

RUXOLITINIB FOR USE IN THE TREATMENT OF PRURIGO NODULARIS

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This application claims priority to U.S. Application No. 18/500,214, filed November 2, 2023, which is a continuation-in-part of U.S. Application No. 18/480,898, filed October 4, 2023, which claims priority to U.S. Application No. 17/735,273, filed May 3, 2022, which claims the benefit of U.S. Provisional Application No. 63/183,225, filed May 3, 2021, all of which are incorporated herein by reference in their entirety.

TECHNICAL FIELD

This disclosure relates to ruxolitinib, or a pharmaceutically acceptable salt thereof, for use thereof in treating prurigo nodularis.

BACKGROUND

15 Prurigo nodularis (PN) is a chronic skin disorder characterized by firm, dome-shaped, intensely pruritic nodules ranging in size from a few millimeters to several centimeters. The nodules are often symmetrically distributed on the extensor surfaces of the arms and legs and on the trunk. PN has an estimated prevalence of 72 per 100,000 persons in the US, based on people with health insurance. Reports vary on whether it more frequently in women versus
20 men or occurs equally in men and women. People with darker or greater degrees of pigmentation in their skin are substantially more likely to have PN than patients with lighter or less pigmentation in their skin. In particular, one study found that African American patients were 3.4 times more likely to have PN than Caucasian patients.

Quality of life can be substantially negatively impacted by PN. In particular, quality
25 of life issues include sleep disturbance, impact on job performance, and avoidance of social activities. In addition, the burden of systemic comorbidities in prurigo nodularis often exceeds that of other inflammatory skin disorders (e.g., atopic dermatitis or psoriasis). Prurigo nodularis is associated with increased rates of mental health (specifically anxiety and

5 depression), endocrine, cardiovascular, and renal disorders, as well as HIV and malignancy.

Approximately half of all patients with PN report a history of atopic dermatitis.

Pharmacologic therapy with first-generation sedating antihistamines (e.g., hydroxyzine, diphenhydramine) administered at bedtime may be useful in controlling nocturnal pruritus. Both selective serotonin reuptake inhibitors and tricyclic antidepressants
10 are also employed for chronic pruritus, especially when a component of depression is present.

Super-potent topical corticosteroids are considered first-line therapy. Patients with widespread disease may be given phototherapy. Patients with recalcitrant PN may be given systemic treatments including systemic immunosuppressants, thalidomide, lenalidomide, and anticonvulsants. These treatments are associated with potential significant toxicity, and their
15 efficacy in patients with recalcitrant PN has not been established. Accordingly, there is a need to develop new therapies for the treatment of prurigo nodularis. This application addresses this need and others.

DESCRIPTION OF THE DRAWINGS

FIG. 1 depicts a representation of skin punch biopsies used for the JAK1/JAK2
20 mediated pharmacological inhibition of PN pathophysiology.

FIG. 2 depicts a graphical representation of JAK1/JAK2 mediated pharmacological inhibition of PN pathophysiology using JAK1/JAK2 inhibitor ruxolitinib.

SUMMARY

Provided herein are methods for the treatment of prurigo nodularis in a subject in need
25 thereof, comprising administering to the subject a therapeutically effective amount of ruxolitinib, or a pharmaceutically acceptable salt thereof.

Provided herein is ruxolitinib, or a pharmaceutically acceptable salt thereof, for the treatment of prurigo nodularis in a subject in need thereof.

5 Provided herein is a use of ruxolitinib, or a pharmaceutically acceptable salt thereof,
for manufacture of a medicament for use in treating prurigo nodularis in a subject in need
thereof.

DETAILED DESCRIPTION

 The present invention provides, *inter alia*, a method of treating prurigo nodularis in a
10 subject in need thereof, comprising administering to the subject a therapeutically effective
amount of ruxolitinib, or a pharmaceutically acceptable salt thereof. Ruxolitinib is a
JAK1/JAK2 inhibitor which is selective for JAK1 and JAK2 over JAK3.

 In some embodiments, the ruxolitinib is present in the form of ruxolitinib phosphate.

 In some embodiments, the ruxolitinib is present in the form of ruxolitinib phosphate
15 (1:1 salt).

 In some embodiments, the ruxolitinib, or a pharmaceutically acceptable salt thereof, is
administered topically to an affected skin area.

 In some embodiments, the ruxolitinib, or a pharmaceutically acceptable salt thereof, is
an administered as a topical formulation.

20 In some embodiments, the topical formulation is an administered as a topical
formulation comprising about 0.1% to about 3% of the ruxolitinib, or the pharmaceutically
acceptable salt thereof, on a free base basis.

 In some embodiments, the topical formulation is an administered as a topical
formulation comprising about 0.5% to about 2% of the ruxolitinib, or the pharmaceutically
25 acceptable salt thereof, on a free base basis.

 In some embodiments, the topical formulation is an administered as a topical
formulation comprising about 0.5% to about 1.5% of the ruxolitinib, or the pharmaceutically
acceptable salt thereof, on a free base basis.

5 In some embodiments, the topical formulation is administered as a topical formulation comprising about 0.75% to about 1.5% of the ruxolitinib, or the pharmaceutically acceptable salt thereof, on a free base basis.

 In some embodiments, the topical formulation is administered as a topical formulation comprising about 0.5% of the ruxolitinib, or the pharmaceutically acceptable salt thereof, on a free base basis. In some embodiments, the topical formulation is an administered as a topical formulation comprising about 0.75% of the ruxolitinib, or the pharmaceutically acceptable salt thereof, on a free base basis. In some embodiments, the topical formulation is administered as a topical formulation comprising about 1% of the ruxolitinib, or the pharmaceutically acceptable salt thereof, on a free base basis. In some
10 embodiments, the topical formulation is administered as a topical formulation comprising about 1.5% of the ruxolitinib, or the pharmaceutically acceptable salt thereof, on a free base basis.

 In some embodiments, the topical formulation is administered twice per day (BID). In some embodiments, the topical formulation is administered once per day (QD).

20 In some embodiments, the administering is continued for 12 weeks.

 In some embodiments, the administering is continued every day for 12 weeks.

 In some embodiments, the ruxolitinib, or pharmaceutically acceptable salt thereof, is administered in combination with a further therapeutic agent.

 In some embodiments, the administering comprises administering the ruxolitinib, or pharmaceutically acceptable salt thereof, together with at least one pharmaceutically acceptable carrier or excipient.

 In some embodiments, efficacy of the treatment method disclosed herein can be established based upon an Investigator's Global Assessment (IGA). In some embodiments, the IGA-TS (Investigator's Global Assessment Treatment Success) is defined as an IGA score

5 of 0 or 1 with 2: 2 grade improvement from baseline. Efficacy may be established if by evaluating a proportion of subjects achieving an IGA-TS (IGA of 0 or 1 with a 2-point decrease) at a designated point of time (e.g., week 2, week 4, week 8, or week 16).

In some embodiments, efficacy of the treatment method disclosed herein can be established based upon Itch Numerical Rating Scale (Itch NRS). In some embodiments, efficacy may be demonstrated by achieving a preset proportion of subjects achieving at least 2
10 or 4-point improvement in Itch NRS (e.g., at Week 16). In some embodiments, efficacy may be demonstrated by observing time to 2: 2-point or 2: 4-point improvement from baseline in Itch NRS. In some embodiments, the ruxolitinib, or the pharmaceutically acceptable salt thereof, and/or methods of use described herein result in an improvement in a subject's
15 response to Itch NRS from baseline. In some embodiments, the ruxolitinib, or the pharmaceutically acceptable salt thereof, and/or methods of use described herein result in about a 5%, about a 10%, about a 20%, about a 30%, about a 40%, about a 50%, about a 60%, about a 70%, about a 80%, about a 90%, or about a 95% improvement in a subject's response to Itch NRS from baseline. The itch NRS is a daily patient-reported measure (24-
20 hour recall) of itch intensity. Subjects will be asked to rate the itching severity because of their AD by selecting a number from 0 (no itch) to 10 (worst imaginable itch) that best describes their worst level of itching in the past 24 hours. In a non-limiting example, patients can be issued a hand-held device (eDiary) on which to record itch severity. The patient can be instructed to complete the eDiary each night.

25 In some embodiments, efficacy of the treatment method disclosed herein can be established based upon the Prurigo Activity Score (PAS). In some embodiments, the ruxolitinib, or the pharmaceutically acceptable salt thereof, and/or methods of use described herein result in an improvement in a subject's response in Prurigo Activity Score (PAS) from baseline. In some embodiments, the ruxolitinib, or the pharmaceutically acceptable salt

5 thereof, and/or methods of use described herein result in about a 5%, about a 10%, about a 20%, about a 30%, about a 40%, about a 50%, about a 60%, about a 70%, about a 80%, about a 90%, or about a 95% improvement in a subject's response in Prurigo Activity Score (PAS) from baseline. The activity in terms of percentage of PN lesions with excoriations/crusts on top (reflecting active scratching) and the percentage of healed pruriginous lesions is measured
10 by the subitem "Activity" of PAS in order to quantify change of PN skin lesions.

In some embodiments, efficacy of the treatment method disclosed herein can be established based upon Itchy Quality of Life (Itchy QoL). In some embodiments, the ruxolitinib, or the pharmaceutically acceptable salt thereof, and/or methods of use described herein result in an improvement in a subject's response in Itchy Quality of Life (Itchy QoL)
15 from baseline. In some embodiments, the ruxolitinib, or the pharmaceutically acceptable salt thereof, and/or methods of use described herein result in about a 5%, about a 10%, about a 20%, about a 30%, about a 40%, about a 50%, about a 60%, about a 70%, about a 80%, about a 90%, or about a 95% improvement in a subject's response in Itchy Quality of Life (Itchy QoL) from baseline. ItchyQoL is a pruritus-specific instrument that was developed and
20 validated by Chen et al., Arch Dermatol, 147(10):1153–6 (2011). The 22-question questionnaire can be applied to patients with pruritus, independent of the underlying cause. ItchyQoL is a 3-dimensional instrument, which contains the domains symptoms, functioning and emotions.

In some embodiments, efficacy of the treatment method disclosed herein can be
25 established based upon Dynamic Pruritus Score (DPS). In some embodiments, the ruxolitinib, or the pharmaceutically acceptable salt thereof, and/or methods of use described herein result in an improvement in a subject's response in Dynamic Pruritus Score (DPS) from baseline. In some embodiments, the ruxolitinib, or the pharmaceutically acceptable salt thereof, and/or methods of use described herein result in about a 5%, about a 10%, about a 20%, about a

5 30%, about a 40%, about a 50%, about a 60%, about a 70%, about a 80%, about a 90%, or about a 95% improvement in a subject's response in Dynamic Pruritus Score (DPS) from baseline. The DPS evaluates the change in pruritus intensity, compared with a defined earlier time-point, and is comprised of a horizontal line measuring itch improvement via 11 marks on a scale, each labelled with both a numerical and verbal description.

10 In some embodiments, efficacy of the treatment method disclosed herein can be established based upon patient-reported outcomes (PROs). In some embodiments, efficacy of the treatment method disclosed herein can be established based upon a Dermatology Life Quality Index (DLQI). In some embodiments, the ruxolitinib, or the pharmaceutically acceptable salt thereof, and/or methods of use described herein result in an improvement in a
15 subject's response to DLQI from baseline. In some embodiments, the ruxolitinib, or the pharmaceutically acceptable salt thereof, and/or methods of use described herein result in about a 5%, about a 10%, about a 20%, about a 30%, about a 40%, about a 50%, about a 60%, about a 70%, about a 80%, about a 90%, or about a 95% improvement in a subject's response to DLQI from baseline. A dermatology-specific Quality of Life instrument. It is a validated
20 10-question questionnaire that has been used in over 40 different skin conditions in over 80 countries and is available in over 90 languages.

 In some embodiments, efficacy can be evaluated based upon improvement in a subject's PROMIS Sleep Scale. In some embodiments, the ruxolitinib, or pharmaceutically acceptable salt thereof, and/or methods of use described herein result in an improvement in a
25 subject's response to PROMIS Sleep Scale from baseline. In some embodiments, the ruxolitinib, or the pharmaceutically acceptable salt thereof, and/or methods of use described herein result in about a 5%, about a 10%, about a 20%, about a 30%, about a 40%, about a 50%, about a 60%, about a 70%, about a 80%, about a 90%, or about a 95% improvement in a subject's response to PROMIS Sleep Scale from baseline.

- 5 In some embodiments, the patient has an itch Numerical Rating Scale of at least 4 at baseline.
- In some embodiments, the patient is aged 18 years or older.
- In some embodiments, the patient has a clinical diagnosis of prurigo nodularis for at least 3 months at baseline.
- 10 In some embodiments, the patient has at least 6 or greater pruriginous lesions on ≥ 2 different body areas at baseline.
- In some embodiments, the patient has an IGA-CPG-S score of 2 or greater at baseline.
- In some embodiments, the patient has a PN-related WI-NRS score of at least 7 or greater.
- 15 In some embodiments, the patient has a body surface area involvement of prurigo nodularis of 20% or less at baseline. In some embodiments, the patient has:
- an IGA-CPG-S score of 2 or greater at baseline;
- a PN-related WI-NRS score of at least 7 or greater; and
- a body surface area involvement of prurigo nodularis of 20% or less at baseline.
- 20 In some embodiments, the patient achieves a WI-NRS4 response at Week 8 of administration, and the WI-NRS4 response is a ≥ 4 -point improvement (reduction) in WI-NRS score from baseline.
- In some embodiments, the patient achieves a WI-NRS4 response at Week 12 of administration, and the WI-NRS4 response is a ≥ 4 -point improvement (reduction) in WI-
- 25 NRS score from baseline.
- In some embodiments, the patient achieves an overall-TS at Week 8 and the overall-TS is both a WI-NRS4 response and an IGA-CPG-S-TS, wherein the WI-NRS4 response is a ≥ 4 -point improvement (reduction) in WI-NRS score from baseline and the IGA-CPG-S-TS is defined as an IGA-CPG-S score of 0 or 1 with a ≥ 2 grade improvement from baseline.

5 In some embodiments, the patient achieves an overall-TS at Week 12 and the overall-TS is both a WI-NRS4 response and an IGA-CPG-S-TS, wherein the WI-NRS4 response is a ≥ 4 -point improvement (reduction) in WI-NRS score from baseline and the IGA-CPG-S-TS is defined as an IGA-CPG-S score of 0 or 1 with a ≥ 2 grade improvement from baseline.

 In some embodiments, the patient achieves an IGA-CPG-S-TS at Week 8 and the
10 IGA-CPG-S-TS is defined as an IGA-CPG-S score of 0 or 1 with a ≥ 2 grade improvement from baseline.

 In some embodiments, the patient achieves an IGA-CPG-S-TS at Week 12 and the IGA-CPG-S-TS is defined as an IGA-CPG-S score of 0 or 1 with a ≥ 2 grade improvement from baseline.

15 In some embodiments, the present disclosure is directed to methods for treating prurigo nodularis in a patient, the method comprising administering to the patient a therapeutically effective amount of ruxolitinib, or a pharmaceutically acceptable salt thereof, wherein the patient achieves a WI-NRS4 response at Week 12 of administration, and the WI-NRS4 response is a ≥ 4 -point improvement (reduction) in WI-NRS score from baseline.

20 In some embodiments, the present disclosure is directed to methods for treating prurigo nodularis in a patient, the method comprising administering to the patient a therapeutically effective amount of ruxolitinib, or a pharmaceutically acceptable salt thereof, wherein the patient achieves a WI-NRS4 response at Week 4 and the WI-NRS4 response is a ≥ 4 -point improvement (reduction) in WI-NRS score from baseline. In some embodiments,
25 the patient achieves the WI-NRS4 response at Week 6. In some embodiments, the patient achieves the WI-NRS4 response at Week 8. In some embodiments, the patient achieves the WI-NRS4 response at Week 12.

 In some embodiments, the present disclosure is directed to methods for treating prurigo nodularis in a patient, the method comprising administering to the patient a

5 therapeutically effective amount of ruxolitinib, or a pharmaceutically acceptable salt thereof, wherein the patient achieves an overall-TS at Week 12 and the overall-TS is both a WI-NRS4 response and an IGA-CPG-S-TS, wherein the WI-NRS4 response is a ≥ 4 -point improvement (reduction) in WI-NRS score from baseline and the IGA-CPG-S-TS is defined as an IGA-CPG-S score of 0 or 1 with a ≥ 2 grade improvement from baseline.

