

RUXOLITINIB FOR TREATING HIDRADENITIS SUPPURATIVA (HS)

[0001] The present application claims priority to U.S. Provisional Application Nos. 63/604,937, filed December 1, 2023, 63/617,826, filed January 5, 2024, 63/551,210, filed February 8, 2024, and 63/643,875, filed May 7, 2024; the content of each application is incorporated herein by reference in its entirety.

FIELD

[0002] This disclosure relates to methods for treating patients with hidradenitis suppurativa (HS) by administering a ruxolitinib formulation one to two times per day. The present disclosure is also directed to methods for reducing skin pain and/or reducing itch in patients with HS by administering a ruxolitinib formulation one to two times per day.

BACKGROUND

[0003] Hidradenitis suppurativa is a debilitating, chronic inflammatory skin condition that affects the hair follicle leading to a perifollicular lympho-histiocytic inflammation. Zouboulis CC, Desai N, Emtestam L, et al. European S1 guideline for the treatment of hidradenitis suppurativa/acne inversa. J Eur Acad Dermatol Venereol 2015;29:619-644. It is characterized by persistent or recurrent painful inflamed nodules and abscesses, and purulent-discharging tunnels referred to as sinus tracts and fistulas often localized in skin folds of axillary, inguinal, gluteal, and perianal areas of the body. Saunte DML, Jemec GBE. Hidradenitis suppurativa: advances in diagnosis and treatment. JAMA 2017;318:2019-2032. In more severe disease, irreversible scarring is identified. Sabat R, Jemec GBE, Matusiak Ł, Kimball AB, Prens E, Wolk K. Hidradenitis suppurativa. Nat Rev Dis Primers 2020;6:18. Hidradenitis suppurativa diagnosis is made on clinical assessment and disease severity may be measured based on clinical manifestations including nodule

phenotype in intertriginous body areas. The course of the disease may vary from mild disease (recurrent appearance of solitary or multiple isolated abscess formation without sinus tracts or scarring) to severe disease (deep fluctuant abscesses, draining sinuses, and severe, interconnected sinus tracts or scars. Frew JW. Therapeutic biomarkers in hidradenitis suppurativa: one step closer to the clinic. *Br J Dermatol* 2021;185:696-697. The quality of life of HS patients is significantly impacted leading to psychological impairment (e.g., anxiety, depression, etc.) and poor-body image. Kurek A, Johanne Peters EM, Sabat R, Sterry W, Schneider-Burrus S. Depression is a frequent co-morbidity in patients with acne inversa. *J Dtsch Derm Ges* 2013;11:743-750; Schneider-Burrus S, Jost A, Peters EMJ, Witte-Haendel E, Sterry W, Sabat R. Association of hidradenitis suppurativa with body image. *JAMA Dermatol* 2018;154:447-451.

[0004] The estimated prevalence of HS varies depending on the different populations and methods of reporting. The highest prevalence (approximately 4%) has been reported in those between 20 to 40 years of age with onset of disease usually at 20 years of age and declining after the fifth decade of life. Jemec GBE, Kimball AB. Hidradenitis suppurativa: epidemiology and scope of the problem. *J Am Acad Dermatol* 2015;73(suppl 1):S4-S7. The incidence of HS in females has been reported to be as high as 3 times that of men. Canoui-Poitrine F, Le Thuaut A, Revuz JE, et al. Identification of three hidradenitis suppurativa phenotypes: latent class analysis of a cross-sectional study. *J Invest Dermatol* 2013;133:1506-1511.

[0005] The etiology of HS is multifactorial, comprised of genetic and environmental factors, lifestyle (e.g., smoking), hormonal status, and other comorbidities (metabolic syndrome, cardiovascular disorders, inflammatory bowel disease, etc. Zouboulis CC, Tzellos T, Kyrgidis A, et al. Development and validation

of the International Hidradenitis Suppurativa Severity Score System (IHS4), a novel dynamic scoring system to assess HS severity. *Br J Dermatol* 2017;177:1401-1409.

[0006] Current treatment guidelines recommend tailoring HS treatment based on its individual subjective impact and objective severity of disease. Zouboulis CC, Desai N, Emtestam L, et al. European S1 guideline for the treatment of hidradenitis suppurativa/acne inversa. *J Eur Acad Dermatol Venereol* 2015;29:619-644. The aim of initial management of patients with HS is to reduce lesion development and minimizing disease progression. Treatments may include topical antiseptics, antibiotics (clindamycin, rifampin, tetracyclines) as the first line of therapy, followed by intralesional steroid injections (triamcinolone), retinoids (acitretin), hormonal therapy (Estrace, Prefest), biologics (adalimumab, infliximab) and in more advanced cases, surgery. Currently, adalimumab (Humira®), a TNF- α fully human monoclonal antibody administered via subcutaneous injection, is the only FDA-approved therapy for patients 12 years of age and older with moderate-to-severe HS. Adalimumab has shown modest HiSCR response rates (42% and 59% vs placebo 26% and 28%, respectively) in each of the Phase 3 trials. Frew JW, Jiang CS, Singh N, et al. Clinical response rates, placebo response rates, and significantly associated covariates are dependent on choice of outcome measure in hidradenitis suppurativa: a post hoc analysis of PIONEER 1 and 2 individual patient data. *J Am Acad Dermatol* 2020;82:1150-1157. At this time, there are no FDA-approved therapies for patients with mild HS. Therapies to treat patients with mild HS remain an unmet medical need to manage disease progression into a moderate-to-severe condition. This disclosure addresses this need and others.

SUMMARY OF THE DISCLOSURE

[0007] The present disclosure provides, *inter alia*, methods for treating human patients suffering from hidradenitis suppurative (HS) comprising administering ruxolitinib, or a pharmaceutically acceptable salt thereof.

[0008] The present disclosure is also directed to methods of reducing skin pain in human patients with HS comprising administering ruxolitinib, or a pharmaceutically acceptable salt thereof.

[0009] The present disclosure is further directed to methods of reducing itch in human patients with HS comprising administering ruxolitinib, or a pharmaceutically acceptable salt thereof.

[0010] The present disclosure further provides a topical formulation comprising ruxolitinib, or a pharmaceutically acceptable salt thereof, for use in any of the methods described herein.

[0011] The present disclosure also provides use of a topical formulation, comprising ruxolitinib, or a pharmaceutically acceptable salt thereof, for manufacture of a medicament for use in any of the methods described herein.

[0012] The details of one or more embodiments of the disclosure are set forth in the description below. Other features, objects, and advantages of the disclosure will be apparent from the description and drawings, and from the claims.

BRIEF DESCRIPTION OF DRAWINGS

[0013] **FIG. 1** graphically illustrates the mean and standard error of the abscess and inflammatory nodules (AN) count during the treatment period from baseline to week 32.

