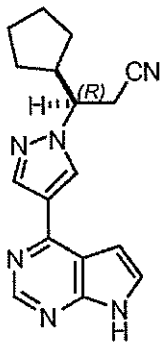
including interleukins -2, -4, -6, -7, -12, -15, -18, and -23 as well as GM-CSF and IFNg, signal through the Janus (JAK) kinases (*Adv Pharmacol.* 2000;47:113-74). As such, blocking signal transduction at the level of JAK kinases may result in therapeutic benefits in patients suffering from psoriasis or other immune disorders of the skin.

Given the usefulness of JAK inhibitors in the treatment of skin disorders, there is a need for improved topical formulations of JAK inhibitors. In particular, there is a need for stable, easily applied formulations for JAK inhibitors with good skin permeation characteristics. The formulations of the invention, as well the methods described herein are directed toward this need and other ends.

SUMMARY

A potent JAK1/JAK2 inhibitor, (R)-3-(4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl)-3-cyclopentylpropanenitrile, and its pharmaceutically acceptable salts, has previously been described in U.S. Patent No. 7,598,257, U.S. Patent Publ. No. 2009/0181959, and U.S. Patent Publ. No. 2008/0312259, each of which is incorporated herein by reference in its entirety. The present invention describes an oil-in-water formulation of (R)-3-(4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl)-3-cyclopentylpropanenitrile suitable for topical administration and treatment of skin disorders.



Accordingly, the present invention provides, *inter alia*, an oil-in-water emulsion cream pharmaceutical formulation for topical skin application, comprising:

an oil-in-water emulsion, ~~and a therapeutically effective amount of~~ comprising water, an oil component, an emulsifier component, a solvent component, and a therapeutic agent which is (R)-3-cyclopentyl-3-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-

1H-pyrazol-1-yl]propanenitrile, or a pharmaceutically acceptable salt thereof, wherein the oil-in-water emulsion forms a cream, wherein the therapeutic agent is present in an amount of about 0.5% to about 1.5% by weight of the formulation on a free base basis, and wherein the solvent component is a liquid substance or mixture of liquid substances capable of dissolving (R)-3-(4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl)-3-cyclopentylpropanenitrile.

are also intended to fall within the scope of the appended claims. Each reference cited in the present application is incorporated herein by reference in its entirety.

Where the terms "comprise", "comprises", "comprised" or "comprising" are used in this specification , they are to be interpreted as specifying the presence of the stated features, integers, steps or components referred to, but not to preclude the presence or addition of one or more other feature, integer, step, component or group thereof.

Further, any prior art reference or statement provided in the specification is not to be taken as an admission that such art constitutes, or is to be understood as constituting, part of the common general knowledge.

WHAT IS CLAIMED IS:

1. An oil-in-water emulsion cream pharmaceutical formulation for topical skin application, comprising an oil-in-water emulsion~~; and~~

~~a therapeutically effective amount of~~, comprising water, an oil component, an emulsifier component, a solvent component, and a therapeutic agent which is (R)-3-cyclopentyl-3-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]propanenitrile, or a pharmaceutically acceptable salt thereof, wherein the oil-in-water emulsion forms a cream, wherein the therapeutic agent is present in an amount of about 0.5% to about 1.5% by weight of the formulation on a free base basis, and wherein the solvent component is a liquid substance or mixture of liquid substances capable of dissolving (R)-3-(4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl)-3-cyclopentylpropanenitrile.

~~2. A pharmaceutical formulation according to claim 1, wherein the emulsion comprises water, an oil component, and an emulsifier component.~~

~~3. A pharmaceutical formulation according to claim 2, wherein the oil component is present in an amount of about 10% to about 40% by weight of the formulation.~~

~~4. A pharmaceutical formulation according to claim 2, wherein the oil component is present in an amount of about 17% to about 27% by weight of the formulation.~~

~~5.~~2. ~~A~~ The pharmaceutical formulation according to claim ~~2~~1, wherein the oil component is present in an amount of about 20% to about 27% by weight of the formulation.