10 In some embodiments, the present disclosure is directed to methods for treating prurigo nodularis in a patient, the method comprising administering to the patient a therapeutically effective amount of ruxolitinib, or a pharmaceutically acceptable salt thereof, wherein the patient achieves an IGA-CPG-S-TS at Week 12 and the IGA-CPG-S-TS is defined as an IGA-CPG-S score of 0 or 1 with a ≥ 2 grade improvement from baseline.

15 In some embodiments, the present disclosure is directed to methods for treating prurigo nodularis in a patient, the method comprising administering to the patient a therapeutically effective amount of ruxolitinib, or a pharmaceutically acceptable salt thereof, wherein the patient achieves a WI-NRS4 response on Day 7. In some embodiments, the patient achieves a WI-NRS4 response on Day 8. In some embodiments, the patient achieves a
20 WI-NRS4 response on Day 9. In some embodiments, the patient achieves a WI-NRS4 response on Day 10. In some embodiments, the patient achieves a WI-NRS4 response on Day 11. In some embodiments, the patient achieves a WI-NRS4 response on Day 12. In some embodiments, the patient achieves a WI-NRS4 response on Day 13. In some embodiments, the patient achieves a WI-NRS4 response on Day 14.

25 In some embodiments, the present disclosure is directed to methods for treating prurigo nodularis in a patient, the method comprising administering to the patient a therapeutically effective amount of ruxolitinib, or a pharmaceutically acceptable salt thereof, wherein the patient achieves a WI-NRS4 response at each postbaseline visit. In some embodiments, the postbaseline visit ranges from 2 weeks to 12 weeks. In some embodiments,

5 the postbaseline visit is 2 weeks. In some embodiments, the postbaseline visit is 4 weeks. In some embodiments, the postbaseline visit is 8 weeks. In some embodiments, the postbaseline visit is 12 weeks.

In some embodiments, the present disclosure is directed to methods for treating prurigo nodularis in a patient, the method comprising administering to the patient a
10 therapeutically effective amount of ruxolitinib, or a pharmaceutically acceptable salt thereof, wherein the patient achieves a change from baseline in WI-NRS score at each postbaseline visit. In some embodiments, the postbaseline visit ranges from 2 weeks to 12 weeks. In some embodiments, the postbaseline visit is 2 weeks. In some embodiments, the postbaseline visit is 4 weeks. In some embodiments, the postbaseline visit is 8 weeks. In some embodiments,
15 the postbaseline visit is 12 weeks.

In some embodiments, the present disclosure is directed to methods for treating prurigo nodularis in a patient, the method comprising administering to the patient a therapeutically effective amount of ruxolitinib, or a pharmaceutically acceptable salt thereof, wherein the patient achieves a ≥ 2 -point improvement from baseline in WI-NRS score in a
20 time ranging from 1 week to 12 weeks. In some embodiments, the time is 1 week. In some embodiments, the time is 2 weeks. In some embodiments, the time is 3 weeks. In some embodiments, the time is 4 weeks. In some embodiments, the time is 5 weeks. In some embodiments, the time is 6 weeks. In some embodiments, the time is 7 weeks. In some embodiments, the time is 8 weeks. In some embodiments, the time is 9 weeks. In some
25 embodiments, the time is 10 weeks. In some embodiments, the time is 11 weeks. In some embodiments, the time is 12 weeks.

In some embodiments, the present disclosure is directed to methods for treating prurigo nodularis in a patient, the method comprising administering to the patient a therapeutically effective amount of ruxolitinib, or a pharmaceutically acceptable salt thereof,

5 wherein the patient achieves a ≥ 4 -point improvement from baseline in WI-NRS score in a time ranging from 1 week to 12 weeks. In some embodiments, the time is 1 week. In some embodiments, the time is 2 weeks. In some embodiments, the time is 3 weeks. In some embodiments, the time is 4 weeks. In some embodiments, the time is 5 weeks. In some
10 embodiments, the time is 6 weeks. In some embodiments, the time is 7 weeks. In some embodiments, the time is 8 weeks. In some embodiments, the time is 9 weeks. In some embodiments, the time is 10 weeks. In some embodiments, the time is 11 weeks. In some embodiments, the time is 12 weeks.

In some embodiments, the present disclosure is directed to methods for treating prurigo nodularis in a patient, the method comprising administering to the patient a
15 therapeutically effective amount of ruxolitinib, or a pharmaceutically acceptable salt thereof, wherein the patient achieves a ≥ 2 -point improvement (reduction) in Skin Pain NRS score from baseline. In some embodiments, the patient achieves a ≥ 3 -point improvement (reduction) in Skin Pain NRS score from baseline. In some embodiments, the patient achieves a ≥ 4 -point improvement (reduction) in Skin Pain NRS score from baseline.

20 In some embodiments, the present disclosure is directed to methods for treating prurigo nodularis in a patient, the method comprising administering to the patient a therapeutically effective amount of ruxolitinib, or a pharmaceutically acceptable salt thereof, wherein the patient achieves a change from baseline in Skin Pain NRS score at each postbaseline visit. In some embodiments, the postbaseline visit ranges from 2 weeks to 12
25 weeks. In some embodiments, the postbaseline visit is 2 weeks. In some embodiments, the postbaseline visit is 4 weeks. In some embodiments, the postbaseline visit is 8 weeks. In some embodiments, the postbaseline visit is 12 weeks.

In some embodiments, the present disclosure is directed to methods for treating prurigo nodularis in a patient, the method comprising administering to the patient a

5 therapeutically effective amount of ruxolitinib, or a pharmaceutically acceptable salt thereof,
wherein the patient achieves an IGA-CPG-A score of 0 or 1 with at least a 2 grade
improvement (reduction) at each postbaseline visit. In some embodiments, the postbaseline
visit ranges from 2 weeks to 12 weeks. In some embodiments, the postbaseline visit is 2
weeks. In some embodiments, the postbaseline visit is 4 weeks. In some embodiments, the
10 postbaseline visit is 8 weeks. In some embodiments, the postbaseline visit is 12 weeks.

In some embodiments, the present disclosure is directed to methods for treating
prurigo nodularis in a patient, the method comprising administering to the patient a
therapeutically effective amount of ruxolitinib, or a pharmaceutically acceptable salt thereof,
wherein the patient achieves > 75% healed lesions from PAS at each postbaseline visit. In
15 some embodiments, the postbaseline visit ranges from 2 weeks to 12 weeks. In some
embodiments, the postbaseline visit is 2 weeks. In some embodiments, the postbaseline visit
is 4 weeks. In some embodiments, the postbaseline visit is 8 weeks. In some embodiments,
the postbaseline visit is 12 weeks.

In some embodiments, the present disclosure is directed to methods for treating
20 prurigo nodularis in a patient, the method comprising administering to the patient a
therapeutically effective amount of ruxolitinib, or a pharmaceutically acceptable salt thereof,
wherein the patient achieves a change from baseline in a Dermatology Life Quality Index
(DLQI) score at each postbaseline visit. In some embodiments, the postbaseline visit ranges
from 2 weeks to 12 weeks. In some embodiments, the postbaseline visit is 2 weeks. In some
25 embodiments, the postbaseline visit is 4 weeks. In some embodiments, the postbaseline visit
is 8 weeks. In some embodiments, the postbaseline visit is 12 weeks.

In some embodiments, the present disclosure is directed to methods for treating
prurigo nodularis in a patient, the method comprising administering to the patient a
therapeutically effective amount of ruxolitinib, or a pharmaceutically acceptable salt thereof,

5 wherein the patient achieves a change from baseline in EQ-5D-5L score at each postbaseline visit. In some embodiments, the postbaseline visit ranges from 2 weeks to 12 weeks. In some embodiments, the postbaseline visit is 2 weeks. In some embodiments, the postbaseline visit is 4 weeks. In some embodiments, the postbaseline visit is 8 weeks. In some embodiments, the postbaseline visit is 12 weeks.

10 In some embodiments, the patient is aged 18 or older.

The term "about" means "approximately" (e.g., plus or minus approximately 10% of the indicated value).

In some embodiments, the ruxolitinib, or the pharmaceutically acceptable salt thereof, is administered as one or more sustained release dosage forms each comprising the
15 ruxolitinib, or the pharmaceutically acceptable salt thereof.

The embodiments described herein are intended to be combined in any suitable combination as if the embodiments are multiply dependent claims (e.g., the embodiments related to ruxolitinib and doses of the same, the embodiments related to any salt forms of the compounds disclosed herein, the embodiments related to the individual types of cytokine
20 related diseases or disorders, and the embodiments related to composition and/or administration can be combined in any combination).

All possible combinations are not separately listed herein merely for the sake of brevity.

Compounds described herein can also include isotopically-labeled compounds of the
25 disclosure. An "isotopically" or "radio-labeled" compound is a compound of the disclosure where one or more atoms are replaced or substituted by an atom having an atomic mass or mass number different from the atomic mass or mass number typically found in nature (i.e., naturally occurring). Suitable radionuclides that may be incorporated in compounds of the present disclosure include but are not limited to ^2H (also written as D for deuterium), ^3H (also

5 written as T for tritium), ^{11}C , ^{13}C , ^{14}C , ^{13}N , ^{15}N , ^{15}O , ^{17}O , ^{18}O , ^{18}F , ^{35}S , ^{36}Cl , ^{82}Br , ^{75}Br , ^{76}Br ,
 ^{77}Br , ^{123}I , ^{124}I , ^{125}I and ^{131}I . For example, one or more hydrogen atoms in a compound of the
present disclosure can be replaced by deuterium atoms (e.g., one or more hydrogen atoms of a
 C_{1-6} alkyl group of Formulae (I), (II), or (III) can be optionally substituted with deuterium
atoms, such as $-\text{CD}_3$ being substituted for $-\text{CH}_3$). The term, "compound," as used herein is
10 meant to include all stereoisomers, geometric isomers, tautomers, and isotopes of the
structures depicted, unless the name indicates a specific stereoisomer. Compounds herein
identified by name or structure as one particular tautomeric form are intended to include other
tautomeric forms unless otherwise specified.

All compounds, and pharmaceutically acceptable salts thereof, can be found together
15 with other substances such as water and solvents (e.g. hydrates and solvates) or can be
isolated.

In some embodiments, the compounds described herein, or salts thereof, are
substantially isolated. By "substantially isolated" is meant that the compound is at least
partially or substantially separated from the environment in which it was formed or detected.
20 Partial separation can include, for example, a composition enriched in the compounds
described herein. Substantial separation can include compositions containing at least about
50%, at least about 60%, at least about 70%, at least about 80%, at least about 90%, at least
about 95%, at least about 97%, or at least about 99% by weight of the compounds described
herein, or salt thereof. Methods for isolating compounds and their salts are routine in the art.

25 The phrase "pharmaceutically acceptable" is employed herein to refer to those
compounds, materials, compositions, and/or dosage forms which are, within the scope of
sound medical judgment, suitable for use in contact with the tissues of human beings and
animals without excessive toxicity, irritation, allergic response, or other problem or
complication, commensurate with a reasonable benefit/risk ratio.

5 The expressions, “ambient temperature” and “room temperature” or “rt” as used herein, are understood in the art, and refer generally to a temperature, e.g. a reaction temperature, that is about the temperature of the room in which the reaction is carried out, for example, a temperature from about 20 °C to about 30 °C.

 The present invention also includes pharmaceutically acceptable salts of the
10 compounds described herein. As used herein, “pharmaceutically acceptable salts” refers to derivatives of the disclosed compounds wherein the parent compound is modified by converting an existing acid or base moiety to its salt form. Examples of pharmaceutically acceptable salts include, but are not limited to, mineral or organic acid salts of basic residues such as amines; alkali or organic salts of acidic residues such as carboxylic acids; and the like.
15 The pharmaceutically acceptable salts of the present invention include the conventional non-toxic salts of the parent compound formed, for example, from non-toxic inorganic or organic acids. The pharmaceutically acceptable salts of the present invention can be synthesized from the parent compound which contains a basic or acidic moiety by conventional chemical methods. Generally, such salts can be prepared by reacting the free acid or base forms of
20 these compounds with a stoichiometric amount of the appropriate base or acid in water or in an organic solvent, or in a mixture of the two; generally, non-aqueous media like ether, ethyl acetate, alcohols (e.g., methanol, ethanol, iso-propanol, or butanol) or acetonitrile (ACN) are preferred. Lists of suitable salts are found in *Remington's Pharmaceutical Sciences*, 17th ed., Mack Publishing Company, Easton, Pa., 1985, p. 1418 and *Journal of Pharmaceutical*
25 *Science*, 66, 2 (1977), each of which is incorporated herein by reference in its entirety.

 As used herein, the term “subject”, “individual,” or “patient,” used interchangeably, refers to any animal, including mammals, preferably mice, rats, other rodents, rabbits, dogs, cats, swine, cattle, sheep, horses, or primates, and most preferably humans. In some embodiments, the “subject,” “individual,” or “patient” is in need of said treatment.

5 In some embodiments, the ruxolitinib, or the pharmaceutically acceptable salt thereof, is administered in a therapeutically effective amount. As used herein, the phrase “therapeutically effective amount” refers to the amount of active compound or pharmaceutical agent that elicits the biological or medicinal response that is being sought in a tissue, system, animal, individual or human by a researcher, veterinarian, medical doctor or
10 other clinician.

 As used herein, the term “treating” or “treatment” refers to one or more of (1) inhibiting the disease; for example, inhibiting a disease, condition or disorder in an individual who is experiencing or displaying the pathology or symptomatology of the disease, condition or disorder (i.e., arresting further development of the pathology and/or symptomatology); (2)
15 ameliorating the disease; for example, ameliorating a disease, condition or disorder in an individual who is experiencing or displaying the pathology or symptomatology of the disease, condition or disorder (i.e., reversing the pathology and/or symptomatology) such as decreasing the severity of disease.

 In some embodiments, the ruxolitinib, or the pharmaceutically acceptable salt thereof,
20 can prevent prurigo nodularis in an individual who may be predisposed to the disease. The term “preventing” refers to blocking the occurrence of disease in a patient who may be predisposed to the disease but does not yet experience or display the pathology or symptomatology of the disease.

Combination Therapies

25 The methods described herein can further comprise administering one or more additional therapeutic agents. The one or more additional therapeutic agents can be administered to a patient simultaneously or sequentially. The one or more additional therapeutic agents can be administered using different methods (e.g., topically).

5 In some embodiments, the additional therapeutic agent is selected from JAK inhibitors. Additional JAK inhibitors may include ATI-50002 (JAK1/3 selective). Additional JAK inhibitors may include PF-06651600 (JAK3 selective). Additional JAK inhibitors may include PF06700841 (JAK1/TYK2 selective). Additional JAK inhibitors may include baricitinib (JAK1/JAK2 selective). Additional JAK inhibitors may include TYK2 selective
10 inhibitors.

 In some embodiments, the additional therapeutic agent is selected from antioxidants. Antioxidants may be selected from pseudocatalase, vitamin E, vitamin C, ubiquinone, lipoic acid, Polypodium leucotomos, catalase/superoxide dismutase combination, and Ginkgo biloba. In some embodiments, antioxidants may be further administered in combination with
15 phototherapy. The administration of antioxidants during or before phototherapy aims to counteract the oxidative stress induced by UV radiation itself, increasing the phototherapy effectiveness.

 In some embodiments, the additional therapeutic agent includes anti-histamines.

 In some embodiments, the additional therapeutic agent is an antimetabolite.
20 Antimetabolites may include 5-fluorouracil.

 In some embodiments, the additional therapeutic agent is selected from topical corticosteroids, immunomodulators, calcineurin inhibitors, and phototherapy. In some embodiments, the additional therapies are systemic steroids or immunosuppressants.

 In some embodiments, the additional therapeutic agent includes steroids (e.g., orally
25 administered steroids) including systemic steroids. Steroid treatment may include oral steroid minipulse therapy (e.g., using betamethasone and/or dexamethasone).