[0014] **FIG. 2** plots the number of participants at each visit versus the proportion of AN50 responses. An AN50 responder is as a subject achieving $\geq 50\%$ reduction in AN count relative to baseline.

[0015] **FIG. 3** plots the number of participants at each visit versus the proportion of AN75 responses. An AN75 responder is as a subject achieving $\geq 75\%$ reduction in AN count relative to baseline.

[0016] **FIG. 4** plots the proportion of patients achieving Hidradenitis Suppurativa Clinical Response (HiSCR) during the treatment period.

[0017] **FIG. 5** graphically illustrates the mean and standard error by visit of Skin Pain NRS during the treatment period.

[0018] **FIG. 6** graphically illustrates the mean and standard error by visit of Itch NRS score during the treatment period.

[0019] **FIG. 7** graphically illustrates the mean and standard error by visit of the IHS4 score.

DESCRIPTION

[0020] Definitions

[0021] As used herein, "an affected skin area" refers to an area of the patient's skin having hidradenitis suppurativa (HS).

[0022] As used herein, "ruxolitinib phosphate" means the phosphoric acid salt of ruxolitinib, wherein the ruxolitinib and phosphoric acid are in a 1:1 ratio.

[0023] In some embodiments, "cream" means an emulsion, semisolid dosage form for application to the skin.

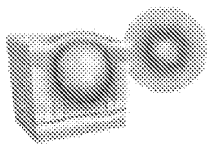
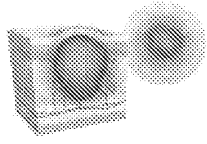
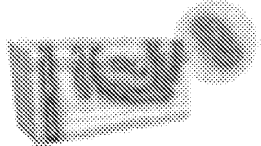
[0024] When the methods refer to "at day 2", "at week 4", "at week 8", "at week 12", "within 36 hours", or "within 12 hours" of the administering, this refers to the time

period following the first dose of the topical formulation wherein there is no interruption in the administration.

[0025] Definitions and schematics of various HS lesions are provided in

Table 1 to aid in the identification of the different morphologies.

[0026] **Table 1:** Definition of Hidradenitis Suppurativa Lesions

HS Lesion	Definition	Schematic
Abscess	A tender, fluctuant (compressible), palpable lesion, with erythema.	
Inflammatory nodule	A solid, spherical, palpable lesion >1 cm; tender and/or erythematous. Note: a noninflammatory nodule is defined as nontender, nonerythematous nodule.	
Tunnel (nondraining)	Compression of surrounding structures does not elicit drainage of contents.	
Tunnel (draining) ^a	A linear tract that may open onto the skin surface; drainage expressed at rest or with compression of surrounding structures.	

[0027] As used herein, “Hidradenitis Suppurativa Clinical Response” or “HiSCR” is defined as at least 50% reduction in AN count with no increase in either abscess or draining fistula counts, relative to baseline. As used herein, “AN count” is directed to a total abscess and inflammatory nodule counts. As used herein, “modified Hidradenitis Suppurativa Clinical Response” or “mHiSCR” is defined as at least 50% reduction in inflammatory nodule count with no increase in either abscess or draining fistula counts, relative to baseline. As discussed above, “an inflammatory nodule” refers to as nontender, nonerythematous nodule.

[0028] As used herein, “International Hidradenitis Suppurativa Severity Score System” or “IHS4” is a composite, dynamic score, and validated tool used to determine HS severity. Zouboulis CC, Tzellos T, Kyrgidis A, et al. Development and validation of the International Hidradenitis Suppurativa Severity Score System (IHS4), a novel dynamic scoring system to assess HS severity. *Br J Dermatol* 2017;177:1401-1409. It employs a weighted scale using the number of inflammatory nodules, the number of abscesses, and the number of draining tunnels (fistulas or sinuses), with respective weight factors of 1, 2, and 4 (Example: IHS4 score equals the number of inflammatory nodules [multiplied by 1] plus the number of abscesses [multiplied by 2] plus the number of draining tunnels [multiplied by 4]). As under herein, “ISH4-554” refers to $\geq$ 55% reduction from baseline in the total IHS4 score. In some embodiments, the IHS4-55 score is measured at a time point, e.g., at 16 weeks. The IHS4-55 score represents a milder patient population for moderate to severe HS.

[0029] As used herein, “flare incidence” is the measurement of flares is an important component of treatment and its incidence is correlated with the deterioration of a patient's quality of life (Sabat R, Jemec GBE, Matusiak Ł, Kimball AB, Prens E, Wolk K. Hidradenitis suppurativa. *Nat Rev Dis Primers* 2020;6:18.). Flare is defined as at least a 25% increase in AN count with a minimum increase in AN of 2, relative to baseline.

[0030] As used herein, the “Hurley classification” is a static score and the Hurley Stages of Hidradenitis Suppurativa are provided in **Table 2**.

[0031] **Table 2:** Hurley Stages of Hidradenitis Suppurativa

Hurley Stage	Description
I	Abscess formation, single or multiple, without sinus tracts and cicatrization/scarring.

Hurley Stage	Description
II	One or more widely separated recurrent abscesses with tract formation and cicatrization/scarring.
III	Multiple interconnected tracts and abscesses across the entire area, with diffuse or near diffuse involvement.

[0032] As used herein, total % body surface area (BSA) assessment can be approximated to the nearest 0.1% using the Palmar Method as a guide, with the palm plus 5 digits, with fingers tucked together and thumb tucked to the side (handprint), considered as 1% BSA and the thumb as 0.1% BSA.

[0033] As used herein, the Skin Pain and Itch NRS via an eDiary is a daily patient-reported measure (24-hour recall) of the worst level of skin pain and itch intensity related to HS. As used herein, "Itch NRS" and "Skin Pain NRS" are the following rated by the patient:

[0034] Skin Pain NRS: Pain severity of their HS by selecting a number from 0 (no pain) to 10 (worst imaginable pain) that best describes their worst level of pain in the past 24 hours.

[0035] Itch NRS: Itch severity of their HS 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.

[0036] As used herein, "Hidradenitis Suppurativa Quality of Life" or "HiSQOL" is a 17-item HS-specific health-related quality of life instrument with a 7-day recall period (Kirby JS, Thorlacius L, Villumsen B, et al. The Hidradenitis Suppurativa Quality of Life (HiSQOL) score: development and validation of a measure for clinical trials. Br J Dermatol 2020;183:340-348), and it can be used to assess the HS symptoms and the impact of HS problems on quality of life.