~~6.~~3. The~~A~~ pharmaceutical formulation according to any one of claims ~~2 to 5~~1 to 2, wherein the oil component comprises one or more substances independently selected from petrolatums, fatty alcohols, mineral oils, triglycerides, and silicone oils.

~~7.~~4. The~~A~~ pharmaceutical formulation according to any one of claims ~~2 to 5~~1 to 2, wherein the oil component comprises one or more substances independently selected from white

petrolatum, cetyl alcohol, stearyl alcohol, light mineral oil, medium chain triglycerides, and dimethicone.

~~8.~~5. The~~A~~ pharmaceutical formulation according to claim ~~2~~1, wherein the oil component comprises an occlusive agent component.

~~9. A pharmaceutical formulation according to claim 8, wherein the occlusive agent component is present in an amount of about 2% to about 15% by weight of the formulation.~~

~~10.~~6. The ~~A~~ pharmaceutical formulation according to claim ~~8~~5, wherein the occlusive agent component is present in an amount of about 5% to about 10% by weight of the formulation.

~~11. A pharmaceutical formulation according to any one of claims 8 to 10, wherein the occlusive agent component comprises a petrolatum.~~

~~12.~~7. The~~A~~ pharmaceutical formulation according to any one of claims ~~8 to 10~~5 to 6, wherein the occlusive agent component comprises white petrolatum.

~~13.~~8. The~~A~~ pharmaceutical formulation according to claim ~~2~~1, wherein the oil component comprises a stiffening agent component.

~~14. A pharmaceutical formulation according to claim 13, wherein the stiffening agent component is present in an amount of about 2% to about 8% by weight of said formulation.~~

~~15. A pharmaceutical formulation according to claim 13, wherein the stiffening agent component is present in an amount of about 3% to about 6% by weight of said formulation.~~

~~16.~~9. The ~~A~~ pharmaceutical formulation according to claim ~~13~~8, wherein the stiffening agent component is present in an amount of about 4% to about 7% by weight of said formulation.

~~17. A pharmaceutical formulation according to any one of claims 13 to 16, wherein the stiffening agent component comprises one or more substances independently selected from fatty alcohols.~~

~~18. A pharmaceutical formulation according to any one of claims 13 to 16, wherein the stiffening agent component comprises one or more substances independently selected from C_{12-20} fatty alcohols.~~

~~19. A pharmaceutical formulation according to any one of claims 13 to 16, wherein the stiffening agent component comprises one or more substances independently selected from C_{16-18} fatty alcohols.~~

~~20.~~10. The~~A~~ pharmaceutical formulation according to any one of claims ~~13~~8 to ~~16~~9, wherein the stiffening agent component comprises one or more substances independently selected from cetyl alcohol and stearyl alcohol.

~~21.~~11. A pharmaceutical formulation according to claim ~~2~~1, wherein the oil component comprises an emollient component.

~~22. A pharmaceutical formulation according to claim 21, wherein the emollient component is present in an amount of about 5% to about 15% by weight of the formulation.~~

~~23.~~12. The~~A~~ pharmaceutical formulation according to claim ~~21~~11, wherein the emollient component is present in an amount of about 7% to about 13% by weight of the formulation.

~~24. A pharmaceutical formulation according to any one of claims 21 to 23, wherein the emollient component comprises one or more substances independently selected from mineral oils and triglycerides.~~

~~25. A pharmaceutical formulation according to any one of claims 21 to 23, wherein the emollient component comprises one or more substances independently selected from light mineral oil and medium chain triglycerides.~~

~~26.~~13. The~~A~~ pharmaceutical formulation according to any one of claims ~~21~~ 11 to ~~23~~12, wherein the emollient component comprises one or more substances independently selected from light mineral oil, medium chain triglycerides, and dimethicone.