 In some embodiments, topical corticosteroids are selected from augmented betamethasone dipropionate, clobetasol propionate, diflorasone diacetate, halobetasol

- 5 propionate amcinonide, betamethasone valerate, desoximetasone, diflorasone diacetate, fluocinolone acetonide, halcinonide, and triamcinolone acetonide.

 In some embodiments, the additional therapeutic agent includes immunomodulators.

Immunomodulators may include anti-IL15 therapy (e.g., AMG 714 monoclonal antibody).

Immunomodulators may include anti-IL36 therapy (e.g., imsidolimab and spesolimab).

- 10 Immunomodulators may include anti-TNFalpha therapy (e.g., etanercept and infliximab).

 In some embodiments, immunomodulators are selected from apremilast, crisaborole, afamelanotide, minocycline, zinc, tofacitinib, AMG 714 monoclonal antibodies, imsidolimab, spesolimab, cyclosporine, etanercept, infliximab, cyclophosphamide, ciclosporin, methotrexate, and sodium oxo-dihydro-acridinylacetate (ODHAA).

- 15 In some embodiments, calcineurin inhibitors are selected from tacrolimus (FK-506) and pimecrolimus.

 In some embodiments, phototherapy includes exposure to ultraviolet (e.g., excimer lamps or lasers).

 In some embodiments, the additional therapeutic agent is a Janus kinase inhibitor. In

- 20 some embodiments, the Janus kinase inhibitor is administered topically.

 In some embodiments, the additional therapeutic agent is a Neurokinin 1 receptor antagonists (e.g., Aprepitant).

 In some embodiments, the additional therapeutic agent include anti-IL-4 / IL-13 antibodies. In some embodiments, anti-IL-4 / IL-13 antibodies are selected from dupilumab,

- 25 lebrikizumab and tralokinumab.

 In some embodiments, the additional therapeutic agent include anti-IL-5 antibodies. In some embodiments, anti-IL-5 antibodies are selected from benralizumab, mepolizumab, and reslizumab.

5 In some embodiments, the additional therapeutic agent include anti-IL-31 antibodies.

In some embodiments, anti-IL-31 antibodies include nemolizumab.

In some embodiments, the additional therapeutic agent is an IL-6 antagonist or receptor antagonist. In some embodiments, the IL-6 receptor antagonist is tocilizumab.

Pharmaceutical Formulations and Dosage Forms

10 When employed as pharmaceuticals, the ruxolitinib, or the pharmaceutically acceptable salt thereof, can be administered in the form of a pharmaceutical composition. These compositions can be prepared in a manner well known in the pharmaceutical art, and can be administered by a variety of routes, depending upon whether local or systemic treatment is desired and upon the area to be treated. Administration may be topical (including

15 transdermal, epidermal, ophthalmic and to mucous membranes including intranasal, vaginal and rectal delivery), pulmonary (e.g., by inhalation or insufflation of powders or aerosols, including by nebulizer; intratracheal or intranasal), oral or parenteral. Parenteral administration includes intravenous, intraarterial, subcutaneous, intraperitoneal intramuscular or injection or infusion; or intracranial, e.g., intrathecal or intraventricular, administration.

20 Parenteral administration can be in the form of a single bolus dose, or may be, for example, by a continuous perfusion pump. Pharmaceutical compositions and formulations for topical administration may include transdermal patches, ointments, lotions, creams, gels, drops, suppositories, sprays, foams, liquids and powders. Conventional pharmaceutical carriers, aqueous, powder or oily bases, thickeners and the like may be necessary or desirable.

25 This invention also includes pharmaceutical compositions which contain, as the active ingredient, the ruxolitinib, or the pharmaceutically acceptable salt thereof, described herein, or a pharmaceutically acceptable salt thereof, in combination with one or more pharmaceutically acceptable carriers (excipients). In some embodiments, the composition is suitable for topical administration. In making the compositions, the active ingredient is typically mixed with an

5 excipient, diluted by an excipient or enclosed within such a carrier in the form of, for
example, a capsule, sachet, paper, or other container. When the excipient serves as a diluent,
it can be a solid, semi-solid, or liquid material, which acts as a vehicle, carrier or medium for
the active ingredient. Thus, the compositions can be in the form of tablets, pills, powders,
lozenges, sachets, cachets, elixirs, suspensions, emulsions, solutions, syrups, aerosols (as a
10 solid or in a liquid medium), ointments containing, for example, up to 10% by weight of the
active compound, soft and hard gelatin capsules, suppositories, sterile injectable solutions,
and sterile packaged powders.

 In preparing a formulation, the active compound can be milled to provide the
appropriate particle size prior to combining with the other ingredients. If the active compound
15 is substantially insoluble, it can be milled to a particle size of less than 200 mesh. If the active
compound is substantially water soluble, the particle size can be adjusted by milling to
provide a substantially uniform distribution in the formulation, e.g., about 40 mesh.

 The ruxolitinib, or the pharmaceutically acceptable salt thereof, may be milled using
known milling procedures such as wet milling to obtain a particle size appropriate for tablet
20 formation and for other formulation types. Finely divided (nanoparticulate) preparations can
be prepared by processes known in the art, e.g., see International App. No. WO 2002/000196.

 The compositions can be formulated in a unit dosage form, each dosage containing a
set amount of the active ingredient as the free form or a salt form. The term “unit dosage
forms” refers to physically discrete units suitable as unitary dosages for human subjects and
25 other mammals, each unit containing a predetermined quantity of active material calculated to
produce the desired therapeutic effect, in association with a suitable pharmaceutical
excipient.

 Similar dosages may be used of the compounds described herein in the methods and
uses of the invention.

5 The active compound can be effective over a wide dosage range and is generally administered in a pharmaceutically effective amount. It will be understood, however, that the amount of the compound actually administered will usually be determined by a physician, according to the relevant circumstances, including the condition to be treated, the chosen route of administration, the actual compound administered, the age, weight, and response of
10 the individual patient, the severity of the patient's symptoms, and the like.

 For preparing solid compositions such as tablets, the principal active ingredient is mixed with a pharmaceutical excipient to form a solid preformulation composition containing a homogeneous mixture of a compound of the present invention. When referring to these preformulation compositions as homogeneous, the active ingredient is typically dispersed
15 evenly throughout the composition so that the composition can be readily subdivided into equally effective unit dosage forms such as tablets, pills and capsules. This solid preformulation is then subdivided into unit dosage forms of the type described above containing from, for example, about 0.1 to about 1000 mg of the active ingredient of the present invention.

20 The tablets or pills of the present invention can be coated or otherwise compounded to provide a dosage form affording the advantage of prolonged action. For example, the tablet or pill can comprise an inner dosage and an outer dosage component, the latter being in the form of an envelope over the former. The two components can be separated by an enteric layer which serves to resist disintegration in the stomach and permit the inner component to pass
25 intact into the duodenum or to be delayed in release. A variety of materials can be used for such enteric layers or coatings, such materials including a number of polymeric acids and mixtures of polymeric acids with such materials as shellac, cetyl alcohol, and cellulose acetate.

5 The liquid forms in which the compounds and compositions of the present invention can be incorporated for administration orally or by injection include aqueous solutions, suitably flavored syrups, aqueous or oil suspensions, and flavored emulsions with edible oils such as cottonseed oil, sesame oil, coconut oil, or peanut oil, as well as elixirs and similar pharmaceutical vehicles.

10 Compositions for inhalation or insufflation include solutions and suspensions in pharmaceutically acceptable, aqueous or organic solvents, or mixtures thereof, and powders. The liquid or solid compositions may contain suitable pharmaceutically acceptable excipients as described *supra*. In some embodiments, the compositions are administered by the oral or nasal respiratory route for local or systemic effect. Compositions can be nebulized by use of
15 inert gases. Nebulized solutions may be breathed directly from the nebulizing device or the nebulizing device can be attached to a face mask, tent, or intermittent positive pressure breathing machine. Solution, suspension, or powder compositions can be administered orally or nasally from devices which deliver the formulation in an appropriate manner.

 Topical formulations can contain one or more conventional carriers. In some
20 embodiments, ointments can contain water and one or more hydrophobic carriers selected from, for example, liquid paraffin, polyoxyethylene alkyl ether, propylene glycol, white Vaseline, and the like. Carrier compositions of creams can be based on water in combination with glycerol and one or more other components, e.g., glycerinmonostearate, PEG-glycerinmonostearate and cetylstearyl alcohol. Gels can be formulated using isopropyl
25 alcohol and water, suitably in combination with other components such as, for example, glycerol, hydroxyethyl cellulose, and the like.

 The amount of compound or composition administered to a patient will vary depending upon what is being administered, the purpose of the administration, such as prophylaxis or therapy, the state of the patient, the manner of administration, and the like. In

5 therapeutic applications, compositions can be administered to a patient already suffering from a disease in an amount sufficient to cure or at least partially arrest the symptoms of the disease and its complications. Effective doses will depend on the disease condition being treated as well as by the judgment of the attending clinician depending upon factors such as the severity of the disease, the age, weight and general condition of the patient, and the like.

10 The compositions administered to a patient can be in the form of pharmaceutical compositions described above. These compositions can be sterilized by conventional sterilization techniques, or may be sterile filtered. Aqueous solutions can be packaged for use as is, or lyophilized, the lyophilized preparation being combined with a sterile aqueous carrier prior to administration. The pH of the compound preparations typically will be between 3 and
15 11, more preferably from 5 to 9 and most preferably from 7 to 8. It will be understood that use of certain of the foregoing excipients, carriers, or stabilizers will result in the formation of pharmaceutical salts.

The therapeutic dosage of a compound of the present invention can vary according to, for example, the particular use for which the treatment is made, the manner of administration
20 of the compound, the health and condition of the patient, and the judgment of the prescribing physician. The proportion or concentration of a compound described herein in a pharmaceutical composition can vary depending upon a number of factors including dosage, chemical characteristics (e.g., hydrophobicity), and the route of administration. The dosage is likely to depend on such variables as the type and extent of progression of the disease or
25 disorder, the overall health status of the particular patient, the relative biological efficacy of the compound selected, formulation of the excipient, and its route of administration. Effective doses can be extrapolated from dose-response curves derived from *in vitro* or animal model test systems.

5 The compositions of the invention can further include one or more additional
pharmaceutical agents such as a chemotherapeutic, steroid, anti-inflammatory compound, or
immunosuppressant, examples of which are listed herein.

 In some embodiments, the topical formulation is a cream formulation. In some
embodiments, the cream formulation is an oil-in-water emulsion. In some embodiments, the
10 cream is a solubilized cream. In some embodiments, the cream has a pH from about 2.8 to
about 3.6. In the context of pH, “about” refers to ± 0.3 (preferably ± 0.2 or more preferably $\pm$
0.1). In some embodiments, the cream comprises an oil-in-water emulsion, comprising 1.5%
(w/w) on a free base basis of ruxolitinib phosphate.

 In some embodiments, the cream is an oil-in-water emulsion as described in US
15 2015/0250790, which is incorporated herein by reference in its entirety. In particular,
Examples 3-6 of US 2015/0250790 (and particularly Tables 3-5 and accompanying text) are
incorporated herein by reference.

 In some embodiments, the oil component is present in an amount of about 10% to
about 40% by weight of the emulsion.

20 In some embodiments, the oil component is present in an amount of about 10% to
about 24% by weight of the emulsion.

 In some embodiments, the oil component is present in an amount of about 15% to
about 24% by weight of the emulsion.

 In some embodiments, the oil component is present in an amount of about 18% to
25 about 24% by weight of the emulsion.

 In some embodiments, the oil component comprises one or more substances
independently selected from petrolatums, fatty alcohols, mineral oils, triglycerides, and
silicone oils.

5 In some embodiments, 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.

 In some embodiments, the oil component comprises an occlusive agent component.

 In some embodiments, the occlusive agent component is present in an amount of about
10 2% to about 15% by weight of the emulsion.

 In some embodiments, the occlusive agent component is present in an amount of about 5% to about 10% by weight of the emulsion.

 In some embodiments, the occlusive agent component comprises one or more substances selected from fatty acids (e.g., lanolin acid), fatty alcohols (e.g., lanolin alcohol),
15 hydrocarbon oils & waxes (e.g., petrolatum), polyhydric alcohols (e.g., propylene glycol), silicones (e.g., dimethicone), sterols (e.g., cholesterol), vegetable or animal fat (e.g., cocoa butter), vegetable wax (e.g., Carnauba wax), and wax ester (e.g., bees wax).

 In some embodiments, the occlusive agent component comprises one or more substances selected from lanolin acid fatty alcohols, lanolin alcohol, petrolatum, propylene
20 glycol, dimethicone, cholesterol, cocoa butter, Carnauba wax, and bees wax.

 In some embodiments, the occlusive agent component comprises petrolatum.

 In some embodiments, the occlusive agent component comprises white petrolatum.

 In some embodiments, the oil component comprises a stiffening agent component.

 In some embodiments, the stiffening agent component is present in an amount of about
25 2% to about 8% by weight of the emulsion.

 In some embodiments, the stiffening agent component is present in an amount of about 3% to about 6% by weight of the emulsion.

 In some embodiments, the stiffening agent component is present in an amount of about 4% to about 7% by weight of the emulsion.

5 In some embodiments, the stiffening agent component comprises one or more substances independently selected from fatty alcohols.

 In some embodiments, the stiffening agent component comprises one or more substances independently selected from C₁₂₋₂₀ fatty alcohols.

 In some embodiments, the stiffening agent component comprises one or more
10 substances independently selected from C₁₆₋₁₈ fatty alcohols.

 In some embodiments, the stiffening agent component comprises one or more substances independently selected from cetyl alcohol and stearyl alcohol.

 In some embodiments, the oil component comprises an emollient component.

 In some embodiments, the emollient component is present in an amount of about 5%
15 to about 15% by weight of the emulsion.

 In some embodiments, the emollient component is present in an amount of about 7% to about 13% by weight of the emulsion.

 In some embodiments, the emollient component comprises one or more substances independently selected from mineral oils and triglycerides.

20 In some embodiments, the emollient component comprises one or more substances independently selected from light mineral oil and medium chain triglycerides.

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

 In some embodiments, the water is present in an amount of about 35% to about 65%
25 by weight of the emulsion.

 In some embodiments, the water is present in an amount of about 40% to about 60% by weight of the emulsion.

 In some embodiments, the water is present in an amount of about 45% to about 55% by weight of the emulsion.

5 In some embodiments, the emulsifier component is present in an amount of about 1% to about 9% by weight of the emulsion.

 In some embodiments, the emulsifier component is present in an amount of about 2% to about 6% by weight of the emulsion.

 In some embodiments, the emulsifier component is present in an amount of about 3%
10 to about 5% by weight of the emulsion.

 In some embodiments, the emulsifier component is present in an amount of about 4% to about 7% by weight of the emulsion.

 In some embodiments, the emulsion comprises an emulsifier component and a stiffening agent component, wherein the combined amount of emulsifier component and
15 stiffening agent component is at least about 8% by weight of the emulsion.

 In some embodiments, the emulsifier component comprises one or more substances independently selected from glyceryl fatty esters and sorbitan fatty esters.

 In some embodiments, the emulsifier component comprises one or more substances independently selected from glyceryl stearate, and polysorbate 20.

20 In some embodiments, the emulsion further comprises a stabilizing agent component. In some embodiments, the stabilizing agent component is present in an amount of about 0.05% to about 5% by weight of the emulsion.

 In some embodiments, the stabilizing agent component is present in an amount of about 0.1% to about 2% by weight of the emulsion.

25 In some embodiments, the stabilizing agent component is present in an amount of about 0.3% to about 0.5% by weight of the emulsion.

 In some embodiments, the stabilizing agent component comprises one or more substances independently selected from polysaccharides.

5 In some embodiments, the stabilizing agent component comprises xanthan gum. In some embodiments, the emulsion further comprises a solvent component.

 In some embodiments, the solvent component is present in an amount of about 10% to about 35% by weight of the emulsion.

 In some embodiments, the solvent component is present in an amount of about 15% to
10 about 30% by weight of the emulsion.

 In some embodiments, the solvent component is present in an amount of about 20% to about 25% by weight of the emulsion.

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

15 In some embodiments, the solvent component comprises one or more substances independently selected from propylene glycol and polyethylene glycol.

