an unmet need for novel pharmaceutical compositions and methods of administering drugs via the pilosebaceous unit.

SUMMARY ~~OF THE INVENTION~~

[0007] The present ~~invention~~ disclosure relates to pharmaceutical compositions for the topical administration of a drug to the pilosebaceous unit and methods for administering the same. The inventors of the present disclosure ~~invention~~ have made the surprising discovery that a pharmaceutical composition comprising small particles of an active pharmaceutical ingredient and a silicone, such as dimethicone or cyclomethicone, can be delivered to the pilosebaceous unit resulting in deeper penetration into the dermis and improved efficacy. In preferred ~~embodiments~~examples, the pharmaceutical composition comprises SHR0302 or spironolactone as an active pharmaceutical ingredient.

[0008] In certain examples ~~embodiments~~ of the present disclosure~~invention~~, a pharmaceutical composition is provided comprising a therapeutically effective amount of an active pharmaceutical ingredient and a silicone selected from the group consisting of dimethicone, cyclomethicone, and combinations thereof. The active pharmaceutical ingredient has a primary particle size distribution that is characterized by a D90 value of less than about 20 µm. In certain examples~~embodiments~~, the pharmaceutical ingredient has a primary particle size distribution that is characterized by a D90 value of less than about 10 µm or more preferably less than about 5 µm. In certain examples~~embodiments~~, the composition comprises about 0.10% w/w to about 7.5% w/w of the active pharmaceutical ingredient. The pharmaceutical compositions of the present disclosure ~~invention~~ can be capable of delivering the active pharmaceutical ingredient to the pilosebaceous unit. In certain examples~~embodiments~~, the active pharmaceutical ingredient is capable of achieving dermal penetration of at least 1 mm in the subject.

[0009] In certain examples ~~embodiments~~ of the present disclosure~~invention~~, a pharmaceutical composition is provided comprising a therapeutically effective amount of SHR0302 or a pharmaceutically acceptable salt thereof. The SHR0302 can have a primary particle size distribution characterized by a D90 value of less than about 20 μm, less than about 10 μm, or more preferably less than about 5 μm. The SHR0302 can further have a primary particle size distribution characterized by a D50 value of less than about 5 μm, less than about 1 μm, or more preferably less than about 0.7 μm. The SHR0302 can further have a primary particle size distribution characterized by a D10 value of less than about 1 μm, less than about 0.5 μm, or more preferably less than about 0.25 μm.

[00010] The pharmaceutical composition further comprises a silicone selected from the group consisting of dimethicone, cyclomethicone, and combinations thereof. In certain examples ~~embodiments~~ of the present disclosure~~invention~~, the pharmaceutical composition comprises SHR0302 suspended in at least one of dimethicone and cyclomethicone.

[00010a] In one aspect, the present disclosure provides a pharmaceutical composition comprising: a therapeutically effective amount of SHR0302 or a pharmaceutically acceptable salt thereof, wherein a primary particle size distribution of the SHR0302 is characterized by a D90 value of less than about 20 μm; and a silicone selected from the group consisting of dimethicone and cyclomethicone.

[00010b] In another aspect, the present disclosure provides a pharmaceutical composition comprising: a therapeutically effective amount of an active pharmaceutical ingredient, wherein a primary particle size distribution of the active pharmaceutical ingredient is characterized by a D90 value of less than about 20 μm; and a silicone selected from the group consisting of dimethicone and cyclomethicone.

[00011] In certain examples~~embodiments~~, the pharmaceutical composition can comprise about 0.10% w/w to about 5% w/w of SHR0302 or a salt thereof. In preferred examples~~embodiments~~, the pharmaceutical composition can comprise from about 0.1% w/w to about 3% w/w of SHR0302 or a salt thereof.

[00012] In certain examples ~~embodiments~~ of the present disclosure~~invention~~, a method of treating alopecia areata in a subject in need thereof is provided. The method comprises topically administering to the subject the pharmaceutical compositions of SHR0302 described herein. In the methods of the present disclosure~~invention~~, the SHR0302 or salt thereof can be delivered to the pilosebaceous unit. In the methods disclosed herein, administration of the pharmaceutical composition can result in dermal penetration of SHR0302 of at least about 1 mm in the subject, and preferably to the depth of the

hair bulb for a terminal hair, about 2 to 3 mm in the subject.

[00012a] In another aspect, the present disclosure provides use of a pharmaceutical composition comprising: (a) a therapeutically effective amount of SHR0302 or a pharmaceutically acceptable salt thereof, wherein a primary particle size distribution of the SHR0302 is characterized by a D90 value of less than about 20 µm; and (b) a silicone selected from the group consisting of dimethicone and cyclomethicone, in the manufacture of a medicament for the treatment of alopecia areata in a subject, wherein said pharmaceutical composition is to be topically administered to the subject.

[00012b] In another aspect, the present disclosure provides pharmaceutical composition comprising: (a) a therapeutically effective amount of SHR0302 or a pharmaceutically acceptable salt thereof, wherein a primary particle size distribution of the SHR0302 is characterized by a D90 value of less than about 20 µm; and (b) a silicone selected from the group consisting of dimethicone and cyclomethicone, for use in therapy.

[00013] In certain examples ~~embodiments~~ of the present disclosure~~invention~~, a pharmaceutical composition is provided comprising a therapeutically effective amount of spironolactone or a pharmaceutically acceptable salt thereof. The spironolactone can have a primary particle size distribution characterized by a D90 value of less than about 6 µm, less than about 1 µm, or more preferably less than about 0.25 µm. The spironolactone can further have a primary particle size distribution characterized by a D50 value of less than about 2.7 µm, less than about 0.75 µm, or more preferably less than about 0.15 µm. The spironolactone can further have a primary particle size distribution characterized by a D10 value of less than about 1.2 µm, less than about 0.50 µm, or more preferably less than about 0.10 µm.

