ of any one of the preceding claims, wherein the Compound 1, or a pharmaceutically acceptable salt thereof, is the sole active ingredient in the pharmaceutical dosage form.

~~41.~~24. The use~~method~~ of any one of the preceding claims, wherein the individual has greater than or equal to 50% scalp hair loss.

~~42.~~25. The use~~method~~ of any one of the preceding claims, wherein the use~~method~~ is therapeutically effective to achieve at least a 50% improvement from the individual's baseline Severity of Alopecia Tool (SALT) score.

~~43. The method of claim 42, wherein the method is therapeutically effective to achieve at least a 50% improvement from the individual's baseline SALT score in a period of time of at least about 24 weeks.~~

~~44. The method of claim 43, wherein the method is therapeutically effective to achieve at least a 50% improvement from the individual's baseline SALT score in a period of time of about 24 weeks.~~

~~45.~~26. A compound that is (R)-2-(7-(4-cyclopentyl-3-(trifluoromethyl)benzyloxy)-1,2,3,4-tetrahydrocyclopenta[b]indol-3-yl)acetic acid (Compound 1), or a pharmaceutically

acceptable salt thereof, for use in ~~a method of~~the treatment of alopecia areata in an individual.

~~46. The compound for use according to claim 45, wherein the alopecia areata is moderate to severe alopecia areata.~~

~~47. The compound for use according to claim 45 or claim 46, wherein the alopecia areata is moderate alopecia areata.~~

~~48.~~27. The compound for use according to ~~any one of claims 45-47~~claim 26, wherein the use further comprises administration of a therapeutically effective amount of Compound 1 in an amount equivalent to about 0.5 to about 5.0 mg of Compound 1.

~~49. The compound for use according to claim 48, wherein the therapeutically effective amount is in an amount equivalent to 2 mg of Compound 1.~~

~~50. The compound for use according to claim 48, wherein the therapeutically effective amount is in an amount equivalent to 3 mg of Compound 1.~~

~~51.~~28. The compound for use according to any one of claims ~~45-50~~26-27, wherein the Compound 1 is to be administered to the individual in need thereof at a frequency of once daily.

~~52.~~29. The compound for use according to any one of claims ~~45-51~~26-28, wherein the Compound 1, or a pharmaceutically acceptable salt thereof, is selected from:

Compound 1;

a calcium salt of Compound 1; and

an L-arginine salt of Compound 1.

~~53.~~30. The compound for use according to claim ~~52~~29, wherein the Compound 1, or a pharmaceutically acceptable salt thereof, is an L-arginine salt of Compound 1, an anhydrous, non-solvated crystalline form of an L-arginine salt of Compound 1, or an anhydrous, non-solvated crystalline form of Compound 1.

~~54. The compound for use according to claim 52, wherein the Compound 1, or a pharmaceutically acceptable salt thereof, is an anhydrous, non-solvated crystalline form of an L-arginine salt of Compound 1.~~

~~55. The compound for use according to claim 52, wherein the Compound 1, or a pharmaceutically acceptable salt thereof, is an anhydrous, non-solvated crystalline form of Compound 1.~~