[0037] As used herein, "Dermatology Life Quality Index" or "DLQI" is a 10-question validated questionnaire to measure how much the skin problem has affected the participant over the previous 7 days (Finlay AY, Khan GK. Dermatology Life Quality Index (DLQI) — a simple practical measure for routine clinical use. Clin Exp Dermatol 1994;19:210-216). The participant will answer the questionnaire with either (1) very much, (2) a lot, (3) a little, or (4) not at all. The questionnaire is analyzed under 6 headings as follows:

[0038] Symptoms and feelings (Questions 1 and 2)

[0039] Daily activities (Questions 3 and 4)

[0040] Leisure (Questions 5 and 6)

[0041] Work and school (Question 7)

[0042] Personal relations (Questions 8 and 9)

[0043] Treatment (Question 10)

[0044] As used herein, "Patient Global Impression of Change" or "PGIC" is a self-reporting measure that reflects the patient's belief about the efficacy of treatment. The PGIC is a 7-point scale depicting a participant's rating of overall improvement and will be captured during site visits as outlined in the SoA (Hurst H, Bolton J. Assessing the clinical significance of change scores recorded on subjective outcome measures. J Manipulative Physiol Ther 2004;27:26-35). The patient will answer the following: "Since the start of the treatment you've received in this study, your HS has: (1) very much improved, (2) much improved, (3) minimally improved, (4) no change, (5) minimally worse, (6) much worse, and (7) very much worse."

[0045] As used herein, "Work Productivity and Activity Impairment – Hidradenitis Suppurativa" or "WPAI-HS" is a questionnaire used to measure impairments in both paid work and unpaid work. It measures absenteeism,

presenteeism as well as the impairments in unpaid activity because of hidradenitis suppurativa and other health problems during the past 7 days. Minimal clinically important difference is defined as one-half standard deviation of the total population's baseline score. Absenteeism, presenteeism, and overall work impairment will be assessed only for employed patients (Reilly MC, Zbrozek AS, Dukes EM. The validity and reproducibility of a work productivity and activity impairment instrument. *Pharmacoeconomics* 1993;4:353-365).

[0046] As used herein, "EQ-5D-5L" is a questionnaire 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* 2011;20:1727-1736). The EQ-5D-5L provides data for use in economic models and analyses including developing health utilities or quality adjusted life years. The EQ-5D-5L consists of 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. Each dimension has 5 levels: no problems, slight problems, moderate problems, severe problems, and extreme problems. The EQ VAS records the participant's self-rated health on a vertical visual analogue scale (0 to 100), where the endpoints are labeled 'The best health you can imagine' and 'The worst health you can imagine'.

[0047] As used herein, "BID" refers to two times per day.

[0048] As used herein, "QD" refers to once per day.

[0049] As used herein, "statistically significant" means a p-value of < 0.05 (for example, < 0.001, and such as < 0.0001).

[0050] As used herein, the phrase "pharmaceutically acceptable" means those compounds, materials, compositions, and/or dosage forms, which are, within

the scope of sound medical judgment, suitable for use in contact with tissues of humans and animals. In some embodiments, "pharmaceutically acceptable" means approved by a regulatory agency of the Federal or a state government or listed in the U.S. Pharmacopeia or other generally recognized pharmacopeia for use in animals, and more particularly in humans.

[0051] The present disclosure also includes pharmaceutically acceptable salts of the 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. The pharmaceutically acceptable salts of the present disclosure 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 disclosure can be synthesized from the parent compound that 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 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, nonaqueous media like ether, ethyl acetate, ethanol, isopropanol, or acetonitrile (MeCN) 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 Science*, 66, 2 (1977), each of which is incorporated herein by reference in its entirety. In some embodiments, the pharmaceutically acceptable salt is a phosphoric acid salt, a sulfuric acid salt, or a maleic acid salt.

[0052] As used herein, the term “emulsifier component” refers, in one aspect, to a substance, 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.

[0053] As used herein, the term “occlusive agent component” refers to a hydrophobic agent 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.

[0054] 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 rheology of the cream.

[0055] As used herein, the term “emollient component” refers to an agent that softens or soothes the skin or soothes an irritated internal surface.

[0056] 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 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.

[0057] 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 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 3. In some embodiments,

a solvent is a substance or mixture thereof, in 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.

[0058] As used herein, the phrase “antimicrobial preservative component” is a substance or mixtures of substances, which inhibits microbial growth in the cream.

[0059] 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.

[0060] 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 = $[(\text{mass of component A}) / (\text{total mass of the emulsion})] \times 100$.

[0061] 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, ruxolitinib).

[0062] As used herein, “% by weight of the formulation 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 formulation. For example, “1.5% w/w on a free base basis” of ruxolitinib phosphate means that for 100 grams of total formulation, there are 0.66 grams of ruxolitinib phosphate in the formulation (which equates to 1.5 grams of the free base, ruxolitinib).

[0063] As used herein, the term “component” can mean one substance or a mixture of substances.

[0064] 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 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 acid, sesquioleic acid, sesqui-9-octadecanoic acid, sesquiisooctadecanoic acid, behenic acid, isobehenic acid, and arachidonic acid, or mixtures thereof.

[0065] 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 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 alcohol, isobehenyl alcohol, selachyl alcohol, chimyl alcohol, and linoleyl alcohol, or mixtures thereof.

[0066] 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 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.

[0067] 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 sorbitan esters and polyethoxylated sorbitan esters. In some embodiments, the sorbitan fatty ester is a polyethoxylated sorbitan ester.

[0068] 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. 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 reference in its entirety.

[0069] 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 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, 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 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.

[0070] 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.

[0071] As used herein, the term “triglycerides” refers to a triglyceride of a fatty acid. In some embodiments, the triglyceride is medium chain triglycerides.

[0072] As used herein, the term “alkylene glycol” refers to a group of formula $-O\text{-alkylene-}$, 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).

[0073] As used herein, the term “polyethylene glycol” refers to a polymer containing ethylene glycol monomer units of formula $-O\text{-CH}_2\text{-CH}_2\text{-}$. 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 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 glycol-600, and polyethylene glycol-900. The number following the dash in the name refers to the average molecular weight of the polymer.

[0074] As used herein, the term “contacting” refers to the bringing together of indicated moieties in an *in vitro* system or an *in vivo* system. For example, “contacting”

a JAK with a compound of the disclosure includes the administration of a compound of the present application to an individual or patient, such as a human, having a JAK, as well as, for example, introducing a compound of the disclosure into a sample containing a cellular or purified preparation containing the JAK.

[0075] As used herein, “contains” is equivalent to “comprises”.

[0076] As used herein, the term “subject,” “individual,” or “patient,” used interchangeably, refers to humans. In some embodiments, the “subject,” “individual,” or “patient” is in need of said treatment.

[0077] In some embodiments, the compounds, or pharmaceutically acceptable salts thereof, or pharmaceutical formulations thereof, topical formulations thereof, as described herein are 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 other clinician.