~~27. A pharmaceutical formulation according to any one of claims 2 to 26, wherein the water is present in an amount of about 35% to about 65% by weight of the formulation.~~

~~28. A pharmaceutical formulation according to any one of claims 2 to 26, wherein the water is present in an amount of about 40% to about 60% by weight of the formulation.~~

~~29.~~14. The~~A~~ pharmaceutical formulation according to any one of claims ~~2~~ 1 to ~~26~~13, wherein the water is present in an amount of about 45% to about 55% by weight of the formulation.

~~30. A pharmaceutical formulation according to any one of claims 2 to 29, wherein the emulsifier component is present in an amount of about 1% to about 9% by weight of the formulation.~~

~~31. A pharmaceutical formulation according to any one of claims 2 to 29, wherein the emulsifier component is present in an amount of about 2% to about 6% by weight of the formulation.~~

~~32. A pharmaceutical formulation according to any one of claims 2 to 29, wherein the emulsifier component is present in an amount of about 3% to about 5% by weight of the formulation.~~

~~33.~~15. The~~A~~ pharmaceutical formulation according to any one of claims ~~2~~ 1 to ~~29~~14, wherein the emulsifier component is present in an amount of about 4% to about 7% by weight of the formulation.

~~34.~~16. The~~A~~ pharmaceutical formulation according to any one of claims ~~2~~ 1 to ~~29~~15, wherein the pharmaceutical formulation comprises an emulsifier component and a stiffening agent component, wherein the combined amount of emulsifier component and stiffening agent component is at least about 8% by weight of the formulation.

~~35. A pharmaceutical formulation according to any one of claims 2 to 34, wherein the emulsifier component comprises one or more substances independently selected from glyceryl fatty esters and sorbitan fatty esters.~~

~~36.~~17. The~~A~~ pharmaceutical formulation according to any one of claims ~~2~~ 1 to ~~34~~16, wherein the emulsifier component comprises one or more substances independently selected from glyceryl stearate, and polysorbate 20.

~~37.~~18. The~~A~~ pharmaceutical formulation according to any one of claims 1 to ~~36~~17, wherein said pharmaceutical formulation further comprises a stabilizing agent component.

~~38. A pharmaceutical formulation according to claim 37, wherein the stabilizing agent component is present in an amount of about 0.05% to about 5% by weight of the formulation.~~

~~39. A pharmaceutical formulation according to claim 37, wherein the stabilizing agent component is present in an amount of about 0.1% to about 2% by weight of the formulation.~~

~~40.~~19. The~~A~~ pharmaceutical formulation according to claim ~~37~~18, wherein the stabilizing agent component is present in an amount of about 0.3 to about 0.5% by weight of the formulation.

~~41. A pharmaceutical formulation according to any one of claims 37 to 40, wherein the stabilizing agent component comprises one or more substances independently selected from polysaccharides.~~

~~42.~~20. The~~A~~ pharmaceutical formulation according to any one of claims ~~37~~18 to ~~40~~19, wherein the stabilizing agent component comprises xanthan gum.

~~43. A pharmaceutical formulation according to any one of claims 1 to 42, wherein said pharmaceutical formulation further comprises a solvent component.~~

~~44. A pharmaceutical formulation according to claim 43, wherein the solvent component is present in an amount of about 10% to about 35% by weight of the formulation.~~

~~45. A pharmaceutical formulation according to claim 43, wherein the solvent component is present in an amount of about 15% to about 30% by weight of the formulation.~~

~~46.~~21. The~~A~~ pharmaceutical formulation according to ~~claim 43~~any one of claims 1 to 20, wherein the solvent component is present in an amount of about 20% to about 25% by weight of the formulation.

~~47. A pharmaceutical formulation according to any one of claims 43 to 46, wherein the solvent component comprises one or more substances independently selected from alkylene glycols and polyalkylene glycols.~~

48.22. TheA pharmaceutical formulation according to any one of claims 43 to 46claim 21, wherein the solvent component comprises one or more substances independently selected from propylene glycol and polyethylene glycol.

49. A pharmaceutical formulation according to any one of claims 1 to 48, wherein the therapeutic agent agent is present in an amount of about 0.5% to about 1.5% by weight of the formulation on a free base basis.