 In some embodiments, the emulsion comprises:

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

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

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

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

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

 from 0.5% to 1.5% of ruxolitinib, or a pharmaceutically acceptable salt thereof, by
25 weight of the emulsion on a free base basis.

 In some embodiments, the emulsion comprises:

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

 from about 10% to about 24% of an oil component by weight of the emulsion;

5 from about 1% to about 9% of an emulsifier component by weight of the emulsion;
from about 10% to about 35% of a solvent component by weight of the emulsion;
from about 0.05% to about 5% of a stabilizing agent component by weight of the
emulsion; and

10 from 0.5% to 1.5% of ruxolitinib, or a pharmaceutically acceptable salt thereof, by
weight of the emulsion on a free base basis.

In some embodiments, the emulsion comprises:

from about 40% to about 60% of water by weight of the emulsion;
from about 15% to about 30% of an oil component by weight of the emulsion;
from about 2% to about 6% of an emulsifier component by weight of the emulsion;
15 from about 15% to about 30% of a solvent component by weight of the emulsion;
from about 0.1% to about 2% of a stabilizing agent component by weight of the
emulsion; and

from 0.5% to 1.5% of ruxolitinib, or a pharmaceutically acceptable salt thereof, by
weight of the emulsion on a free base basis.

20 In some embodiments, the emulsion comprises:

from about 40% to about 60% of water by weight of the emulsion;
from about 15% to about 30% of an oil component by weight of the emulsion;
from about 2% to about 6% of an emulsifier component by weight of the emulsion;
from about 15% to about 24% of a solvent component by weight of the emulsion;
25 from about 0.1% to about 2% of a stabilizing agent component by weight of the
emulsion; and

from 0.5% to 1.5% of ruxolitinib, or a pharmaceutically acceptable salt thereof, by
weight of the emulsion on a free base basis.

In some embodiments, the emulsion comprises:

5 from about 45% to about 55% of water by weight of the emulsion;
 from about 15% to about 24% of an oil component by weight of the emulsion;
 from about 3% to about 5% of an emulsifier component by weight of the emulsion;
 from about 20% to about 25% of a solvent component by weight of the emulsion;
 from about 0.3% to about 0.5% of a stabilizing agent component by weight of the

10 emulsion; and

 from 0.5% to 1.5% of ruxolitinib, or a pharmaceutically acceptable salt thereof, by
weight of the emulsion on a free base basis.

 In some embodiments, the emulsion comprises:

 from about 45% to about 55% of water by weight of the emulsion;
15 from about 15% to about 24% of an oil component by weight of the emulsion;
 from about 4% to about 7% of an emulsifier component by weight of the emulsion;
 from about 20% to about 25% of a solvent component by weight of the emulsion;
 from about 0.3% to about 0.5% of a stabilizing agent component by weight of the
emulsion; and

20 from 0.5% to 1.5% of ruxolitinib, or a pharmaceutically acceptable salt thereof, by
weight of the emulsion on a free base basis.

 In some embodiments:

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

25 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

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

 In some embodiments:

 the oil component comprises one or more substances independently selected from white petrolatum, cetyl alcohol, stearyl alcohol, light mineral oil, medium chain triglycerides,
10 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

15 the stabilizing agent component comprises xanthan gum.

 In some embodiments, the emulsion comprises:

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

 from about 2% to about 15% of an occlusive agent component by weight of the emulsion; from about 2% to about 8% of a stiffening agent component by weight of the

20 emulsion;

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

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

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

25 from about 10% to about 35% of a solvent component by weight of the emulsion; and from 0.5% to 1.5% of ruxolitinib, or a pharmaceutically acceptable salt thereof, by weight of the emulsion on a free base basis.

 In some embodiments, the emulsion comprises:

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

- 5 from about 5% to about 10% of an occlusive agent component by weight of the emulsion; from about 2% to about 8% of a stiffening agent component by weight of the emulsion;
- from about 7% to about 12% of an emollient component by weight of the emulsion;
- from about 2% to about 6% of an emulsifier component by weight of the emulsion;
- 10 from about 0.1% to about 2% of a stabilizing agent by weight of the emulsion;
- from about 15% to about 30% of a solvent component by weight of the emulsion; and
- from 0.5% to 1.5% of ruxolitinib, or a pharmaceutically acceptable salt thereof, by weight of the emulsion on a free base basis.

In some embodiments, the emulsion comprises:

- 15 from about 45% to about 55% of water by weight of the emulsion;
- from about 5% to about 10% of an occlusive agent component by weight of the emulsion;
- from about 3% to about 6% of a stiffening agent component by weight of the emulsion;
- 20 from about 7% to about 13% of an emollient component by weight of the emulsion;
- from about 3% to about 5% of an emulsifier component by weight of the emulsion;
- from about 0.3% to about 0.5% of a stabilizing agent component by weight of the emulsion;
- from about 20% to about 25% of a solvent component by weight of the emulsion; and
- 25 from 0.5% to 1.5% of ruxolitinib, or a pharmaceutically acceptable salt thereof, by weight of the emulsion on a free base basis.
- In some embodiments, the emulsion comprises:
- from about 45% to about 55% of water by weight of the emulsion;

- 5 from about 5% to about 10% of an occlusive agent component by weight of the emulsion;
- from about 4% to about 7% of a stiffening agent component by weight of the emulsion;
- from about 7% to about 13% of an emollient component by weight of the emulsion;
- 10 from about 4% to about 7% of an emulsifier component by weight of the emulsion;
- from about 0.3% to about 0.5% of a stabilizing agent component by weight of the emulsion;
- from about 20% to about 25% of a solvent component by weight of the emulsion; and
- from 0.5% to 1.5% of ruxolitinib, or a pharmaceutically acceptable salt thereof, by
- 15 weight of the emulsion on a free base basis.
- In some embodiments, the emulsion comprises:
- from about 45% to about 55% of water by weight of the emulsion; about 7% of an occlusive agent component by weight of the emulsion;
- from about 4.5% to about 5% of a stiffening agent component by weight of the
- 20 emulsion; about 10% of an emollient component by weight of the emulsion;
- from about 4% to about 4.5% of an emulsifier component by weight of the emulsion;
- about 0.4% of a stabilizing agent component by weight of the emulsion;
- about 22% of a solvent component by weight of the emulsion; and
- from 0.5% to 1.5% of ruxolitinib, or a pharmaceutically acceptable salt thereof, by
- 25 weight of the emulsion on a free base basis.
- In some embodiments, the ruxolitinib, or pharmaceutically acceptable salt thereof, is present as ruxolitinib phosphate.
- In some embodiments, the emulsion comprises 1.5% of ruxolitinib, or a pharmaceutically acceptable salt thereof, by weight of the emulsion.
- 30 In some embodiments, the emulsion comprises 1.5% of ruxolitinib phosphate by weight of the emulsion.

5 In some embodiments, the emulsion comprises 0.75% of ruxolitinib, or a pharmaceutically acceptable salt thereof, by weight of the emulsion.

 In some embodiments, the emulsion comprises 0.75% of ruxolitinib phosphate by weight of the emulsion.

 In some embodiments, the combined amount of the stiffening agent component and
10 the emulsifier component is at least about 8% by weight of the emulsion.

 In some embodiments:

 the occlusive agent component comprises a petrolatum;

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

15 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
20 selected from polysaccharides; and

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

 the occlusive agent component comprises white petrolatum;

 the stiffening agent component comprises one or more substances independently
25 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;

30 the stabilizing agent component comprises xanthan gum; and

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

 In some embodiments, the emulsion further comprises an antimicrobial preservative component.

35 In some embodiments, the antimicrobial preservative component is present in an amount of about 0.05% to about 3% by weight of the emulsion.

5 In some embodiments, the antimicrobial preservative component is present in an amount of about 0.1% to about 1% by weight of the emulsion.

 In some embodiments, the antimicrobial preservative component comprises one or more substances independently selected from alkyl parabens and phenoxyethanol.

 In some embodiments, the antimicrobial preservative component comprises one or
10 more substances independently selected from methyl paraben, propyl paraben, and phenoxyethanol.

 In some embodiments, the emulsion further comprises a chelating agent component. In some embodiments, the chelating agent component comprises edetate disodium.

 As used herein, the term “emulsifier component” refers, in one aspect, to a substance,
15 or mixtures of substances that maintains an element or particle in suspension within a fluid medium. In some embodiments, the emulsifier component allows an oil phase to form an emulsion when combined with water. In some embodiments, the emulsifier component refers to one or more non-ionic surfactants.

 As used herein, the term “occlusive agent component” refers to a hydrophobic agent
20 or mixtures of hydrophobic agents that form an occlusive film on skin that reduces transepidermal water loss (TEWL) by preventing evaporation of water from the stratum corneum.

 As used herein, the term “stiffening agent component” refers to a substance or mixture of substances that increases the viscosity and/or consistency of the cream or improves the
25 rheology of the cream.

 As used herein, the term “emollient component” refers to an agent that softens or soothes the skin or soothes an irritated internal surface.

 As used herein, the term “stabilizing agent component” refers to a substance or mixture of substances that improves the stability of the cream and/or the compatibility of the
30 components in the cream. In some embodiments, the stabilizing agent component prevents agglomeration of the emulsion and stabilizes the droplets in the oil-in-water emulsion.

 As used herein, the term “solvent component” is a liquid substance or mixture of liquid substances capable of dissolving ruxolitinib (or its salt) or other substances in the cream. In some embodiments, the solvent component is a liquid substance or mixture of
35 liquid substances in which ruxolitinib, or its pharmaceutically acceptable salt, has reasonable solubility. For example, solubilities of ruxolitinib (free base) or its phosphate salt (1:1 salt) are reported in Table 1. In some embodiments, a solvent is a substance or mixture thereof, in

5 which ruxolitinib, or its pharmaceutically acceptable salt (whichever is used), has a solubility of at least about 10 mg/mL or greater, at least about 15 mg/mL or greater, or at least about 20 mg/mL or greater, when measured as described in Example 2.

As used herein, the phrase “antimicrobial preservative component” is a substance or mixtures of substances which inhibits microbial growth in the cream.

10 As used herein, the phrase “chelating agent component” refers to a compound or mixtures of compounds that has the ability to bind strongly with metal ions.

As used herein, “% by weight of the emulsion” means the percent concentration of the component in the emulsion is on weight/weight basis. For example, 1% w/w of component A = [(mass of component A) / (total mass of the emulsion)] x 100.

15 As used herein, “% by weight of the emulsion on a free base basis” of ruxolitinib, or pharmaceutically acceptable salt thereof” means that the % w/w is calculated based on the weight of ruxolitinib in the total emulsion. For example, “1.5% w/w on a free base basis” of ruxolitinib phosphate means that for 100 grams of total formulation, there are 1.98 grams of ruxolitinib phosphate in the emulsion (which equates to 1.5 grams of the free base, 20 ruxolitinib).

As used herein, the term “component” can mean one substance or a mixture of substances.

As used herein, the term “fatty acid” refers to an aliphatic acid that is saturated or unsaturated. In some embodiments, the fatty acid is in a mixture of different fatty acids. In 25 some embodiments, the fatty acid has between about eight to about thirty carbons on average. In some embodiments, the fatty acid has about 12 to 20, 14-20, or 16-18 carbons on average. Suitable fatty acids include, but are not limited to, cetyl acid, stearic acid, lauric acid, myristic acid, erucic acid, palmitic acid, palmitoleic acid, capric acid, caprylic acid, oleic acid, linoleic acid, linolenic acid, hydroxystearic acid, 12-hydroxystearic acid, cetostearic acid, isostearic 30 acid, sesquioleic acid, sesqui-9-octadecanoic acid, sesquiisooctadecanoic acid, behenic acid, isobehenic acid, and arachidonic acid, or mixtures thereof.

As used herein, the term “fatty alcohol” refers to an aliphatic alcohol that is saturated or unsaturated. In some embodiments, the fatty alcohol is in a mixture of different fatty 35 alcohols. In some embodiments, the fatty alcohol has between about 12 to about 20, about 14 to about 20, or about 16 to about 18 carbons on average. Suitable fatty alcohols include, but are not limited to, stearyl alcohol, lauryl alcohol, palmityl alcohol, cetyl alcohol, capryl alcohol, caprylyl alcohol, oleyl alcohol, linolenyl alcohol, arachidonic alcohol, behenyl

5 alcohol, isobehenyl alcohol, selachyl alcohol, chimyl alcohol, and linoleyl alcohol, or mixtures thereof.

As used herein, the term “polyalkylene glycol”, employed alone or in combination with other terms, refers to a polymer containing oxyalkylene monomer units, or copolymer of different oxyalkylene monomer units, wherein the alkylene group has 2 to 6, 2 to 4, or 2 to 3
10 carbon atoms. As used herein, the term “oxyalkylene”, employed alone or in combination with other terms, refers to a group of formula –O-alkylene-. In some embodiments, the polyalkylene glycol is polyethylene glycol.

As used herein, the term, “sorbitan fatty ester” includes products derived from sorbitan or sorbitol and fatty acids and, optionally, poly(ethylene glycol) units, including
15 sorbitan esters and polyethoxylated sorbitan esters. In some embodiments, the sorbitan fatty ester is a polyethoxylated sorbitan ester.

As used herein, the term “sorbitan ester” refers to a compound, or mixture of compounds, derived from the esterification of sorbitol and at least one fatty acid. Fatty acids useful for deriving the sorbitan esters include, but are not limited to, those described herein.
20 Suitable sorbitan esters include, but are not limited to, the Span™ series (available from Uniqema), which includes Span 20 (sorbitan monolaurate), 40 (sorbitan monopalmitate), 60 (sorbitan monostearate), 65 (sorbitan tristearate), 80 (sorbitan monooleate), and 85 (sorbitan trioleate). Other suitable sorbitan esters include those listed in R. C. Rowe and P. J. Shesky, Handbook of pharmaceutical excipients, (2006), 5th ed., which is incorporated herein by
25 reference in its entirety.

As used herein, the term “polyethoxylated sorbitan ester” refers to a compound, or mixture thereof, derived from the ethoxylation of a sorbitan ester. The polyoxyethylene portion of the compound can be between the fatty ester and the sorbitan moiety. As used herein, the term “sorbitan ester” refers to a compound, or mixture of compounds, derived
30 from the esterification of sorbitol and at least one fatty acid. Fatty acids useful for deriving the polyethoxylated sorbitan esters include, but are not limited to, those described herein. In some embodiments, the polyoxyethylene portion of the compound or mixture has about 2 to about 200 oxyethylene units. In some embodiments, the polyoxyethylene portion of the compound or mixture has about 2 to about 100 oxyethylene units. In some embodiments,
35 the polyoxyethylene portion of the compound or mixture has about 4 to about 80 oxyethylene units. In some embodiments, the polyoxyethylene portion of the compound or mixture has about 4 to about 40 oxyethylene units. In some embodiments, the

5 polyoxyethylene portion of the compound or mixture has about 4 to about 20 oxyethylene units. Suitable polyethoxylated sorbitan esters include, but are not limited to the Tween™ series (available from Uniqema), which includes Tween 20 (POE(20) sorbitan monolaurate), 21 (POE(4) sorbitan monolaurate), 40 (POE(20) sorbitan monopalmitate), 60 (POE(20) sorbitan monostearate), 60K (POE(20) sorbitan monostearate), 61 (POE(4) sorbitan monostearate), 65 (POE(20) sorbitan tristearate), 80 (POE(20) sorbitan monooleate), 80K (POE(20) sorbitan monooleate), 81 (POE(5) sorbitan monooleate), and 85 (POE(20) sorbitan trioleate). As used herein, the abbreviation “POE” refers to polyoxyethylene. The number following the POE abbreviation refers to the number of oxyethylene repeat units in the compound. Other suitable polyethoxylated sorbitan esters include the polyoxyethylene sorbitan fatty acid esters listed in R. C. Rowe and P. J. Shesky, Handbook of pharmaceutical excipients, (2006), 5th ed., which is incorporated herein by reference in its entirety. In some embodiments, the polyethoxylated sorbitan ester is a polysorbate. In some embodiments, the polyethoxylated sorbitan ester is polysorbate 20.