[0078] 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); or (2) 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, treating refers to inhibiting or ameliorating the disease. In some embodiments, treating is preventing the disease.

[0079] In some embodiments, the components are present in exactly the ranges specified (e.g., the term “about” is not present). In some embodiments, “about” means plus or minus 10% of the value.

[0080] **Methods of Treatment**

[0081] The present invention provides, *inter alia*, a method of treating hidradenitis suppurativa (HS) in a human patient in need thereof, comprising topically administering to an affected skin area of the patient ruxolitinib, or a pharmaceutically acceptable salt thereof. The present disclosure is also directed to methods for reducing skin pain and/or reducing itch in patients with HS comprising topically administering to an affected skin area of the patient ruxolitinib, or a pharmaceutically acceptable salt thereof. In some embodiments, the ruxolitinib or the salt thereof is administered as a topical ruxolitinib formulation one to two times per day. Ruxolitinib is a JAK1/JAK2 inhibitor which is selective for JAK1 and JAK2 over JAK3.

[0082] In some embodiments, the ruxolitinib, or a pharmaceutically acceptable salt thereof, is ruxolitinib phosphate.

[0083] In some embodiments, the ruxolitinib, or a pharmaceutically acceptable salt thereof, is administered as a topical formulation.

[0084] In some embodiments, 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.

[0085] In some embodiments, the topical formulation is administered as a topical formulation comprising about 0.5% to about 2% of the ruxolitinib, or the pharmaceutically acceptable salt thereof, on a free base basis.

[0086] In some embodiments, 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.

[0087] 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.

[0088] 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 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 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.

[0089] In some embodiments, the topical formulation is administered twice per day (BID). In some embodiments, the topical formulation is administered once per day (QD).

[0090] In some embodiments, the administering is continued for 16 weeks.

[0091] In some embodiments, the administering is continued every day for 16 weeks.

[0092] In some embodiments, the ruxolitinib, or pharmaceutically acceptable salt thereof, is administered in combination with a further therapeutic agent.

[0093] In some embodiments, the administering comprises administering the ruxolitinib, or pharmaceutically acceptable salt thereof, together with at least one pharmaceutically acceptable carrier or excipient.

[0094] In some embodiments, the patient is aged 18 years or older.

[0095] In some embodiments, the patient has a diagnosis of HS for at least 3 months. In some embodiments, the patient has Hurley I or Hurley II HS. In some embodiments, the patient has no draining tunnels. In some embodiments, the patient has a total abscess and inflammatory nodule counts (AN count) of less than 10. In some embodiments, the patient has Hurley I or Hurley II HS with no draining tunnels. In some embodiments, the patient has Hurley I or Hurley II HS with an AN count of less than 10. In some embodiments, the patient has Hurley I or Hurley II HS with no draining tunnels and an AN count of less than 10. In some embodiments, the diagnosis of HS (Hurley I or II) with the following: (a) a total AN count of 3 to ≤ 10 , with no draining tunnels at screening and baseline visits, and (b) the AN count at the screening and baseline visits: AN of 3 should affect at least 1 distinct anatomical area and AN of > 3 to ≤ 10 should affect at least 2 distinct anatomical areas.

[0096] In some embodiments, the patient's baseline Skin Pain or Itch NRS score is ≥ 1 .

[0097] In some embodiments, efficacy of the treatment method disclosed herein can be established based upon change from baseline in AN count in a patient. The "abscess and inflammatory nodule counts" (AN counts) calculate change in AN count relative to baseline, as well as AN50, AN75, AN90, and AN100, defined respectively as at least a 50%, 75%, 90%, and 100% decrease in AN count relative to baseline.

[0098] In some embodiments, the present disclosure is directed to methods for treating hidradenitis suppurativa (HS) 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 after at least 2, 4, 8, 12, or 16 weeks of administering, a reduction in the total AN count from baseline. In some embodiments, the patient the patient achieves after at least 2 weeks of administering, a reduction in the total AN count from baseline. In some embodiments, the patient the patient achieves after at least 4 weeks of administering, a reduction in the total AN count from baseline. In some embodiments, the patient the patient achieves after at least 8 weeks of administering, a reduction in the total AN count from baseline. In some embodiments, the patient the patient achieves after at least 12 weeks of administering, a reduction in the total AN count from baseline. In some embodiments, the patient the patient achieves after at least 16 weeks of administering, a reduction in the total AN count from baseline.

[0099] In some embodiments, the present disclosure is directed to methods for treating hidradenitis suppurativa (HS) 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 after at least 16 weeks of administering, a reduction in the total AN count from baseline. In some embodiments, the patient achieves after at least 16 weeks of administering, a reduction of at least 1 in the total AN count from baseline. In some embodiments, the patient achieves after at least 16 weeks of administering, a reduction of at least 2 in the total AN count from baseline. In some embodiments, the patient achieves after at

least 16 weeks of administering, a reduction of at least 3 in the total AN count from baseline.

[0100] In some embodiments, efficacy of the treatment methods disclosed herein can be established based a patient achieving AN50 at week 16. An AN50 responder was defined as a participant achieving $\geq 50\%$ reduction in AN count relative to baseline. In some embodiments, the present disclosure is directed to methods for treating hidradenitis suppurativa (HS) 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 AN50 by at least week 16.

[0101] In some embodiments, efficacy of the treatment methods disclosed herein can be established based a patient achieving AN75 at week 16. An AN75 responder was defined as a participant achieving $\geq 75\%$ reduction in AN count relative to baseline. In some embodiments, the present disclosure is directed to methods for treating hidradenitis suppurativa (HS) 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 AN75 by at least week 16.

[0102] In some embodiments, efficacy of the treatment methods disclosed herein can be established based a patient achieving AN90 at week 16. An AN90 responder was defined as a participant achieving $\geq 90\%$ reduction in AN count relative to baseline. In some embodiments, the present disclosure is directed to methods for treating hidradenitis suppurativa (HS) 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 AN90 at week 16.

[0103] In some embodiments, efficacy of the treatment methods disclosed herein can be established based a patient achieving AN100 at week 16. An AN100 responder was defined as a participant achieving $\geq 100\%$ reduction in AN count relative to baseline. In some embodiments, the present disclosure is directed to methods for treating hidradenitis suppurativa (HS) 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 AN100 at week 16.

[0104] In some embodiments, the present disclosure is directed to methods for treating hidradenitis suppurativa (HS) in a human patient in need thereof, comprising: topically administering to an affected skin area of the patient, two times per day, a topical formulation comprising 1.5% (w/w) on a free base basis of ruxolitinib, or a pharmaceutically acceptable salt thereof, wherein the patient has no draining tunnels, wherein the patient is ≥ 18 years of age and at baseline, and wherein after at least one of 2, 4, 8, 12, or 16 weeks of administering, the patient has a reduction in abscesses and/or inflammatory nodules from baseline.