50.23. The A pharmaceutical formulation according to any one of claims 1 to 4822, wherein said therapeutic agent is present in an amount of about 0.5% by weight of the formulation on a free base basis.

51.24. TheA pharmaceutical formulation according to any one of claims 1 to 4822, wherein said therapeutic agent is present in an amount of about 1% by weight of the formulation on a free base basis.

52.25. TheA pharmaceutical formulation according to any one of claims 1 to 4822, wherein said therapeutic agent is present in an amount of about 1.5% by weight of the formulation on a free base basis.

53.26. TheA pharmaceutical formulation according to any one of claims 1 to 5225, wherein said therapeutic agent is (R)-3-cyclopentyl-3-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]propanenitrile phosphoric acid salt.

54.27. TheA pharmaceutical formulation according to claim 1, comprising:

from about 35% to about 65% of water by weight of the formulation;

from about 10% to about 40% of an oil component by weight of the formulation;

from about 1% to about 9% of an emulsifier component by weight of the formulation;

from about 10% to about 35% of a solvent component by weight of the formulation;

from about 0.05% to about 5% of a stabilizing agent component by weight of the formulation; and

from about 0.5% to about 1.5% of (R)-3-cyclopentyl-3-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]propanenitrile, or a pharmaceutically acceptable salt thereof, by weight of the formulation on a free base basis.

~~55.~~28. The~~A~~ pharmaceutical formulation according to claim 1, comprising:

from about 40% to about 60% of water by weight of the formulation;

from about 15% to about 30% of an oil component by weight of the formulation;

from about 2% to about 6% of an emulsifier component by weight of the formulation;

from about 15% to about 30% of a solvent component by weight of the formulation;

from about 0.1% to about 2% of a stabilizing agent component by weight of the formulation; and

from about 0.5% to about 1.5% of (R)-3-cyclopentyl-3-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]propanenitrile, or a pharmaceutically acceptable salt thereof, by weight of the formulation on a free base basis.

~~56.~~29. The~~A~~ pharmaceutical formulation according to claim 1, comprising:

from about 45% to about 55% of water by weight of the formulation;

from about 17% to about 27% of an oil component by weight of the formulation;

from about 3% to about 5% of an emulsifier component by weight of the formulation;

from about 20% to about 25% of a solvent component by weight of the formulation;

from about 0.3% to about 0.5% of a stabilizing agent component by weight of the formulation; and

from about 0.5% to about 1.5% of (R)-3-cyclopentyl-3-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]propanenitrile, or a pharmaceutically acceptable salt thereof, by weight of the formulation on a free base basis.

~~57.~~30. The~~A~~ pharmaceutical formulation according to claim 1, comprising:

from about 45% to about 55% of water by weight of the formulation;

from about 17% to about 27% of an oil component by weight of the formulation;

from about 4% to about 7% of an emulsifier component by weight of the formulation;

from about 20% to about 25% of a solvent component by weight of the formulation;

from about 0.3% to about 0.5% of a stabilizing agent component by weight of the formulation; and

from about 0.5% to about 1.5% of (R)-3-cyclopentyl-3-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]propanenitrile, or a pharmaceutically acceptable salt thereof, by weight of the formulation on a free base basis.

~~58.~~31. The~~A~~ pharmaceutical formulation according to any one of claims ~~54~~27 to ~~57~~30, wherein:

the oil component comprises one or more substances independently selected from petrolatums, fatty alcohols, mineral oils, triglycerides, and dimethicones;

the emulsifier component comprises one or more substances independently selected from glyceryl fatty esters and sorbitan fatty esters;

the solvent component comprises one or more substances independently selected from alkylene glycols and polyalkylene glycols; and

the stabilizing agent component comprises one or more substances independently selected from polysaccharides.