As used herein, the term “glyceryl fatty esters” refers to mono-, di- or triglycerides of fatty acids. The glyceryl fatty esters may be optionally substituted with sulfonic acid groups, or pharmaceutically acceptable salts thereof. Suitable fatty acids for deriving glycerides of fatty acids include, but are not limited to, those described herein. In some embodiments, the glyceryl fatty ester is a mono-glyceride of a fatty acid having 12 to 18 carbon atoms. In some embodiments, the glyceryl fatty ester is glyceryl stearate.

As used herein, the term “triglycerides” refers to a triglyceride of a fatty acid. In some embodiments, the triglyceride is medium chain triglycerides.

As used herein, the term “alkylene glycol” refers to a group of formula –O–alkylene–, wherein the alkylene group has 2 to 6, 2 to 4, or 2 to 3 carbon atoms. In some embodiments, the alkylene glycol is propylene glycol (1,2-propanediol).

As used herein, the term “polyethylene glycol” refers to a polymer containing ethylene glycol monomer units of formula –O–CH₂–CH₂–. Suitable polyethylene glycols may have a free hydroxyl group at each end of the polymer molecule, or may have one or more hydroxyl groups etherified with a lower alkyl, e.g., a methyl group. Also suitable are derivatives of polyethylene glycols having esterifiable carboxy groups. Polyethylene glycols useful in the present disclosure can be polymers of any chain length or molecular weight, and can include branching. In some embodiments, the average molecular weight of the polyethylene glycol is from about 200 to about 9000. In some embodiments, the

5 average molecular weight of the polyethylene glycol is from about 200 to about 5000. In some embodiments, the average molecular weight of the polyethylene glycol is from about 200 to about 900. In some embodiments, the average molecular weight of the polyethylene glycol is about 400. Suitable polyethylene glycols include, but are not limited to polyethylene glycol-200, polyethylene glycol-300, polyethylene glycol- 400, polyethylene
10 glycol-600, and polyethylene glycol-900. The number following the dash in the name refers to the average molecular weight of the polymer.

Kits

The present invention also includes pharmaceutical kits useful, for example, in the treatment and/or prevention of prurigo nodularis, which include one or more containers
15 containing a pharmaceutical composition comprising a therapeutically effective amount of a compound described herein. Such kits can further include, if desired, one or more of various conventional pharmaceutical kit components, such as, for example, containers with one or more pharmaceutically acceptable carriers, additional containers, etc., as will be readily apparent to those skilled in the art. Instructions, either as inserts or as labels,
20 indicating quantities of the components to be administered, guidelines for administration, and/or guidelines for mixing the components, can also be included in the kit.

EXAMPLES

The invention will be described in greater detail by way of specific examples. The following examples are offered for illustrative purposes, and are not intended to limit the
25 invention in any manner. Those of skill in the art will readily recognize a variety of non-critical parameters which can be changed or modified to yield essentially the same results. The compounds of the Examples have been found to be JAK inhibitors according to at least one assay described herein.

Example 1. Upregulated JAK-STAT pathway expression

30 RNA are isolated from formalin-fixed paraffin embedded (FFPE) skin biopsies from active disease, untreated, prurigo nodularis patients. RNA are processed using the nCounter autoimmune profiling codeset (770 genes) or the neuropathology profiling codeset (770 genes) (Nanostring, USA), according to the manufacturer's protocol. After an 18 h hybridization, the samples were run on an nCounter SPRINT Profiler (Nanostring,

- 5 USA). Data was analyzed using nSolver 4.0 Advanced Analysis software (Nanostring, USA). P-values were adjusted using the Benjamini-Yekutieli false discovery rate method.

Ruxolitinib-mediated pharmacological inhibition of PN pathophysiology

- Full-thickness cutaneous skin biopsies were obtained from active disease, untreated, prurigo nodularis patients. Single 4 mm-punch biopsies were obtained from the same
 10 lesion for each patient and longitudinally divided into two pieces (see FIG. 1). FIG. 1 depicts a representation of skin punch biopsies used for the JAK1/JAK2 mediated pharmacological inhibition of PN pathophysiology. Biopsies were cultured for 8 days in KBM media + CaCl₂ and refreshed every 2-3 days. Ruxolitinib phosphate or DMSO (control) was added to the cell culture media. Conditioned supernatants collected during
 15 /prior to media refresh were stored at - 80°C for subsequent analysis. On day 8, cultures were terminated and tissue RNA isolated for subsequent analysis.

- Collected supernatants were analyzed to quantify chemokines, cytokines, and growth factors secreted by skin explants in culture and which are involved in inflammation. A total of 51 proteins were detected and quantified in culture supernatants by Procarta
 20 Multiplex Immunoassay (Thermo Fisher, Waltham, MA). Supernatants and standards were incubated at 4°C overnight. Assay plates were read on a Luminex 200 Instrument (Luminex Corporation, Austin, TX). The concentration was extrapolated from the antigen standard curve of each analyte. The percent inhibition determined for each analyte as the difference in protein concentration in cultures with DMSO (C_D) versus those with
 25 ruxolitinib (C_I), (C_D - C_I)/C_D (see FIG. 2).

Results

- Ruxolitinib was shown to inhibit key chemokines, cytokines, and growth factors involved in key disease pathways (see Table 1 and FIG. 2). Further, when the same assays were conducted for a JAK1 inhibitor, 4-[3-(cyanomethyl)-3-(3',5'-dimethyl-1H,1'H-4,4'-
 30 bipyrazol-1-yl)azetidin-1-yl]-2,5-difluoro-N-[(1S)-2,2,2-trifluoro-1-methylethyl]benzamide, IL-5 and IL-22 were also shown to be inhibited at 48 hours (percent inhibition of 20.25% and 11.16%, respectively. These key chemokines, cytokines, and growth factors are involved in inflammation, pruritus (itching), or lesion development that can be associated with PN. For example, PN lesional skin has been shown to have

5 increased levels of CXCL8, CXCL10, and interferon- gamma when compared to non-lesional control skin (Tsoi et al., J Allergy Clin Immunol 149, 1329-39 (2022)).

Further other cytokines, such as IL-31 and IL-17, have also been shown to play a role in PN. For example, CD4+ T-cells has been shown to significantly infiltrate lesional PN skin as compared to non-lesional control skin (Wong, et al., J Investigative

10 Dermatology, 140(3), 702- 706.e2 (2020)). CD4+ T-cells can express interleukin 31(IL-31), which has been shown to be a mediator of pruritus—an important symptom of PN (Ständer, et al., N Engl J Med, 382:706-716 (2020)). The expressed IL-31 has also been shown to play a role in the development of PN with inhibition of IL-31 by nemolizumab resulting in improvement in pruritus and skin lesions in PN patients (Ständer, *supra*).

15 When PN skin was cultured nemolizumab (an IL-31 inhibitor), a reduction in IL-17 levels in lesional skin was observed, suggesting that inhibiting IL31R signaling can impact IL-17 expression (Tsoi, *supra*). Further, cells expressing IL-17 has been shown to be increased in the dermis of PN lesional skin as compared to control skin (Wong, *supra*). Activated T-cells have also shown increased IL-22 cytokine expression in patients with PN compared

20 with healthy controls (Belzberg, et al., J Invest Dermatol, 141(9):2208-2218.e14 (2021)). Further, IL-2 is critical to the development, maintenance and function of the infiltrating CD4+ T-cells (Furtado, J Exp Med, 196(6):851-7 (2002)) and is a strong itch mediator (Xie, et al., J Dermatol, 46(3), 177–185 2019)). Further, the epidermis of PN skin has been shown to be positive for STAT6, a marker for Th2 cytokines, such as IL-5 and IL-31

25 (Mullins, et al., NLM, StatPearls Publishing, <https://www.ncbi.nlm.nih.gov/books/NBK459204>), Sep. 14, 2021)). Finally, keratinocytes are implicated in the pathogenesis of PN, particularly around pruritus (Zhong et al, Acta Dermato-Venereologica volume 99, 579-5861 May (2019)). In skin, keratinocytes produce IL-34.

Hence, ruxolitinib has been shown to inhibit multiple key chemokines, cytokines,

30 and growth factors involved in PN and/or the underlying inflammation and pruritus associated with PN.

Table A (showing percent inhibition due to ruxolitinib)

Analyte	48 hr	96 hr
IP-10 (CXCL10)	9.7	60.3
IL-8 (CXCL8)	13.7	**
IL-10	36.2	39.9
IL-17 alpha (CTLA-8)	63.9	57.6
IFN-gamma	5.0	11.6
IL-2	17.8	16.6

5

** no measureable inhibition

Example 2: Preparation of Oil-In-Water Cream Formulations of Ruxolitinib Phosphate

First, in order to determine the solubility of ruxolitinib (free base) or its 1:1 phosphate salt, approximately 5 mL of a potential solvent was added to approximately 50 mg of the API or its salt at room temperature. The mixtures were suspended and rotated on a wheel. If the mixtures became clear solutions, more solid material was added. The suspensions were then suspended over 24 hours. The samples were filtered through 0.2 micron filters. The liquid portions were collected and diluted with 50/50 water methanol/water. The concentrations of the diluted samples were analyzed by HPLC. When the free base or salt was fairly insoluble, the results are approximate only.

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Table 1

Potential Solvent	Solubility of Phosphate Salt (mg/mL)	Solubility of Free Base (mg/mL)
Water	2.7	2.0
pH 4, citric buffer, 0.1 M	1.5	1.1
pH 6, citric buffer, 0.1 M	0.2	0.15
Ethanol	7.3	5.5
Isopropanol	0.6	0.45
Benzyl alcohol	3	2.3
Propylene glycol	24	18.2
PEG 200	23	17.4
PEG 300	14	10.6
Glycerin	11	8.3
Transcutol	10	7.6

Potential Solvent	Solubility of Phosphate Salt (mg/mL)	Solubility of Free Base (mg/mL)
Trolamine	51	38.6
Water/PEG 200 (50/50)	23	17.4
Water/glycerin (50/50)	21	15.9
Water/glycerin/trolamine (40/40/20)	18	13.6
Isopropyl myristate	<0.1	0.08
Isosorbide dimethyl ether	0.4	0.3
Mineral oil	<0.1	0.08
Olelyl alcohol	0.1	0.08
Dimethicone	<0.2	0.15
C12-15 alcohol benzoate	<0.2	0.15
Caprylic triglyceride	<0.2	0.15

An oil-in-water cream formulation was prepared for 1:1 ruxolitinib phosphoric acid salt at 0.5, 1.0 and 1.5% by weight of the formulation (free base equivalent). The compositions for a 15 gram tube are provided in **Table 2** below. The formulation for three strengths were identical except for adjustments to the purified water quantity based on the amount of active ingredient. All excipients used in the formulation were compendial grade (i.e., USP/NF or BP) or are approved for use in topical products.

The quantitative formulae for representative 400 kg batches of the cream formulation at 0.5, 1.0 and 1.5% are also provided in **Tables 3, 4, and 5**, respectively.

The oil-in-water cream formulations were synthesized according to the following procedure at either a 3.5 kg or 400 kg scale (when made at a 3.5 kg batch size, the amounts in **Tables 3-5** were scaled appropriately). Some batches were subject to minor changes

- 5 associated with scale-up, such as the size of mixing vessels and mixers. Generally, overhead mixer with high and low shear mixing blades are suitable for the process.

Procedure

1. A paraben phase was prepared by mixing methyl and propyl parabens with a
10 portion of the propylene glycol (see % in **Tables 2-5**).
2. Next, a xanthan gum phase was prepared by mixing xanthan gum with propylene glycol (see % in **Table 2-5**).
3. An oil phase was then prepared by mixing light mineral oil, glyceryl stearate, polysorbate 20, white petrolatum, cetyl alcohol, stearyl alcohol, dimethicone and medium chain
15 triglycerides. The phase is heated to 70-80 °C to melt and form a uniform mixture.
4. The aqueous phase was next prepared by mixing purified water, polyethylene glycol, and disodium EDTA. The phase is heated to 70-80 °C.
5. The aqueous phase of step 4, paraben phase of step 1, and Example 2 (phosphate salt of API) were combined to form a mixture.
- 20 6. The xanthan gum phase from step 2 was then added to the mixture from step 5.
7. The oil phase from step 3 was then combined under high shear mixing with the mixture from step 6 to form an emulsion.
8. Phenoxyethanol was then added to the emulsion from step 7. Mixing was continued, and then the product was cooled under low shear mixing.

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Table 2

FORMULA		Function	Percentage of Total (% w/w)	Grams/Tube
PHASE	COMPONENT			
Paraben	Propylene Glycol USP	Solvent	10.00	1.5
	Methyl Paraben NF	Antimicrobial preservative	0.10	0.015
	Propyl Paraben NF	Antimicrobial preservative	0.05	0.0075
Xanthan Gum	Propylene Glycol USP	Solvent	5.00	0.75
	Xanthan Gum NF	Suspending, stabilizing, viscosity- increasing agent	0.40	0.06
Oil	Light Mineral Oil NF	Emollient, solvent	4.00	0.6
	Glyceryl Stearate SE	Emulsifier	3.00	0.45
	Polysorbate 20 NF	Emulsifying/ stabilizing agent	1.25	0.1875
	White Petrolatum USP	Occlusive agent	7.00	1.05
	Cetyl Alcohol NF	Stiffening agent, consistency improver	3.00	0.45
	Stearyl Alcohol NF	Stiffening agent	1.75	0.2625
	Dimethicone 360 NF	Skin protectant	1.00	0.15
	Medium Chain Triglyceride NF	Emollient, solvent	5.00	0.75
Aqueous / Active	Purified Water USP	Solvent	50.24 - 48.92	7.536 – 7.338
	Edetate Disodium USP	Chelating agent	0.05	0.0075

FORMULA		Function	Percentage of Total (% w/w)	Grams/Tub e
PHASE	COMPONENT			
	Polyethylene Glycol USP	Solvent	7.00	1.05
	Example 2 *	Active	0.66 – 1.98	0.099 – 0.297
Final	Phenoxyethanol BP	Antimicrobial preservative	0.50	0.075
	Total		100.00%	15

Table 3

Ingredient	Kilograms	Percentage (w/w)
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Ruxolitinib phosphate	2.64 (phosphate salt) / 2.0 (free base)	0.66 (phosphate salt) / 0.5 (free base)
Propylene Glycol USP	40.0	10.00
Methyl Paraben NF	0.4	0.10
Propyl Paraben NF	0.2	0.05
Propylene Glycol USP	20.0	5.00
Xanthan Gum NF	1.6	0.40
Light Mineral Oil NF	16.0	4.00
Glyceryl Stearate SE	12.0	3.00
Polysorbate 20 NF	5.0	1.25
White Petrolatum USP	28.0	7.00
Cetyl alcohol NF	12.0	3.00
Stearyl alcohol NF	7.0	1.75
Dimethicone 360 NF	4.0	1.00
Medium Chain Triglycerides NF	20.0	5.00
Purified Water USP (approximate)	201	50.25
Edetate Disodium USP	0.2	0.05
Polyethylene Glycol USP	28.0	7.00
Phenoxyethanol BP	2.0	0.5
Total (approximate)	400.0	100

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Table 4

Ingredient	Kilograms	Percentage (w/w)
Ruxolitinib phosphate	5.28 (phosphate salt) / 4.0 (free base)	1.32 (phosphate salt) / 1.00 (free base)
Propylene Glycol USP	40.0	10.00
Methyl Paraben NF	0.4	0.10
Propyl Paraben NF	0.2	0.05
Propylene Glycol USP	20.0	5.00
Xanthan Gum NF	1.6	0.40
Light Mineral Oil NF	16.0	4.00
Glyceryl Stearate SE	12.0	3.00
Polysorbate 20 NF	5.0	1.25
White Petrolatum USP	28.0	7.00
Cetyl alcohol NF	12.0	3.00
Stearyl alcohol NF	7.0	1.75
Dimethicone 360 NF	4.0	1.00
Medium Chain Triglycerides NF	20.0	5.00
Purified Water USP (approximate)	198.5	49.6

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Edetate Disodium USP	0.2	0.05
Polyethylene Glycol USP	28.0	7.00
Phenoxyethanol BP	2.0	0.5
Total (approximate)	400.0	100

Table 5

Ingredient	Kilograms	Percentage (w/w)
Ruxolitinib phosphate	7.92 (phosphate salt) / 6.0 (free base)	1.98 (phosphate salt) / 1.5 (free base)
Propylene Glycol USP	40.0	10.00
Methyl Paraben NF	0.4	0.10
Propyl Paraben NF	0.2	0.05
Propylene Glycol USP	20.0	5.00
Xanthan Gum NF	1.6	0.40
Light Mineral Oil NF	16.0	4.00
Glyceryl Stearate SE	12.0	3.00
Polysorbate 20 NF	5.0	1.25
White Petrolatum USP	28.0	7.00
Cetyl alcohol NF	12.0	3.00
Stearyl alcohol NF	7.0	1.75
Dimethicone 360 NF	4.0	1.00
Medium Chain Triglycerides NF	20.0	5.00
Purified Water USP (approximate)	195.5	48.9
Edetate Disodium USP	0.2	0.05
Polyethylene Glycol USP	28.0	7.00
Phenoxyethanol BP	2.0	0.5
Total (approximate)	400.0	100

The batches were tested for stability at 25°C and found to be stable up to 24 months with a pH consistent with the pH range described supra (see Table 7, 9, 11, 12, 13, 15, 17, and 19 in U.S. Patent Publ. No. 2015/0250790, which is incorporated herein by reference in its entirety).