[0105] In some embodiments, after at least one of 2, 4, 8, 12, or 16 weeks of administering, the patient has a reduction in abscesses from baseline. In some embodiments, after at least 12 or 16 weeks, the patient has a reduction in abscesses from baseline. In some embodiments, after at least one of 2, 4, 8, 12, or 16 weeks of administering, the patient has a reduction in inflammatory nodules from baseline. In some embodiments, after at least 12 or 16 weeks, the patient has a reduction in inflammatory nodules from baseline. In some embodiments, after at least one of 2, 4,

8, 12, or 16 weeks of administering, the patient has a reduction in abscesses and inflammatory nodules from baseline. In some embodiments, after at least 12 or 16 weeks, the patient has a reduction in abscesses and inflammatory nodules from baseline.

[0106] In some embodiments, efficacy of the treatment methods disclosed herein can be established based a patient achieving a change from baseline in the Skin Pain NRS score. In some embodiments, the ruxolitinib, or the pharmaceutically acceptable salt thereof, and/or methods of use described herein result in an improvement in a patient's response to Skin Pain 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 patient's response to Skin Pain NRS from baseline. The Skin Pain NRS is a daily patient-reported measure (24-hour recall) of pain intensity. Patients will be asked to rate the pain severity because of their HS by selecting a number from 0 (no pain) to 10 (worst imaginable pain) that best describes their worst level of pain in the past 24 hours. In a non-limiting example, patients can be issued a hand-held device (eDiary) on which to record pain severity. The patient can be instructed to complete the eDiary each night.

[0107] In some embodiments, the present disclosure is directed to methods for treating HS 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 reduction from baseline in the Skin Pain NRS score. In some embodiments, the patient achieves a ≥ 1 -point improvement (reduction) in Skin Pain NRS score from baseline. In some embodiments, 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.

[0108] In some embodiments, the present disclosure is directed to methods for treating HS 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 16 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 postbaseline visit is 12 weeks.

[0109] In some embodiments, the present disclosure is directed to methods for treating HS 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 week 16. In some embodiments, the patient achieves a reduction from baseline in Skin Pain NRS score at week 16. In some embodiments, the patient achieves a ≥ 1 -point improvement (reduction) in Skin Pain NRS score at week 16 from baseline. In some embodiments, the patient achieves a ≥ 2 -point improvement (reduction) in Skin Pain NRS score at week 16 from baseline. In some embodiments, the patient achieves a ≥ 3 -point improvement (reduction) in Skin Pain NRS score at week 16 from baseline. In some embodiments, the patient achieves a ≥ 4 -point improvement (reduction) in Skin Pain NRS score at week 16 from baseline.

[0110] 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 patients achieving at least 2 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 patient's 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 patient's response to Itch NRS from baseline. The itch NRS is a daily patient-reported measure (24-hour recall) of itch intensity. Patients will be asked to rate the itching severity because of their HS 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.

[0111] In some embodiments, the present disclosure is directed to methods for treating HS 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 reduction from baseline in the Itch NRS score. In some embodiments, the patient achieves a ≥ 1 -point improvement (reduction) in Itch NRS score from baseline. In some embodiments, the patient

achieves a ≥ 2 -point improvement (reduction) in Itch NRS score from baseline. In some embodiments, the patient achieves a ≥ 3 -point improvement (reduction) in Itch NRS score from baseline. In some embodiments, the patient achieves a 4-point improvement (reduction) in Itch NRS score from baseline.

[0112] In some embodiments, the present disclosure is directed to methods for treating HS 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 Itch NRS score at each postbaseline visit. In some embodiments, the postbaseline visit ranges from 2 weeks to 16 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 postbaseline visit is 16 weeks.

[0113] In some embodiments, the present disclosure is directed to methods for treating HS 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 Itch NRS score at week 16. In some embodiments, the patient achieves a reduction from baseline in Itch NRS score at week 16. In some embodiments, the patient achieves a ≥ 1 -point improvement (reduction) in Itch NRS score at week 16 from baseline. In some embodiments, the patient achieves a ≥ 2 -point improvement (reduction) in Itch NRS score at week 16 from baseline. In some embodiments, the patient achieves a ≥ 3 -point improvement (reduction) in Itch NRS score at week 16 from baseline. In some embodiments, the patient achieves a ≥ 4 -point improvement (reduction) in Itch NRS score at week 16 from baseline.

[0114] In some embodiments, efficacy of the treatment method disclosed herein can be established based upon Hidradenitis Suppurative Clinical Response (HiSCR). In some embodiments, the achievement of HiSCR is defined as at least 50% reduction in AN count with no increase in abscess or draining fistula counts, relative to baseline. In some embodiments, efficacy of the treatment method disclosed herein can be established based upon a modified Hidradenitis Suppurative Clinical Response or "mHiSCR." mHiSCR is defined as at least 50% reduction in inflammatory nodule count with no increase in either abscess or draining fistula counts, relative to baseline. As used herein, "an inflammatory nodule" refers to a nontender, nonerythematous nodule.

[0115] In some embodiments, the present disclosure is directed to methods for treating HS 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 HiSCR. In some embodiments, the patient achieves HiSCR at week 2. In some embodiments, the patient achieves HiSCR at week 4. In some embodiments, the patient achieves HiSCR at week 8. In some embodiments, the patient achieves HiSCR at week 12. In some embodiments, the patient achieves HiSCR at week 16.

[0116] In some embodiments, the present disclosure is directed to methods for treating HS 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 mHiSCR. In some embodiments, the patient achieves mHiSCR at week 2. In some embodiments, the patient achieves mHiSCR at week 4. In some embodiments, the patient achieves mHiSCR at week 8. In some

embodiments, the patient achieves mHiSCR at week 12. In some embodiments, the patient achieves mHiSCR at week 16.

[0117] In some embodiments, efficacy of the treatment method disclosed herein can be established based upon Hidradenitis Suppurativa International Score System (IHS4). In some embodiments, the achievement of IHS4 is calculated by the number of inflammatory nodules (multiplied by 1) plus the number of abscesses (multiplied by 2) plus the number of draining tunnels (multiplied by 4).

[0118] In some embodiments, the present disclosure is directed to methods for treating HS 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 decrease in IHS4 score demonstrating treatment of HS. In some embodiments, the patient achieves a decrease in IHS4 by at least week 2. In some embodiments, the patient achieves a decrease in IHS4 by at least week 4. In some embodiments, the patient achieves a decrease in IHS4 by at least week 8. In some embodiments, the patient achieves a decrease in IHS4 by at least week 12. In some embodiments, the patient achieves a decrease in IHS4 by at least week 16. In some embodiments, the patient achieves a decrease in IHS4 score by at least week 2, 4, 8, 12, 20, 24, 28, or 32. In some embodiments, the patient achieves a decrease in IHS4 score by at least week 20. In some embodiments, the patient achieves a decrease in IHS4 score by at least week 24. In some embodiments, the patient achieves a decrease in IHS4 score by at least week 28. In some embodiments, the patient achieves a decrease in IHS4 score by at least week 32.