[00014] The pharmaceutical composition further comprises a silicone selected from the group consisting of dimethicone and cyclomethicone. In certain examples ~~embodiments~~ of the present disclosure~~invention~~, the pharmaceutical composition of spironolactone is an oil-in-water emulsion.

[00015] Further, the pharmaceutical composition can comprise about 0.10% w/w to about 7.5% w/w of spironolactone or a salt thereof. In certain examples~~embodiments~~, the pharmaceutical composition can comprise from about 0.5% w/w to about 5% w/w of spironolactone or a salt thereof.

[00016] In certain examples ~~embodiments~~ of the present disclosure~~invention~~, a method of treating acne in a subject in need thereof is provided. In certain examples~~embodiments~~, the subject is a human male or female. In preferred examples~~embodiments~~, the subject is a female human. The method comprises topically administering to the subject the pharmaceutical compositions of spironolactone described herein. In the methods of the present disclosure~~invention~~, the spironolactone or salt thereof can be delivered to the pilosebaceous unit. In the methods disclosed herein, administration of the

CLAIMS

What is claimed is:

1. A pharmaceutical composition comprising:

a therapeutically effective amount of SHR0302 or a pharmaceutically acceptable salt thereof, wherein a primary particle size distribution of the SHR0302 is characterized by a D90 value of less than about 20 μm; and

a silicone selected from the group consisting of dimethicone and cyclomethicone.

2. The pharmaceutical composition of claim 1, wherein the composition is a suspension.

3. The pharmaceutical composition of claim 1, wherein the composition comprises about 0.10% w/w to about 5% w/w of SHR0302 or a salt thereof.

4. The pharmaceutical composition of claim 1, wherein a primary particle size distribution of the SHR0302 is characterized by a D90 value of less than about 10 μm.

5. The pharmaceutical composition of claim 1, wherein a primary particle size distribution of the SHR0302 is characterized by a D90 value of less than about 5 μm.

6. The pharmaceutical composition of claim 1, wherein a primary particle size distribution of the SHR0302 is characterized by a D50 value of less than about 1.0 μm.

7. The pharmaceutical composition of claim 1, wherein a primary particle size distribution of the SHR0302 is characterized by a D10 value of less than about 0.50 µm.

8. Use of ~~A method of treating alopecia areata in a subject in need thereof comprising:~~

~~topically administering to the subject~~ a pharmaceutical composition comprising: (a) a therapeutically effective amount of SHR0302 or a pharmaceutically acceptable salt thereof, wherein a primary particle size distribution of the SHR0302 is characterized by a D90 value of less than about 20 µm; and (b) a silicone selected from the group consisting of dimethicone and cyclomethicone, in the manufacture of a medicament for the treatment of alopecia areata in a subject, wherein said pharmaceutical composition is to be topically administered to the subject.

9. The ~~method~~ use of claim 8, wherein the SHR0302 is to be delivered to ~~the~~ a pilosebaceous unit.

10. The use ~~method~~ of claim 8, wherein the SHR0302 is to achieve~~s~~ dermal penetration of at least 1 mm in the subject.

11. The use ~~method~~ of claim 8, wherein the pharmaceutical composition is a suspension.

12. The use ~~method~~ of claim 8, wherein the composition comprises about 0.10% w/w to about 5% w/w of SHR0302 or a salt thereof.

13. The use ~~method~~ of claim 8, wherein a primary particle size distribution of the SHR0302 is characterized by a D90 value of less than about 10 µm.

14. The use ~~method~~ of claim 8, wherein a primary particle size distribution of the SHR0302 is characterized by a D90 value of less than about 5 µm.

15. The use ~~method~~ of claim 8, wherein a primary particle size distribution of the SHR0302 is characterized by a D50 value of less than about 1.0 µm.

16. The use ~~method~~ of claim 8, wherein a primary particle size distribution of the SHR0302 is characterized by a D10 value of less than about 0.50 µm.

17. A pharmaceutical composition comprising:

(a) a therapeutically effective amount of SHR0302 or a pharmaceutically acceptable salt thereof, wherein a primary particle size distribution of the SHR0302 is characterized by a D90 value of less than about 20 µm; and

(b) a silicone selected from the group consisting of dimethicone and cyclomethicone,

for use in therapy.

~~17.~~18. A pharmaceutical composition comprising:

a therapeutically effective amount of an active pharmaceutical ingredient, wherein a primary particle size distribution of the active pharmaceutical ingredient is characterized by a D90 value of less than about 20 µm; and

a silicone selected from the group consisting of dimethicone and cyclomethicone.

~~18.~~19. The pharmaceutical composition of claim ~~17~~18, wherein the composition comprises about 0.10% w/w to about 5% w/w of the active pharmaceutical ingredient.

~~19.~~20. The pharmaceutical composition of claim ~~17~~18, wherein a primary particle size distribution of the active pharmaceutical ingredient is characterized by a D90 value of less than about 10 µm.

~~20.~~21. The pharmaceutical composition of claim ~~17~~18, wherein a primary particle size distribution of the active pharmaceutical ingredient is characterized by a D90 value of less than about 5 µm.

~~21.~~22. The pharmaceutical composition of claim ~~17~~18, wherein the active pharmaceutical ingredient is delivered to ~~the~~ a pilosebaceous unit.

~~22.~~23. The pharmaceutical composition of claim ~~17~~18, wherein the active pharmaceutical ingredient is capable of achieving dermal penetration of at least 1 mm in the subject.