Example 3: CLINICAL STUDY - A Phase 3, Double-Blinded, Randomized, Vehicle-Controlled, Efficacy and Safety Study of Ruxolitinib Cream in Participants with Prurigo Nodularis (PN)

This is a Phase 3, multicenter, randomized, double-blinded, vehicle-controlled (DBVC), parallel-group study in adults with PN (IGA-CPG-S score of ≥ 2 ; ≥ 6 pruriginous lesions on ≥ 2 different body areas; and PN-related WI-NRS score ≥ 7). The total estimated BSA treatment area must be $\leq 20\%$. Treatment area is defined as the area affected by

5 pruriginous lesions plus an ~ 1 cm area surrounding each lesion. Eligible participants will be randomized 1:1 to ruxolitinib 1.5% cream or vehicle cream. Participants will apply either ruxolitinib 1.5% cream or vehicle cream (both twice daily (BID)) through Week 12 to all pruriginous lesions identified at baseline plus an ~ 1 cm surrounding area each lesion.

At Week 12, participants who have completed 12 weeks of treatment with no safety

10 concerns will enter the 40-week open-label extension (OLE) period. The investigator will assess whether the participant requires continuation of therapy (IGA-CPG-S score $\geq$ 1 and/or the presence of PN-related itching). During the OLE period, all participants will apply ruxolitinib 1.5% cream BID to PN affected areas plus an ~ 1 cm area surrounding each pruriginous lesion and/or areas of PN-related itching. After the last application of

15 study cream, participants will be followed for safety; the safety visit will occur at least 30 days after the last application of study cream.

The treatment assignment a participant received during the DBVC period will be blinded to investigators and participants until after all participants have completed treatment or discontinued treatment and completed the safety follow-up period.

20 **Table 6** presents the objectives and endpoints of the study.

Table 6

Objectives	Endpoints
Primary	
To demonstrate the efficacy of ruxolitinib 1.5% cream BID in participants with PN.	• WI-NRS4 response at Week 12, defined as achieving a $\geq$ 4-point improvement (reduction) in WI-NRS score from baseline.
Key Secondary	
To further demonstrate the treatment effects of ruxolitinib 1.5% cream BID in participants with PN.	• WI-NRS4 response at Week 4. • Overall-TS (Treatment Success) at Week 12, defined as achieving both a WI-NRS4 response and an IGA-CPG-S-TS (Treatment Success). (IGA-CPG-S-TS is defined as an IGA-CPG-S score of 0 or 1 with a $\geq$ 2 grade improvement from baseline) • IGA-CPG-S-TS at Week 12. • WI-NRS4 response on Day 7.
Secondary	

To further demonstrate the treatment effects of ruxolitinib 1.5% cream BID in participants with PN.	• WI-NRS4 response at each postbaseline visit. • Change from baseline in WI-NRS score at each postbaseline visit. • Time to ≥ 2-point improvement from baseline in WI-NRS score. • Time to ≥ 4-point improvement from baseline in WI-NRS score. • Achieving a ≥ 2-point improvement (reduction) in Skin Pain NRS score from baseline. • Change from baseline in Skin Pain NRS score at each postbaseline visit. • IGA-CPG-S-TS at each postbaseline visit. • IGA-CPG-A score of 0 or 1 with at least a 2 grade improvement (reduction) at each postbaseline visit. • Achieving $> 75\%$ healed lesions from PAS at each postbaseline visit.
To evaluate the effect of ruxolitinib 1.5% cream BID on QOL.	• Change from baseline in DLQI score at each postbaseline visit. • Change from baseline in EQ-5D-5L score at each postbaseline visit.
To evaluate the safety and tolerability of ruxolitinib 1.5% cream BID in participants with PN.	The type, frequency, and severity of AEs, including changes in vital signs and clinical laboratory blood samples.

5 Inclusion Criteria

Participants are eligible to be included in the study only if all of the following criteria apply:

1. Ability to comprehend and willingness to sign a written informed consent form (ICF) for the study.
- 10 2. Age ≥ 18 years at the time of signing the ICF.
3. Clinical diagnosis of PN ≥ 3 months before screening.
4. There are ≥ 6 pruriginous lesions on ≥ 2 different body areas (such as right and left leg) at screening and baseline. Note: The total estimated BSA treatment area must be $\leq 20\%$.
- 15 5. IGA-CPG-S score of ≥ 2 at screening and baseline.

- 5 6. Baseline PN-related WI-NRS score ≥ 7 . Baseline WI-NRS score is defined as the 7-day average of WI-NRS scores before Day 1 (data from a minimum of 4 out of 7 days prior to Day 1 is needed).
7. Removed during Protocol Amendment 2.
8. Willingness to avoid pregnancy or fathering children based on the criteria below.
- 10 a. Male participants with reproductive potential must agree to take appropriate precautions to avoid fathering children from screening through 90 days (a spermatogenesis cycle) after the last application of study cream and must refrain from donating sperm during this period. Permitted methods in preventing pregnancy should be communicated to the participants and their understanding confirmed.
- 15 b. Female participants who are WOCBP must have a negative serum pregnancy test at screening and negative urine pregnancy test before the first application of study cream on Day 1 and must agree to take appropriate precautions to avoid pregnancy from screening through 30 days (1 menstrual cycle) after the last application of study cream and must refrain from donating oocytes during this period. Permitted methods in preventing pregnancy should be communicated to the participants and their understanding confirmed.
- 20 c. A female participant not considered to be of childbearing potential is eligible.

25 **Exclusion Criteria**

Participants are excluded from the study if any of the following criteria apply:

1. Acute or chronic pruritus due to a condition other than PN. (Conditions such as: scabies, insect bite, lichen simplex chronicus, psoriasis, acne, folliculitis, habitual picking, lymphomatoid papulosis, chronic actinic dermatitis, dermatitis herpetiformis, sporotrichosis, bullous disease, excoriation syndrome, venous stasis; systemic hematologic disorders [iron-deficiency anemia, polycythemia rubra vera, lymphoma, leukemia]; gastrointestinal disorders [celiac disease, gastric malignancy, obstructive biliary disease; α -1 antitrypsin deficiency]; infections [HIV, hepatitis B and C, mycobacterial]; endocrine disorders [hyperthyroidism]; psychosocial disorders [depression, anxiety], and chronic renal failure.)
2. Total estimated BSA treatment area (excluding the scalp) $> 20\%$.

- 5 3. Neuropathic and psychogenic pruritus, such as but not limited to notalgia paresthetica, brachioradial pruritus, small fiber neuropathy, skin picking syndrome, or delusional parasitosis.
4. Active AD lesions (signs and symptoms other than dry skin) within 6 months of screening and baseline.
- 10 5. Uncontrolled hypothyroidism or hyperthyroidism at screening as determined by the investigator. Note: If the participant has a history of thyroid disease and is on treatment, the participant must be on a stable thyroid regimen for at least 6 weeks prior to Day 1.
6. Concurrent conditions and history of other diseases:
- 15 a. Any other concomitant skin disorder (eg, generalized erythroderma such as Netherton's syndrome), pigmentation, or extensive scarring that in the opinion of the investigator may interfere with the evaluation of pruriginous lesions or assessments of efficacy or compromise participant safety.
- 20 b. Immunocompromised (eg, lymphoma, acquired immunodeficiency syndrome, Wiskott-Aldrich syndrome).
- 25 c. Chronic or acute infection requiring treatment with systemic antibiotics, antivirals, antiparasitics, antiprotozoals, or antifungals within 2 weeks before baseline.
- d. Active acute bacterial, fungal, or viral skin infection (eg, herpes simplex, herpes zoster, chickenpox, clinically infected AD, or impetigo) within 1 week before baseline.
- e. Unstable asthma or COPD requiring systemic treatment (such as intravenous steroids) or hospital admission or treatment in the emergency department within 3 months of baseline
- or

- 5 f. Acute or chronic active HBV or HCV infection. Participants who have recovered or have been successfully treated with no evidence of active HBV or HCV infection and those who are immune due to HBV vaccination can enroll.
- g. Any underlying condition known to be associated with the clinical presentation of PN that is not under control (stable) prior to the baseline visit.
- 10 7. Any serious illness or medical, physical, or psychiatric condition(s) that, in the investigator's opinion, would interfere with full participation in the study, including application of study cream and attending required study visits; pose a significant risk to the participant; or interfere with interpretation of study data. For example:
- 15 a. Clinically significant or uncontrolled cardiovascular disease, including unstable angina, acute myocardial infarction or stroke within 6 months from Day 1, New York Heart Association Class III or IV congestive heart failure, and arrhythmia requiring therapy or uncontrolled hypertension (blood pressure > 150/90 mmHg) unless approved by the medical monitor/sponsor.
- 20 b. Participants with or a history of malignancy in the 5 years preceding the baseline visit, except for adequately treated, nonmetastatic nonmelanoma skin cancer.
- c. Current and/or history of arterial or venous thrombosis, including deep vein thrombosis and pulmonary embolism.
- d. Current and/or history of active tuberculosis or current and/or history of latent tuberculosis unless adequately treated.
- 25 e. History of severe anemia, severe thrombocytopenia, or severe neutropenia.
8. Any of the following clinical laboratory test results at screening:
- a. Cytopenias, defined as follows:
- 30 – Hemoglobin < 100 g/L (ie, 10 g/dL)
- Absolute neutrophil count < $1.5 \times 10^9/L$ (ie, 1500/ μL)
- Platelet count < $1 \times 10^{11}/L$ (ie, 100,000/ μL)
- b. Liver function tests:
- AST or ALT $\geq 2.5 \times ULN$
- Total bilirubin > $1.5 \times ULN$ unless Gilbert's syndrome

- 5 c. Estimated glomerular filtration rate $< 30 \text{ mL/min/1.73 m}^2$ (using the CKD-EPI 2021 Creatinine Equation).
- d. Positive serology test results at screening for HIV antibody.
- e. Any other clinically significant laboratory result that, in the opinion of the investigator, poses a significant risk to the participant.
- 10 9. Use of any of the following treatments within the indicated washout period before the baseline visit:
- a. Five half-lives or 12 weeks, whichever is longer – biologic agents (eg, dupilumab). For biologic agents with washout periods longer than 12 weeks (eg, rituximab), consult the medical monitor.
- 15 b. Current treatment or treatment within 30 days or 5 half-lives (whichever is longer) before baseline with another investigational medication or current enrollment in another investigational drug protocol.
- c. Four weeks for any topical or systemic JAK or TYK2 inhibitor (eg, abrocitinib, baricitinib, deucravacitinib, filgotinib, lestaurtinib, pacritinib, ruxolitinib, 20 tofacitinib, or upadacitinib).
- d. Four weeks – systemic or intralesional corticosteroids or adrenocorticotropic hormone analogs, cyclosporine, methotrexate, azathioprine, or other systemic immunosuppressive or immunomodulating agents (eg, mycophenolate or tacrolimus).
- 25 e. Four weeks for opioid antagonists (eg, naloxone and naltrexone).
- f. Four weeks for gabapentin, pregabalin, or thalidomide.
- g. Four weeks for the following:
- Paroxetine, fluvoxamine, or other SSRIs
 - SNRIs
 - Tricyclic antidepressants
- 30 h. Four weeks – recreational or medicinal use (topical, inhaled, oral, sublingual, or any other route) of cannabis or cannabinoids (eg, THC, CBD).
- i. Two weeks – systemic antibiotics and immunizations with live-attenuated vaccines.

- 5 Note: Live-attenuated vaccines are prohibited during the DBVC period. COVID-19 vaccination is permitted.
- j. Two weeks – sedating antihistamines.
- k. Two weeks or 5 half-lives, whichever is longer – strong systemic CYP3A4 inhibitors.
- 10 l. Two weeks – any topical treatments for PN (other than bland emollients, eg, Aveeno® creams, ointments, sprays, and soap substitutes), such as corticosteroids, calcineurin inhibitors, topical antipruritics (eg, doxepin cream), PDE4 inhibitors, coal tar (shampoo), topical antibiotics, and antibacterial cleansing body wash/soap.
- 15 m. One week – nonsedating antihistamines used for the treatment of PN.
10. Current use of a medication known to cause pruritus.
11. History of treatment failure (as assessed by the investigator through study participant interview) for PN or any inflammatory condition with any systemic or topical JAK inhibitors (eg, abrocitinib, baricitinib, deucravacitinib, filgotinib, lestaurtinib, pacritinib, ruxolitinib, tofacitinib, or upadacitinib).
- 20 12. Psoralen and ultraviolet A or ultraviolet B therapy within 4 weeks before baseline or
- Ultraviolet light therapy or prolonged exposure to natural or artificial sources of ultraviolet radiation (eg, sunlight or tanning booth) within 2 weeks before baseline
- 25 and/or intention to have such exposure during the study that is thought by the investigator to potentially impact the participant's PN.
13. Pregnant or lactating, or considering pregnancy during study participation.
14. History of alcoholism or drug addiction within 1 year before screening or current alcohol or drug use that, in the opinion of the investigator, will interfere with the
- 30 participant's ability to comply with the application schedule and study assessments.
15. Removed during Protocol Amendment 1.
16. Known allergy or reaction to any of the components of the study cream.

- 5 17. In the opinion of the investigator, unable or unlikely to comply with the application
 schedule and study evaluations.
18. Committed to a mental health institution by virtue of an order issued either by the
 judicial or the administrative authorities.
19. Employees of the sponsor or investigator or otherwise dependents of them.
- 10 20. The following participants are excluded in France:
- a. Vulnerable populations according to article L.1121-6 of the French Public Health
 Code.
- b. Adults under legal protection or who are unable to express their consent per article
 L.1121-8 of the French Public Health Code.
- 15 c. Individuals not affiliated with the social security system.

At several timepoints during the study, various efficacy assessments and patient reported outcomes will be assessed. Descriptions of those assessments are described below.

Efficacy Assessments

Worst-Itch Numeric Rating Scale (WI-NRS)

- 20 The WI-NRS is a PRO comprised of a single item rated on a scale from 0 ("No
itch") to 10 ("Worst imaginable itch"). Each evening beginning on the day of screening
through Week 52 or ET, the participant will assess their worst level of PN-related itch
during the past 24 hours on a scale of 0 to 10 in an eDiary.

- An average of the 7-day WI-NRS scores, prior to the baseline visit (minimum 4 out
25 of 7 days' data required), will be used to determine if a participant meets the inclusion
criteria. The study staff should contact the participant 1 week prior to each visit to confirm
the participant's compliance with completion of the WI-NRS assessment.

Investigator's Global Assessment (IGA)

- The severity and the activity of PN will be assessed via the IGA-CPG-S and the
30 IGA-CPG-A, respectively.

Investigator Global Assessment for Stage of Chronic Prurigo (IGA-CPG-S)

The IGA-CPG-S is an overall severity rating on a scale of 0 to 4 (see **Table 7**).