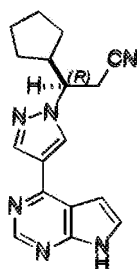
[0119] In some embodiments, the efficacy of the treatment method disclosed herein can be established based upon Hidradenitis Suppurativa International Score

System with $\geq 55\%$ reduction from baseline (ISH4-55) in the total ISH4 score. In some embodiments, the ISH4-55 score ranges from about 55% to about 85% reduction in baseline in the total ISH4 score. In some embodiments, the ISH4-55 score is about 40%, about 50%, about 55%, about 60%, about 65%, about 70%, about 75%, about 80%, or about 85% reduction from baseline in the total ISH4 score. In some embodiments, the ISH4-55 score is about 55%, about 60%, about 65%, about 70%, about 75%, about 80%, or about 85% reduction from baseline in the total ISH4 score. In some embodiments, the ISH4-55 score is about 55% reduction from baseline in the total ISH4 score.

[0120] In some embodiments, the present disclosure is directed to methods for treating HS 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 $\geq 55\%$ reduction from baseline in the total IHS4 score demonstrating treatment of HS. In some embodiments, the patient achieves a decrease in IHS4-55 by at least week 2. In some embodiments, the patient achieves a decrease in IHS4-55 by at least week 4. In some embodiments, the patient achieves a decrease in IHS4-55 by at least week 8. In some embodiments, the patient achieves a decrease in IHS4-55 by at least week 12. In some embodiments, the patient achieves a decrease in IHS4-55 by at least week 16. In some embodiments, the patient achieves a decrease in IHS4-55 score by at least week 2, 4, 8, 12, 20, 24, 28, or 32. In some embodiments, the patient achieves a decrease in IHS4-55 score by at least week 20. In some embodiments, the patient achieves a decrease in IHS4-55 score by at least week 24. In some embodiments, the patient achieves a decrease in IHS4-55 score by at least week 28. In some embodiments, the patient achieves a decrease in IHS4-55 score by at least week 32.

[0121] **Ruxolitinib**

[0122] Ruxolitinib is a potent JAK1/JAK2 inhibitor, (R)-3-(4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl)-3-cyclopentylpropanenitrile (INCB018424; ruxolitinib; active ingredient in JAKAFI®), and its pharmaceutically acceptable salts, has previously been described in U.S. Patent No. 7,598,257, which is incorporated herein by reference in its entirety. Ruxolitinib phosphate was previously described in U.S. Patent Publ. No. 2008/0312259, which is incorporated herein by reference in its entirety.



Ruxolitinib

[0123] Ruxolitinib is a small molecule inhibitor of the JAKs with specificity for JAK1 and JAK2, which play an important role in signal transduction following cytokine and growth factor binding to their receptors. Increased production of cytokines and growth factors has been associated with several chronic inflammatory conditions, including AD, vitiligo, and other autoimmune diseases of the skin. In cell-based assays relevant to the pathogenesis of inflammatory skin diseases, such as IL-2-stimulated phosphorylation of STATs and IL-2-induced proliferation of T cells, ruxolitinib demonstrates excellent potency (IC₅₀ values of 10 to 40 nM). Ruxolitinib also potently inhibited the phosphorylation of STAT proteins and the production of proinflammatory factors induced by cytokines such as IL-23 and IFN-γ.

[0124] Ruxolitinib cream has shown efficacy in AD and vitiligo. Ruxolitinib cream has shown statistically significant and clinically meaningful efficacy in 2 pivotal Phase 3 studies (INCB 18424-303 and -304) in adults and adolescents with mild to moderate AD and 3% to 20% affected BSA (excluding the scalp). In both AD Phase 3 studies, over 50% (53.8 and 51.3%) of participants (≥ 12 years of age) who applied ruxolitinib 1.5% cream BID for 8 weeks achieved an IGA-TS (i.e., IGA score of 0 or 1 with ≥ 2 -point improvement from baseline) compared with 15.1% and 7.9% of participants who applied vehicle cream, respectively. Participants who applied ruxolitinib cream also saw a substantial improvement in itch (4-point reduction in Itch NRS) compared with participants who applied vehicle in both studies (50.7% and 52.2% for ruxolitinib cream vs 16.3% and 15.4% for vehicle, respectively). In addition, ruxolitinib 1.5% cream administered BID was safe and well tolerated in adolescent and adult participants with AD. Ruxolitinib 1.5% cream is approved in the US as Opzelura™ for the topical short-term and noncontinuous chronic treatment of mild to moderate AD in nonimmune compromised patients 12 years of age and older whose disease is not adequately controlled with topical prescription therapies or when those therapies are not advisable.

[0125] Ruxolitinib cream 1.5% has demonstrated efficacy in vitiligo. Studies INCB 18424-306 and -307 were identically designed randomized, VC, Phase 3 studies in adolescent and adult participants (≥ 12 years old, $\approx 10\%$ of whom were adolescents) with vitiligo. Participants received blinded study treatment for 24 weeks and were then offered the opportunity to receive an additional 28 weeks of treatment with ruxolitinib 1.5% cream BID. Both studies met the primary endpoint ($p < 0.0001$), demonstrating that significantly more participants treated with ruxolitinib 1.5% cream BID achieved a $\geq 75\%$ improvement from baseline in the Facial Vitiligo Area Scoring Index at Week

24 compared to participants treated with a vehicle control. In addition, ruxolitinib 1.5% cream was safe and well tolerated in both adolescents and adults with vitiligo.

[0126] ***Cream Formulations***

[0127] In some embodiments, the cream formulation is an oil-in-water emulsion. In some embodiments, the cream is a solubilized cream. In some embodiments, the cream has a pH from about 2.7 to about 3.9, from about 2.7 to about 3.6, or from about 2.8 to about 3.6. In the context of pH, "about" refers to ± 0.3 (for example, ± 0.2 or such as, ± 0.1).

[0128] In some embodiments, the cream comprises an oil-in-water emulsion, comprising 1.5% (w/w) on a free base basis of ruxolitinib phosphate.

[0129] In some embodiments, the cream is an oil-in-water emulsion as described in US 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.

[0130] In some embodiments, the oil component is present in an amount of about 10% to about 40% by weight of the emulsion.

[0131] In some embodiments, the oil component is present in an amount of about 10% to about 24% by weight of the emulsion.