~~59.~~32. The~~A~~ pharmaceutical formulation according to any one of claims 27 to 30~~54 to 57~~, wherein:

the oil component comprises one or more substances independently selected from white petrolatum, cetyl alcohol, stearyl alcohol, light mineral oil, medium chain triglycerides, and dimethicone;

the emulsifier component comprises one or more substances independently selected from glyceryl stearate and polysorbate 20;

the solvent component comprises one or more substances independently selected from propylene glycol and polyethylene glycol; and

the stabilizing agent component comprises xanthan gum.

~~60.~~33. The~~A~~ pharmaceutical formulation according to claim 1, comprising:

from about 35% to about 65% of water by weight of the formulation;

from about 2% to about 15% of an occlusive agent component by weight of the formulation;

from about 2% to about 8% of a stiffening agent component by weight of said formulation;

from about 5% to about 15% of an emollient component by weight of the formulation;

from about 1% to about 9% of an emulsifier component by weight of the formulation;

from about 0.05% to about 5% of a stabilizing agent component by weight of the formulation;

from about 10% to about 35% of a solvent component by weight of the formulation; and

from about 0.5% to about 1.5% of (R)-3-cyclopentyl-3-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]propanenitrile, or a pharmaceutically acceptable salt thereof, by weight of the formulation on a free base basis.

~~61.~~34. The~~A~~ pharmaceutical formulation according to claim 1, comprising:

from about 40% to about 60% of water by weight of the formulation;

from about 5% to about 10% of an occlusive agent component by weight of the formulation;

from about 2% to about 8% of a stiffening agent component by weight of said formulation;

from about 7% to about 12% of an emollient component by weight of the formulation;

from about 2% to about 6% of an emulsifier component by weight of the formulation;

from about 0.1% to about 2% of a stabilizing agent by weight of the formulation;

from about 15% to about 30% of a solvent component by weight of the formulation; and

from about 0.5% to about 1.5% of (R)-3-cyclopentyl-3-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]propanenitrile, or a pharmaceutically acceptable salt thereof, by weight of the formulation on a free base basis.

~~62.~~35. The~~A~~ pharmaceutical formulation according to claim 1, comprising:

from about 45% to about 55% of water by weight of the formulation;

from about 5% to about 10% of an occlusive agent component by weight of the formulation;

from about 3% to about 6% of a stiffening agent component by weight of said formulation;

from about 7% to about 13% of an emollient component by weight of the formulation;

from about 3% to about 5% of an emulsifier component by weight of the formulation;

from about 0.3% to about 0.5% of a stabilizing agent component by weight of the formulation;

from about 20% to about 25% of a solvent component by weight of the formulation; and

from about 0.5% to about 1.5% of (R)-3-cyclopentyl-3-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]propanenitrile, or a pharmaceutically acceptable salt thereof, by weight of the formulation on a free base basis.

~~63.~~36. The~~A~~ pharmaceutical formulation according to claim 1, comprising:

from about 45% to about 55% of water by weight of the formulation;

from about 5% to about 10% of an occlusive agent component by weight of the formulation;

from about 4% to about 7% of a stiffening agent component by weight of said formulation;

from about 7% to about 13% of an emollient component by weight of the formulation;

from about 4% to about 7% of an emulsifier component by weight of the formulation;

from about 0.3% to about 0.5% of a stabilizing agent component by weight of the formulation;

from about 20% to about 25% of a solvent component by weight of the formulation; and

from about 0.5% to about 1.5% of (R)-3-cyclopentyl-3-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]propanenitrile, or a pharmaceutically acceptable salt thereof, by weight of the formulation on a free base basis.

~~64.~~37. The~~A~~ pharmaceutical formulation according to claim 1, comprising:

from about 45% to about 55% of water by weight of the formulation;

about 7% of an occlusive agent component by weight of the formulation;

from about 4.5% to about 5% of a stiffening agent component by weight of said formulation;

about 10% of an emollient component by weight of the formulation;

from about 4% to about 4.5% of an emulsifier component by weight of the formulation;

about 0.4% of a stabilizing agent component by weight of the formulation;

about 22% of a solvent component by weight of the formulation; and

from about 0.5% to about 1.5% of (R)-3-cyclopentyl-3-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]propanenitrile, or a pharmaceutically acceptable salt thereof, by weight of the formulation on a free base basis.