Table 7

Score	Category	Description: Stage (IGA-CPG-S)
0	Clear	No lesions (0 lesions)
1	Almost clear	Rare palpable pruriginous lesions (approximately 1-5 lesions)
2	Mild	Few palpable pruriginous lesions (approximately 6-19 lesions)
3	Moderate	Many palpable pruriginous lesions (approximately 20-100 lesions)
4	Severe	Abundant palpable pruriginous lesions (over 100 lesions)

5

For a participant to be eligible for enrollment, their IGA-CPG-S score must be ≥ 2 at screening and baseline. Note: The total BSA treatment area must be $\leq 20\%$. The IGA-CPG-S-TS (Treatment Success) is defined as an IGA-CPG-S score of 0 or 1 with ≥ 2 grade improvement from baseline.

10

Investigator Global Assessment for Activity of Chronic Prurigo (IGA-CPG-A)

The IGA-CPG-A is an overall severity rating on a scale of 0 to 4 (see **Table 8**).

Table 8

Score	Category	Description: Activity (IGA-CPG A)
0	Clear	No pruriginous lesions have excoriations or crusts
1	Almost clear	Very small proportion of pruriginous lesions have excoriations or crusts (up to approximately 10% of all pruriginous lesions)
2	Mild	Minority of pruriginous lesions have excoriations or crusts (approximately 11-25% of all pruriginous lesions)
3	Moderate	Many pruriginous lesions have excoriations or crusts (approximately 26-75% of all pruriginous lesions)
4	Severe	Majority of pruriginous lesions have excoriations or crusts (approximately 76-100% of all pruriginous lesions)

Prurigo Activity Score (PAS)

15

The extent and severity of PN will also be assessed via the PAS (v1.2) and will be determined at the noted visits. The first 3 items are descriptive of the type, predominant type, distribution, and quantity of pruriginous lesions. The remaining 2 items of the PAS will assess disease activity in terms of percentage (i.e., 0%, 1%-25%, 26%-50%, 51%-75%, 76%-100%) of pruriginous lesions with excoriations/crusts on top (to reflect active scratching), and the percentage (100%, 76%-99%, 51%-75%, 26%-50%, 0%-25%) of healed pruriginous lesions, in order to quantify change of PN skin lesions. In addition, the total number of pruriginous lesions in a representative area will be identified at screening and followed throughout the study.

20

Body Surface Area (BSA)

5 Total estimation of the %BSA treatment area will be used to determine the number
of tubes of study cream dispensed at each visit. Treatment area is defined as the area
affected by pruriginous lesions plus an ~ 1 cm area surrounding each lesion. Total %BSA
treatment area will be estimated at each visit. Body surface area assessment will be
approximated to the nearest 0.1% using the Palmar Method as a guide. The Palmar Method
10 is the palm plus 5 digits, with fingers tucked together and thumb tucked to the side
(handprint), which is considered as 1% BSA and, the thumb, as 0.1% BSA, respectively.

Photography

At select sites, 2-dimensional photographs of the upper and lower half of the
participant's body will be obtained at the noted visits.

15 Patient-Reported Outcomes

For all patient-reported outcome assessments conducted at the study site, in order to
avoid bias in the participants' responses to the questionnaires, assessments should be
completed before any other evaluations or study procedures on the day of the study visit
and prior to treatment-related discussions with the investigator or study site staff.

20 Electronic Diary Assessments: Worse-Itch Numeric Rating Scale and Skin Pain Numeric Rating Scale

Participants will either bring and use their own device or be issued a handheld
device (eDiary) at the screening visit. Each participant will be instructed to complete the
eDiary each evening beginning on the day of screening through Week 52 or treatment
25 discontinuation. Compliance with the eDiary is calculated electronically in real time via the
vendor portal. If the participant is frequently not completing the eDiary, the site staff will
be informed so compliance can be addressed in a timely manner. Note: Completion of the
WI-NRS a minimum of 4 out of 7 days before study visits is required for the analysis.

Study sites will contact participants 1 week before the baseline visit to confirm
30 compliance with eDiary assessments to ensure information is available to allow
randomization if appropriate.

Skin Pain Numeric Rating Scale

Each evening, the participant will assess their worst level of PN-related skin pain
during the past 24 hours on a scale of 0 to 10.

35 Dermatology Life Quality Index (DLQI)

The DLQI is a simple, 10-question validated questionnaire to measure how much
the skin problem has affected the participant over the previous 7 days and will be

- 5 completed as outlined in the schedule of activities (SoA). The participant will answer the questionnaire as follows: (1) very much, (2) a lot, (3) a little, or (4) not at all.

The questionnaire is analyzed under 6 headings as follows:

Symptoms and feelings (Questions 1 and 2)

Daily activities (Questions 3 and 4)

- 10 Leisure (Questions 5 and 6)

Work and school (Question 7)

Personal relations (Questions 8 and 9)

Treatment (Question 10)

Overall scoring ranges from 0 to 30, with a high score indicative of poor health

- 15 related quality of life (HRQoL).

Patient Global Impression of Severity (PGIS)

The PGIS is a single-item questionnaire that asks the participant to provide the overall severity of PN at the time of assessment on a 4-point scale. As a static assessment, the PGIS will be captured at the designated visits.

- 20 The participant will answer the following:

Please choose the response below that best describes the severity of your prurigo nodularis over the past week.

0 = none, 1 = mild, 2 = moderate, 3 = severe.

Patient Global Impression of Change (PGIC)

- 25 The PGIC is a single-item questionnaire that asks the participant to provide the overall self-assessment of change in their PN on a 7-point scale. The PGIC will be captured during site visits as outlined.

The participant will answer the following:

- 30 Please choose the response below that best describes the severity of your prurigo nodularis over the past week.

0 = none, 1 = mild, 2 = moderate, 3 = severe.

Patient Global Impression of Change

- 35 The PGIC is a single-item questionnaire that asks the participant to provide the overall self-assessment of change in their PN on a 7-point scale. The PGIC will be captured during site visits as outlined.

The participant will answer the following:

Please choose the response below that best describes the overall change in your prurigo nodularis since you started applying the study cream.

- 5 1) Very much better, (2) Moderately better, (3) A little better, (4) No change, (5) A little worse, (6) Moderately worse, and (7) Very much worse.

Hospital Anxiety and Depression Scale (HADS)

- The HADS is a 14-item questionnaire that assesses the levels of anxiety and depression that a person is currently experiencing (Zigmond AS, Snaith RP. The hospital anxiety and depression scale. Acta Psychiatr Scand 1983;67:361-370) and will be
10 completed at the noted visits. There are 7 questions each for measuring anxiety and depression, with 4 possible responses to each question; the responses are scored as 0, 1, 2, or 3, with high scores indicating a poorer state. Separate scores are calculated for anxiety and depression and range from 0 to 21 for each subscale.

- 15 **Functional Assessment of Chronic Illness Therapy – Fatigue Scale (FACIT-Fatigue)**

- The FACIT-Fatigue scale is a validated instrument with a 13-item questionnaire originally designed to assess fatigue in patients with chronic disease as a 7-day recall period (Cella D, Wilson H, Shalhoub H, et al. Content validity and psychometric
20 evaluation of Functional Assessment of Chronic Illness Therapy-Fatigue in patients with psoriatic arthritis. J Patient Rep Outcomes 2019;3:1-12.) and will be completed at the noted visits. Each item uses a 5-point scale ranging from "4 = not at all" to "0 = very much." The total FACIT-Fatigue score ranges from 0 (maximum fatigue) to 52 (no fatigue). The participant should complete the questionnaire before site personnel perform any clinic
25 assessments and before any interaction with the site personnel has occurred to avoid biasing the participant's response.

PROMIS Sleep Scales

- Sleep will be assessed at the noted visits using 2 of the PROMIS Short Forms: Sleep-Related Impairment and Sleep Disturbance.
30 The PROMIS Short Form – Sleep-Related Impairment questionnaire assesses self-reported perceptions of alertness, sleepiness, and tiredness during usual waking hours and the perceived functional impairments during wakefulness associated with sleep problems or impaired alertness (Buysse DJ, Yu L, Moul DE. Development and validation of patient-reported outcome measures for sleep disturbance and sleep-related impairments. Sleep
35 2010;33:781-792.). The questionnaire has 8 questions, which are assessed using a 5-point scale. Scores range from 8 to 40, with higher scores indicating greater severity of sleep-related impairment.

5 The PROMIS Short Form – Sleep Disturbance questionnaire assesses self-reported perceptions of sleep quality, sleep depth, and restoration associated with sleep. Sleep disturbance does not focus on symptoms of specific sleep disorders and does not provide subjective estimates of sleep quantities (e.g., total amount of sleep, time to fall asleep, amount of wakefulness during sleep; Buysse DJ, Yu L, Moul DE. Development and
10 validation of patient-reported outcome measures for sleep disturbance and sleep-related impairments. *Sleep* 2010;33:781-792.). The Sleep Disturbance Short Form is generic rather than disease-specific. The questionnaire has 8 questions and is assessed using a 5-point scale. Scores range from 8 to 40, with higher scores indicating greater severity of sleep disturbance.

15 **EQ-5D-5L**

 Participants will complete the EQ-5D-5L questionnaire at the designated study visits. The EQ-5D-5L questionnaire is a standardized, validated instrument for use as a measure of health outcome (Herdman M, Gudex C, Lloyd A, et al. Development and preliminary testing of the new five-level version of EQ-5D (EQ-5D-5L). *Qual Life Res*
20 2011;20:1727-1736.). The EQ-5D-5L questionnaire will provide data for use in economic models and analyses, including developing health utilities or QALYs. The EQ-5D-5L questionnaire consists of the following 2 sections: the EQ-5D descriptive system and the EQ VAS. The descriptive system comprises 5 dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression.

25 Each dimension has 5 levels: Level 1 = no problems, Level 2 = slight problems, Level 3 = moderate problems, Level 4 = severe problems, and Level 5 = extreme problems. This part of the EQ-5D-5L questionnaire provides a descriptive profile that can be used to generate a health state profile. For example, a participant in "health state 12345" would have no problems with mobility, slight problems with self-care (washing or dressing),
30 moderate problems with doing usual activities, severe pain or discomfort, and extreme anxiety or depression. Each health state can potentially be assigned a summary index score based on societal preference weights for the health state. These weights, sometimes referred to as utilities, are often used to compute quality -adjusted life-years (QALYs) for use in health economic analyses. Health state index scores generally range from < 0 (where
35 0 is the value of a health state equivalent to dead; negative values represent values as worse than dead) to 1 (the value of full health), with higher scores indicating higher health utility. The health state preferences often represent national or regional values and can therefore differ between countries/regions. The EQ VAS records the participant's self-rated health on

- 5 a vertical VAS (0-100), where the endpoints are labeled "the best health you can imagine" (100 score) and "the worst health you can imagine" (0 score).

Work Productivity and Activity Index (WPAI)

- The WPAI is a 6-item questionnaire that measures the effect of the participant's health problems on their ability to work and perform regular activities (Reilly MC, Zbrozek AS, Dukes EM. The validity and reproducibility of a work productivity and activity impairment instrument. *Pharmacoeconomics* 1993;4:353-365.) and will be completed at the noted visits. The WPAI outcomes are expressed as impairment percentages, with higher numbers indicating greater impairment and less productivity (i.e., worse outcomes).
- 10

Administration of Study Treatments

- Ruxolitinib 1.5% cream or matching vehicle cream will be applied as a thin film BID on each pruriginous lesion and the surrounding area of the lesion (~ 1 cm), with applications at least 8 hours apart in the morning and in the evening at least 1 hour before bedtime.
- 20 On Day 1 and at Week 12 (if applicable), the participant will apply a thin film of study cream to the treatment area under the supervision of site staff. The treatment area is defined as the area affected by pruriginous lesions plus an ~ 1 cm area surrounding each lesion. During the DBVC period, all other applications of study cream will be applied by the participant to the treatment area identified at baseline. The total BSA treatment area must be $\leq 20\%$. Participants should not apply the application of study cream at home prior to clinic visits at Week 2, Week 12/end of treatment (EOT)1, and Week 52/EOT2.
- 25

- At the baseline visit, an estimate of the %BSA treatment area will be used by the IRT system to calculate the number of tubes of study cream to be dispensed. All areas identified at baseline should continue to be treated through the end of the DBVC period (Week 12) unless the participant meets criteria for stopping study cream. If there are new pruriginous lesions to be treated, after consultation with the investigator, study cream should be applied to these lesions in addition to the areas treated at baseline (total BSA treatment area must be $\leq 20\%$), and the percentage of BSA to be treated will be recalculated and increased. This new estimate will be entered into the interactive response technology (IRT) system to calculate the number of tubes of study cream to be dispensed.
- 30
- 35

During the OLE period starting at the Week 12 visit, pruriginous lesions will be evaluated by the investigator to confirm whether the participant still requires continuation

5 of therapy (ie, IGA-CPG-S score ≥ 1 and/or the presence of itching related to PN).
Participants with an IGA-CPG-S score of 0 may continue or restart therapy if there is itch
associated with underlying PN, or they can otherwise (re)enter the observation/no-
treatment cycle (i.e., IGA score of 0 and WI-NRS score of 0). At Week 12, the IRT system
will dispense a prespecified number of tubes according to the assessment of total BSA
10 treatment area.

Between OLE study visits, participants will treat all areas identified with
pruriginous lesions and/or itch associated with PN (total BSA treatment area must be $\leq$
20%). If all signs and symptoms of PN resolve between study visits, the participant will
contact the investigator to confirm that study cream applications should be stopped 3 days
15 after the lesions and itch have disappeared. If this 3-day window is during a study visit, and
the IGA-CPG-S score is 0 and itch has resolved, as assessed by the investigator, treatment
is to be stopped at the study visit.

If a participant has stopped treatment during the OLE period, treatment may be
restarted after consultation with the investigator that the participant has an IGA-CPG-S
20 score ≥ 1 and/or the presence of PN-related itching (WI-NRS score > 0). In the event that
new pruriginous lesions are outside of the usual location and/or are more widespread than
at the prior visit, the participant is required to contact the site for approval. Approval to
treat additional areas may occur via telephone or other modes of communication during the
OLE period; however, the investigator, at their discretion, may ask the participant to return
25 for an unscheduled visit.

The amount of study cream used per application will be determined by weighing a
tube (including the cap) before and after the participant applies study cream to the affected
areas at Day 1. All tubes (including caps) of study cream will be weighed before being
dispensed. All returned tubes (including caps) of study cream will also be weighed.

30 Application instructions will be provided by the site staff, and the participant will
record their daily applications in the eDiary.

Table 9 presents the study treatment information.

Table 9

	Ruxolitinib	Vehicle
Mechanism of action	JAK1/2 inhibitor	Not applicable
Dosage formulation	Cream	Cream
Unit dose strength(s)/dosage level(s)	1.5%	Not applicable
Application instructions	<u>DBVC period</u>: Apply a thin film to pruriginous lesions identified at baseline (plus an ~ 1 cm area surrounding each lesion) in the morning and at least 1 hour before bedtime with applications at least 8 hours apart for 12 weeks. <u>OLE period</u>: Apply a thin film to pruriginous lesions (plus an ~ 1 cm area surrounding each lesion) in the morning and at least 1 hour before bedtime with applications at least 8 hours apart as needed for 40 weeks.	
Packaging and labeling	Ruxolitinib or vehicle cream will be provided in a 60-g tube. Each tube will be labeled as required per country requirement.	
Storage	15°C-30°C (59°F-86°F)	
Status of treatment in participating countries	Investigational	

5

Table 10 presents the schedule of activities for the double-blind vehicle-controlled period.