[0132] In some embodiments, the oil component is present in an amount of about 15% to about 24% by weight of the emulsion.

[0133] In some embodiments, the oil component is present in an amount of about 18% to about 24% by weight of the emulsion.

[0134] In some embodiments, the oil component comprises one or more substances independently selected from petrolatums, fatty alcohols, mineral oils, triglycerides, and silicone oils.

[0135] 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.

[0136] In some embodiments, the oil component comprises an occlusive agent component.

[0137] In some embodiments, the occlusive agent component is present in an amount of about 2% to about 15% by weight of the emulsion.

[0138] In some embodiments, the occlusive agent component is present in an amount of about 5% to about 10% by weight of the emulsion.

[0139] 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), 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).

[0140] In some embodiments, the occlusive agent component comprises one or more substances selected from lanolin acid fatty alcohols, lanolin alcohol, petrolatum, propylene glycol, dimethicone, cholesterol, cocoa butter, Carnauba wax, and bees wax.

[0141] In some embodiments, the occlusive agent component comprises petrolatum.

[0142] In some embodiments, the occlusive agent component comprises white petrolatum.

[0143] In some embodiments, the oil component comprises a stiffening agent component.

[0144] In some embodiments, the stiffening agent component is present in an amount of about 2% to about 8% by weight of the emulsion.

[0145] In some embodiments, the stiffening agent component is present in an amount of about 3% to about 6% by weight of the emulsion.

[0146] In some embodiments, the stiffening agent component is present in an amount of about 4% to about 7% by weight of the emulsion.

[0147] In some embodiments, the stiffening agent component comprises one or more substances independently selected from fatty alcohols.

[0148] In some embodiments, the stiffening agent component comprises one or more substances independently selected from C₁₂₋₂₀ fatty alcohols.

[0149] In some embodiments, the stiffening agent component comprises one or more substances independently selected from C₁₆₋₁₈ fatty alcohols.

[0150] In some embodiments, the stiffening agent component comprises one or more substances independently selected from cetyl alcohol and stearyl alcohol.

[0151] In some embodiments, the oil component comprises an emollient component.

[0152] In some embodiments, the emollient component is present in an amount of about 5% to about 15% by weight of the emulsion.

[0153] In some embodiments, the emollient component is present in an amount of about 7% to about 13% by weight of the emulsion.

[0154] In some embodiments, the emollient component comprises one or more substances independently selected from mineral oils and triglycerides.

[0155] In some embodiments, the emollient component comprises one or more substances independently selected from light mineral oil and medium chain triglycerides.

[0156] In some embodiments, the emollient component comprises one or more substances independently selected from light mineral oil, medium chain triglycerides, and dimethicone.

[0157] In some embodiments, the water is present in an amount of about 35% to about 65% by weight of the emulsion.

[0158] In some embodiments, the water is present in an amount of about 40% to about 60% by weight of the emulsion.

[0159] In some embodiments, the water is present in an amount of about 45% to about 55% by weight of the emulsion.

[0160] In some embodiments, the emulsifier component is present in an amount of about 1% to about 9% by weight of the emulsion.

[0161] In some embodiments, the emulsifier component is present in an amount of about 2% to about 6% by weight of the emulsion.

[0162] In some embodiments, the emulsifier component is present in an amount of about 3% to about 5% by weight of the emulsion.

[0163] In some embodiments, the emulsifier component is present in an amount of about 4% to about 7% by weight of the emulsion.

[0164] In some embodiments, the emulsion comprises an emulsifier component and a stiffening agent component, wherein the combined amount of

emulsifier component and stiffening agent component is at least about 8% by weight of the emulsion.

[0165] In some embodiments, the emulsifier component comprises one or more substances independently selected from glyceryl fatty esters and sorbitan fatty esters.

[0166] In some embodiments, the emulsifier component comprises one or more substances independently selected from glyceryl stearate, and polysorbate 20.

[0167] In some embodiments, the emulsion further comprises a stabilizing agent component.

[0168] In some embodiments, the stabilizing agent component is present in an amount of about 0.05% to about 5% by weight of the emulsion.

[0169] In some embodiments, the stabilizing agent component is present in an amount of about 0.1% to about 2% by weight of the emulsion.

[0170] 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.

[0171] In some embodiments, the stabilizing agent component comprises one or more substances independently selected from polysaccharides.

[0172] In some embodiments, the stabilizing agent component comprises xanthan gum.

[0173] In some embodiments, the emulsion further comprises a solvent component.

[0174] In some embodiments, the solvent component is present in an amount of about 10% to about 35% by weight of the emulsion.

[0175] In some embodiments, the solvent component is present in an amount of about 15% to about 30% by weight of the emulsion.

[0176] In some embodiments, the solvent component is present in an amount of about 20% to about 25% by weight of the emulsion.

[0177] In some embodiments, the solvent component comprises one or more substances independently selected from alkylene glycols and polyalkylene glycols.

[0178] In some embodiments, the solvent component comprises one or more substances independently selected from propylene glycol and polyethylene glycol.

[0179] In some embodiments, the emulsion comprises:

[0180] from about 35% to about 65% of water by weight of the emulsion;

[0181] from about 10% to about 40% of an oil component by weight of the emulsion;

[0182] from about 1% to about 9% of an emulsifier component by weight of the emulsion;

[0183] from about 10% to about 35% of a solvent component by weight of the emulsion;

[0184] from about 0.05% to about 5% of a stabilizing agent component by weight of the emulsion; and

[0185] 1.5% of ruxolitinib, or a pharmaceutically acceptable salt thereof, by weight of the emulsion on a free base basis.

[0186] In some embodiments, the emulsion comprises:

[0187] from about 35% to about 65% of water by weight of the emulsion;

[0188] from about 10% to about 24% of an oil component by weight of the emulsion;

[0189] from about 1% to about 9% of an emulsifier component by weight of the emulsion;

[0190] from about 10% to about 35% of a solvent component by weight of the emulsion;

[0191] from about 0.05% to about 5% of a stabilizing agent component by weight of the emulsion; and

[0192] 1.5% of ruxolitinib, or a pharmaceutically acceptable salt thereof, by weight of the emulsion on a free base basis.

[0193] In some embodiments, the emulsion comprises:

[0194] from about 40% to about 60% of water by weight of the emulsion;

[0195] from about 15% to about 30% of an oil component by weight of the emulsion;

[0196] from about 2% to about 6% of an emulsifier component by weight of the emulsion;

[0197] from about 15% to about 30% of a solvent component by weight of the emulsion;

[0198] from about 0.1% to about 2% of a stabilizing agent component by weight of the emulsion; and

[0199] 1.5% of ruxolitinib, or a pharmaceutically acceptable salt thereof, by weight of the emulsion on a free base basis.