~~65.~~38. The~~A~~ pharmaceutical formulation according to any one of claims ~~60~~-33 to ~~64~~37, wherein the combined amount of the stiffening agent component and the emulsifier component is at least about 8% by weight of the formulation.

~~66.~~39. The~~A~~ pharmaceutical formulation according to any one of claims ~~60~~-33 to ~~65~~37, wherein:

the occlusive agent component comprises a petrolatum;

the stiffening agent component comprises one or more substances independently selected from one or more fatty alcohols;

the emollient component comprises one or more substances independently selected from mineral oils and triglycerides;

the emulsifier component comprises one or more substances independently selected from glyceryl fatty esters and sorbitan fatty esters;

the stabilizing agent component comprises one or more substances independently selected from polysaccharides; and

the solvent component comprises one or more substances independently selected from alkylene glycols and polyalkylene glycols.

~~67.~~40. The~~A~~ pharmaceutical formulation according to any one of claims ~~60~~-33 to ~~65~~37, wherein:

the occlusive agent component comprises white petrolatum;

the stiffening agent component comprises one or more substances independently selected from cetyl alcohol and stearyl alcohol;

the emollient component comprises one or more substances independently selected from light mineral oil, medium chain triglycerides, and dimethicone;

the emulsifier component comprises one or more substances independently selected from glyceryl stearate and polysorbate 20;

the stabilizing agent component comprises xanthan gum; and

the solvent component comprises one or more substances independently selected from propylene glycol and polyethylene glycol.

~~68. A pharmaceutical formulation according to any one of claims 1 to 67, further comprising an antimicrobial preservative component.~~

~~69. A pharmaceutical formulation according to claim 68, wherein the antimicrobial preservative component is present in an amount of about 0.05% to about 3% by weight of the formulation.~~

~~70. A pharmaceutical formulation according to claim 68, wherein the antimicrobial preservative component is present in an amount of about 0.1% to about 1% by weight of the formulation.~~

~~71. A pharmaceutical formulation according to any one of claims 68 to 70, wherein the antimicrobial preservative component comprises one or more substances independently selected from alkyl parabens and phenoxyethanol.~~

~~72. A pharmaceutical formulation according to any one of claims 68 to 70, wherein the antimicrobial preservative component comprises one or more substances independently selected from methyl paraben, propyl paraben, and phenoxyethanol.~~

~~73. A pharmaceutical formulation according to any one of claims 1 to 72, further comprising a chelating agent component.~~

~~74. A pharmaceutical formulation according to claim 73, wherein the chelating agent component comprises edetate disodium.~~

~~75.~~41. Use of a pharmaceutical formulation according to any one of claims 1 to 40, for preparation of a medicament for ~~A method of~~ treating a skin disorder in a patient in need thereof~~, comprising applying a pharmaceutical formulation according to any one of claims 1 to 74 to an area of skin of said patient~~.

~~76.~~42. The ~~method~~ use of claim ~~75~~41, wherein the skin disorder is atopic dermatitis or psoriasis.

~~77.~~43. The ~~method~~ use of claim ~~75~~41, wherein the skin disorder is psoriasis.

~~78.~~44. The ~~method~~ use of claim ~~75~~41, wherein said skin disorder is skin sensitization, skin irritation, skin rash, contact dermatitis or allergic contact sensitization.

~~79.~~45. The ~~method~~ use of claim ~~75~~41, wherein said skin disorder is a bullous skin disorder.

~~80.~~46. The ~~method~~ use of claim ~~79~~45, wherein said bullous skin disorder is pemphigus vulgaris (PV) or bullous pemphigoid (BP).

~~81. A pharmaceutical formulation according to any one of claims 1 to 74 for use in treatment of a skin disorder in a patient in need thereof.~~

~~82. Use of a pharmaceutical formulation according to any one of claims 1 to 74 for the preparation of a medicament for use in treatment of a skin disorder in a patient in need thereof.~~