Table 10

	Screening	DBVC Period				
	Days -28 to -1	Baseline/Day 1	Week 2 (± 3 d)	Week 4 (± 3 d)	Week 8 (± 3 d)	Week 12/EOT 1 (± 3 d)
Visit Day (Range)						
Administrative procedures						
Informed consent (including photographic and skin tape ICF, as applicable)	X					
Informed consent for optional qualitative exit interviews Note: A subgroup of participants at sponsor-selected	X					

Visit Day (Range)	Screening	DBVC Period				
	Days –28 to –1	Baseline/Day 1	Week 2 (± 3 d)	Week 4 (± 3 d)	Week 8 (± 3 d)	Week 12/EOT 1 (± 3 d)
sites will be included in a substudy involving exit interviews						
Contact IRT	X	X	X	X	X	X
Inclusion/exclusion criteria review	X	X				
Demography and medical history (general and disease, including Fitzpatrick Skin Type)	X					
Prior/concomitant medications	X	X	X	X	X	X
Apply study cream in clinic under site supervision		X				X
Weigh/dispense study cream		X	X	X	X	X
Distribute reminder cards	X	X	X	X	X	X
Collect/weigh study cream			X	X	X	X
Issue eDiary	X					
Assess eDiary study cream application compliance		X	X	X	X	X
Assess eDiary PRO compliance	X	X	X	X	X	X
Contact participant 1 week prior to each study visit to confirm compliance with WI-NRS assessment		X	X	X	X	X
Safety assessments						
AE assessments	X	X	X	X	X	X
Comprehensive physical examination	X					

Visit Day (Range)	Screening	DBVC Period				
	Days –28 to –1	Baseline/Day 1	Week 2 (± 3 d)	Week 4 (± 3 d)	Week 8 (± 3 d)	Week 12/EOT 1 (± 3 d)
Targeted physical examination (as needed based on AEs)		X	X	X	X	X
Height and body weight	X					
Vital signs	X	X	X	X	X	X
12-lead ECG	X					
Efficacy assessments						
WI-NRS	eDiary is completed each evening from screening through the last application of study cream.					
%BSA of estimated treatment area*†	X	X	X	X	X	X
IGA-CPG-S	X	X	X	X	X	X
IGA-CPG-A	X	X	X	X	X	X
PAS	X	X	X	X	X	X
Photography		X	X	X	X	X
Patient-reported outcomes						
Skin Pain NRS	eDiary is completed each evening from screening through the last application of study cream.					
DLQI		X	X	X	X	X
EQ-5D-5L		X	X	X	X	X
HADS		X	X	X	X	X
PGIS		X	X	X	X	X
PGIC			X	X	X	X
FACIT-Fatigue		X	X	X	X	X
PROMIS Sleep		X	X	X	X	X
WPAI		X	X	X	X	X
Laboratory assessments						
Chemistry assessments	X	X*				X
Hematology assessments	X	X*				X
FSH	X					
Serum pregnancy test	X					
Urine pregnancy test		X		X	X	X
HIV serology	X					
Hepatitis testing	X					

Visit Day (Range)	Screening	DBVC Period				
	Days –28 to –1	Baseline/Day 1	Week 2 (± 3 d)	Week 4 (± 3 d)	Week 8 (± 3 d)	Week 12/EOT 1 (± 3 d)
Thyroid test	X					

- 5 Note: All Week 12 assessments must be completed before the participant can continue into the OLE period. Study cream will not be applied in the clinic at Week 12 for participants not continuing into the OLE period.

Note: Patient-reported outcomes (with the exception of the WI-NRS and Skin Pain NRS) must be conducted before any other assessments.

- 10 Note: Blood draw for clinical laboratory tests must be performed before the in-clinic study cream application.

Note: Pharmacokinetic assessments must be performed before study cream application.

Table 11 presents the schedule of activities for the open-label extension (OLE) period.

15

Table 11

Visit Day (Range)	OLE Period					Safety Follow-Up
	Week 14 (± 3 d)	Week 16, 20, 24 (± 3 d)	Week 28, 32, 36 (± 3 d)	Week 40, 44, 48 (± 3 d)	Week 52/EOT2, ET (± 3 d)	30 Days (+ 7 d) After Last Dose
Administrative procedures						
Contact IRT	X	X	X	X	X	
Prior/concomitant medications	X	X	X	X	X	X
Weigh/dispense study cream	X	X	X	X		
Distribute reminder cards	X	X	X	X	X	
Collect/weigh study cream	X	X	X	X	X	
Assess eDiary study cream application compliance	X	X	X	X	X	
Assess eDiary PRO compliance	X	X	X	X	X	
Contact participant 1 week prior to each study visit to confirm compliance with WI-NRS assessment	X	X	X	X	X	
Safety assessments						
AE assessments*	X	X	X	X	X	X

Visit Day (Range)	OLE Period					Safety Follow-Up
	Week 14 (± 3 d)	Week 16, 20, 24 (± 3 d)	Week 28, 32, 36 (± 3 d)	Week 40, 44, 48 (± 3 d)	Week 52/EOT2, ET (± 3 d)	30 Days (+ 7 d) After Last Dose
Comprehensive physical examination						X
Targeted physical examination (as needed; based on AEs)	X	X	X	X	X	X
Vital signs	X	X	X	X	X	X
Efficacy assessments						
WI-NRS	eDiary is completed each evening from screening through the last application of study cream.					
%BSA of treatment area*	X	X	X	X	X	X
IGA-CPG-S	X	X	X	X	X	X
IGA-CPG-A	X	X	X	X	X	X
PAS	X	X	X	X	X	X
Photography	X	X*	X†	X‡	X	
Patient-reported outcomes						
Skin Pain NRS	eDiary is completed each evening from screening through the last application of study cream.					
DLQI	X	X	X	X	X	X
EQ-5D-5L	X	X	X	X	X	
HADS	X	X	X	X	X	X
PGIS	X	X	X	X	X	X
PGIC	X	X	X	X	X	X
FACIT-Fatigue	X	X	X	X	X	X
PROMIS Sleep	X	X	X	X	X	X
WPAI	X	X	X	X	X	X
Laboratory assessments						
Chemistry assessments		X			X	X
Hematology assessments		X			X	X
Urine pregnancy test	X	X	X	X	X	X
PK assessments						
PK blood					X	

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Example 4: Blinded Clinical Trial Results from Example 3

The clinical trial in Example 3 was conducted and blinded data was available from a small set of patients through week 12. The early blinded data is only a small percentage

- 5 from the total enrollment from this Phase 3, multicenter, randomized, double-blinded, vehicle-controlled (DBVC), parallel-group study in adults with PN. That preliminary blinded data is presented below.

- 10 **Tables 12 and 13** describe the study participant characteristics at the data cut-off date. Specifically, **Table 12** presents summary data of participant dispositions in the DBVC period (intent-to-treat population). **Table 13** presents a summary of demographics and baseline characteristics of the intent-to-treat population at the data cut-off date. As noted in Table 12, the set of blinded patient data is from a treatment group of 62, in which 58 participants were treated.

Table 12

Variable:	Treatment Group Total (N=62)
Number (%) of participants treated	58 (93.5)
Number (%) of participants who completed treatment	17 (27.4)
Number (%) of participants with ongoing treatment	39 (62.9)
Number (%) of participants randomized without treatment information	4 (6.5)
Number (%) of participants discontinued from treatment	2 (3.2)
Primary Reason:	
Adverse Event	0 (0.0)
Death	0 (0.0)
Lost to Follow-up	0 (0.0)
Non-Compliance With Study Drug	0 (0.0)
Physician Decision	0 (0.0)
Pregnancy	0 (0.0)
Lack of Efficacy	0 (0.0)
Protocol Deviation	0 (0.0)
Study Terminated by Sponsor	0 (0.0)
Withdrawal by Subject	1 (1.6)
COVID-19 Pandemic	0 (0.0)
Other	0 (0.0)
Number (%) of participants discontinued from study	4 (6.5)
Primary Reason:	
Adverse Event	0 (0.0)
Death	0 (0.0)
Lost to Follow-up	0 (0.0)
Non-Compliance With Study Drug	0 (0.0)

Physician Decision	0 (0.0)
Pregnancy	0 (0.0)
Lack of Efficacy	0 (0.0)
Protocol Deviation	2 (3.2)
Study Terminated by Sponsor	0 (0.0)
Withdrawal by Subject	2 (3.2)
COVID-19 Pandemic	0 (0.0)
Other	0 (0.0)

5

Table 13

Variable:	Treatment Group Total (N=62)
Age (years)	
N	62
Mean	65.4
STD	9.19
Min	38
Median	67.0
Max	79
12-<18 years - n(%)	0 (0.0)
18-<65 years - n(%)	23 (37.1)
>=65 years - n(%)	39 (62.9)
Sex - n(%)	
Male	17 (27.4)
Female	45 (72.6)
Race - n (%)	
White/Caucasian	47 (75.8)
Black or African American	11 (17.7)
Asian and Others	4 (6.5)
Ethnicity - n (%)	
Hispanic or Latino	2 (3.2)
Not Hispanic or Latino	59 (95.2)
Not Reported	0 (0.0)
Unknown	1 (1.6)
Missing	0 (0.0)
Region - n (%)	
North America	62 (100.0)
Europe	0 (0.0)

- 5 **Table 14** presents a summary and analysis of participants achieving ≥ 4 point improvement in WI-NRS score by visit during the DBVC period (intent-to-treat population). Treatment group total (N=62).

Table 14

Weeks of Treatment	Total Patients	Number (%) of Participants Achieving WI-NRS4
Week 2	51	6 (11.8)
Week 4	47	12 (25.5)
Week 8	36	9 (25.0)
Week 12	26	5 (19.2)

- Abbreviations: WI-NRS = Worst-Itch Numeric Rating Scale; DBVC = Double-blind, Vehicle-controlled; WI-NRS Baseline was derived as averaging the 7 daily WI-NRS scores before Day 1 (Day -7 to Day -1). Note: A WI-NRS4 defined as achieving a ≥ 4 point improvement (reduction) in WI-NRS score from baseline.
- 10

From **Table 14**, the blinded data demonstrates from 11.8% to 25.5% of the participants achieved a WI-NRS4 between weeks 2 to 12.

- 15 **Table 15** presents a summary and analysis of participants achieving a ≥ 4 point improvement in daily WI-NRS score during the first 14 days of DBVC period (intent-to-treat population). Treatment group total (N=62).

Table 15

Days on Treatment	Total Patients	Number (%) of Participants Achieving Daily WI-NRS4
Day 1	54	3 (5.6)
Day 2	55	4 (7.3)
Day 3	54	6 (11.1)
Day 4	55	5 (9.1)
Day 5	53	8 (15.1)
Day 6	55	8 (14.5)
Day 7	47	9 (19.1)
Day 8	50	7 (14.0)
Day 9	47	9 (19.1)
Day 10	44	6 (13.6)
Day 11	51	8 (15.7)
Day 12	45	12 (26.7)
Day 13	51	11 (21.6)
Day 14	48	11 (22.9)

5 Abbreviations: WI-NRS = Worst-Itch Numeric Rating Scale; DBVC = Double-blind, Vehicle-controlled; WI-NRS Baseline was derived as last non-missing record before Day 1 (Day -7 to Day -1).

Note: A WI-NRS4 defined as achieving a ≥ 4 -point improvement (reduction) in WI-NRS score from baseline.

10 As show in **Table 15**, from Day 1 to Day 14, the blinded data show an increase from Day 1 at 5.6% to Day 14 at 22.9% of participants achieving a WI-NRS4, WI-NRS4 defined as achieving a ≥ 4 -point improvement (reduction) in WI-NRS score from baseline.

Table 16 presents a summary and analysis of participants achieving Investigator's Global Assessment for Stage of Chronic Prurigo Treatment Success (IGA-CPG-S-TS) during the DBVC period (intent-to-treat population). Treatment group total (N=62).

Table 16

Weeks on Treatment	Total Patients	Number (%) of Participants Achieving IGA-CPG-S-TS
Week 2	55	1 (1.8)
Week 4	51	2 (3.9)
Week 8	41	7 (17.1)
Week 12	28	3 (10.7)

Abbreviations: IGA-CPG-S-TS = Investigator's Global Assessment for Stage of Chronic Prurigo Treatment Success; DBVC = Double-blind, Vehicle-controlled.

Note: An IGA-CPG-S-TS responder was defined as a participant achieving IGA-CPG-S score of 0 or 1 with at least 2-grade improvement from baseline.

Various modifications of the invention, in addition to those described herein, will be apparent to those skilled in the art from the foregoing description. Such modifications are also intended to fall within the scope of the appended claims. U.S. Provisional Application No. 63/183,249, filed May 3, 2021, and its U.S. non-provisional application entitled "JAK1 Pathway Inhibitors for Treatment Of Prurigo Nodularis", filed May 3, 2022, are incorporated herein by reference in their entireties. Each reference, including all patent, patent applications, and publications, cited in the present application is incorporated herein by reference its entirety.

WHAT IS CLAIMED IS:

1. A method for treating prurigo nodularis in a subject, said method comprising administering to the subject a therapeutically effective amount of ruxolitinib, or a pharmaceutically acceptable salt thereof.
2. The method of claim 1, wherein the ruxolitinib, or a pharmaceutically acceptable salt thereof, is ruxolitinib phosphate.
3. The method of claim 1, wherein the ruxolitinib, or a pharmaceutically acceptable salt thereof, is administered topically to an affected skin area.
4. The method of claim 1, wherein the ruxolitinib, or a pharmaceutically acceptable salt thereof, is administered as a topical formulation.
5. The method of claim 4, wherein the topical formulation is administered as a topical formulation comprising about 0.1% to about 3% of the ruxolitinib, or the pharmaceutically acceptable salt thereof, on a free base basis.
6. The method of claim 4, wherein the topical formulation is administered as a topical formulation comprising about 0.5% to about 1.5% of the ruxolitinib, or the pharmaceutically acceptable salt thereof, on a free base basis.
7. The method of claim 4, wherein the topical formulation is administered as a topical formulation comprising about 0.75% to about 1.5% of the ruxolitinib, or the pharmaceutically acceptable salt thereof, on a free base basis.
8. The method of claim 4, wherein the topical formulation is administered as a topical formulation comprising about 0.75% of the ruxolitinib, or the pharmaceutically acceptable salt thereof, on a free base basis.
9. The method of claim 4, wherein the topical formulation is administered as a topical formulation comprising about 1% of the ruxolitinib, or the pharmaceutically

acceptable salt thereof, on a free base basis.

10. The method of claim 4, wherein the topical formulation is administered as a topical formulation comprising about 1.5% of the ruxolitinib, or the pharmaceutically acceptable salt thereof, on a free base basis.

11. The method of claim 4, wherein the topical formulation is administered twice per day (BID).

12. The method of claim 4, wherein the topical formulation is administered once per day (QD).

13. The method of claim 4, wherein the topical formulation is administered for at least 12 weeks.

14. The method of claim 4, wherein the topical formulation is a cream formulation.

15. The method of claim 1, wherein the subject achieves an IGA score of 0 or 1 with 2: 2 grade improvement from baseline.

16. The method of claim 1, wherein the subject achieves an improvement in a subject's response to Itch NRS from baseline.

17. The method of claim 1, wherein the subject achieves about a 5%, about a 10%, about a 20%, about a 30%, about a 40%, about a 50%, about a 60%, about a 70%, about a 80%, about a 90%, or about a 95% improvement in a subject's response to Itch NRS from baseline.

18. The method of claim 1, wherein the subject achieves about a 5%, about a 10%, about a 20%, about a 30%, about a 40%, about a 50%, about a 60%, about a 70%, about a 80%, about a 90%, or about a 95% improvement in a subject's response in Prurigo Activity Score (PAS) from baseline.

19. The method of claim 1, wherein the subject achieves about a 5%, about a

10%, about a 20%, about a 30%, about a 40%, about a 50%, about a 60%, about a 70%, about a 80%, about a 90%, or about a 95% improvement in a subject's response in Itchy Quality of Life (Itchy QoL) from baseline.

20. The method of claim 1, wherein the subject achieves about a 5%, about a 10%, about a 20%, about a 30%, about a 40%, about a 50%, about a 60%, about a 70%, about a 80%, about a 90%, or about a 95% improvement in a subject's response in Dynamic Pruritus Score (DPS) from baseline.

21. The method of claim 1, wherein the subject achieves about a 5%, about a 10%, about a 20%, about a 30%, about a 40%, about a 50%, about a 60%, about a 70%, about a 80%, about a 90%, or about a 95% improvement in a subject's response to DLQI from baseline.

22. The method of claim 1, wherein the subject has an itch Numerical Rating Scale of at least 4 at baseline.

23. The method of claim 1, wherein the subject is aged 18 or older.

24. The method of claim 1, wherein the ruxolitinib, or pharmaceutically acceptable salt thereof, is administered in combination with a further therapeutic agent.