[0200] In some embodiments, the emulsion comprises:

[0201] from about 40% to about 60% of water by weight of the emulsion;

[0202] from about 15% to about 30% of an oil component by weight of the emulsion;

[0203] from about 2% to about 6% of an emulsifier component by weight of the emulsion;

[0204] from about 15% to about 24% of a solvent component by weight of the emulsion;

[0205] from about 0.1% to about 2% of a stabilizing agent component by weight of the emulsion; and

[0206] 1.5% of ruxolitinib, or a pharmaceutically acceptable salt thereof, by weight of the emulsion on a free base basis.

[0207] In some embodiments, the emulsion comprises:

[0208] from about 45% to about 55% of water by weight of the emulsion;

[0209] from about 15% to about 24% of an oil component by weight of the emulsion;

[0210] from about 3% to about 5% of an emulsifier component by weight of the emulsion;

[0211] from about 20% to about 25% of a solvent component by weight of the emulsion;

[0212] from about 0.3% to about 0.5% of a stabilizing agent component by weight of the emulsion; and

[0213] 1.5% of ruxolitinib, or a pharmaceutically acceptable salt thereof, by weight of the emulsion on a free base basis.

[0214] In some embodiments, the emulsion comprises:

[0215] from about 45% to about 55% of water by weight of the emulsion;

[0216] from about 15% to about 24% of an oil component by weight of the emulsion;

[0217] from about 4% to about 7% of an emulsifier component by weight of the emulsion;

[0218] from about 20% to about 25% of a solvent component by weight of the emulsion;

[0219] from about 0.3% to about 0.5% of a stabilizing agent component by weight of the emulsion; and

[0220] 1.5% of ruxolitinib, or a pharmaceutically acceptable salt thereof, by weight of the emulsion on a free base basis.

[0221] In some embodiments:

[0222] the oil component comprises one or more substances independently selected from petrolatums, fatty alcohols, mineral oils, triglycerides, and dimethicones;

[0223] the emulsifier component comprises one or more substances independently selected from glyceryl fatty esters and sorbitan fatty esters;

[0224] the solvent component comprises one or more substances independently selected from alkylene glycols and polyalkylene glycols; and

[0225] the stabilizing agent component comprises one or more substances independently selected from polysaccharides.

[0226] In some embodiments:

[0227] 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;

[0228] the emulsifier component comprises one or more substances independently selected from glyceryl stearate and polysorbate 20;

[0229] the solvent component comprises one or more substances independently selected from propylene glycol and polyethylene glycol; and

[0230] the stabilizing agent component comprises xanthan gum.

[0231] In some embodiments, the emulsion comprises:

[0232] from about 35% to about 65% of water by weight of the emulsion;

[0233] from about 2% to about 15% of an occlusive agent component by weight of the emulsion;

[0234] from about 2% to about 8% of a stiffening agent component by weight of the emulsion;

[0235] from about 5% to about 15% of an emollient component by weight of the emulsion;

[0236] from about 1% to about 9% of an emulsifier component by weight of the emulsion;

[0237] from about 0.05% to about 5% of a stabilizing agent component by weight of the emulsion;

[0238] from about 10% to about 35% of a solvent component by weight of the emulsion; and

[0239] 1.5% of ruxolitinib, or a pharmaceutically acceptable salt thereof, by weight of the emulsion on a free base basis.

[0240] In some embodiments, the emulsion comprises:

[0241] from about 40% to about 60% of water by weight of the emulsion;

[0242] from about 5% to about 10% of an occlusive agent component by weight of the emulsion;

[0243] from about 2% to about 8% of a stiffening agent component by weight of the emulsion;

[0244] from about 7% to about 12% of an emollient component by weight of the emulsion;

[0245] from about 2% to about 6% of an emulsifier component by weight of the emulsion;

[0246] from about 0.1% to about 2% of a stabilizing agent by weight of the emulsion;

[0247] from about 15% to about 30% of a solvent component by weight of the emulsion; and

[0248] 1.5% of ruxolitinib, or a pharmaceutically acceptable salt thereof, by weight of the emulsion on a free base basis.

[0249] In some embodiments, the emulsion comprises:

[0250] from about 45% to about 55% of water by weight of the emulsion;

[0251] from about 5% to about 10% of an occlusive agent component by weight of the emulsion;

[0252] from about 3% to about 6% of a stiffening agent component by weight of the emulsion;

[0253] from about 7% to about 13% of an emollient component by weight of the emulsion;

[0254] from about 3% to about 5% of an emulsifier component by weight of the emulsion;

[0255] from about 0.3% to about 0.5% of a stabilizing agent component by weight of the emulsion;

[0256] from about 20% to about 25% of a solvent component by weight of the emulsion; and

[0257] 1.5% of ruxolitinib, or a pharmaceutically acceptable salt thereof, by weight of the emulsion on a free base basis.

[0258] In some embodiments, the emulsion comprises:

[0259] from about 45% to about 55% of water by weight of the emulsion;

[0260] from about 5% to about 10% of an occlusive agent component by weight of the emulsion;

[0261] from about 4% to about 7% of a stiffening agent component by weight of the emulsion;

[0262] from about 7% to about 13% of an emollient component by weight of the emulsion;

[0263] from about 4% to about 7% of an emulsifier component by weight of the emulsion;

[0264] from about 0.3% to about 0.5% of a stabilizing agent component by weight of the emulsion;

[0265] from about 20% to about 25% of a solvent component by weight of the emulsion; and

[0266] 1.5% of ruxolitinib, or a pharmaceutically acceptable salt thereof, by weight of the emulsion on a free base basis.

[0267] In some embodiments, the emulsion comprises:

[0268] from about 45% to about 55% of water by weight of the emulsion;

[0269] about 7% of an occlusive agent component by weight of the emulsion;

[0270] from about 4.5% to about 5% of a stiffening agent component by weight of the emulsion;

[0271] about 10% of an emollient component by weight of the emulsion;

[0272] from about 4% to about 4.5% of an emulsifier component by weight of the emulsion;

[0273] about 0.4% of a stabilizing agent component by weight of the emulsion;

[0274] about 22% of a solvent component by weight of the emulsion; and

[0275] 1.5% of ruxolitinib, or a pharmaceutically acceptable salt thereof, by weight of the emulsion on a free base basis.

[0276] In some embodiments, the ruxolitinib, or pharmaceutically acceptable salt thereof, is present as ruxolitinib phosphate.

[0277] In some embodiments, the emulsion comprises 1.5% of ruxolitinib, or a pharmaceutically acceptable salt thereof, by weight of the emulsion.

[0278] In some embodiments, the emulsion comprises 1.5% of ruxolitinib phosphate by weight of the emulsion.

[0279] In some embodiments, the combined amount of the stiffening agent component and the emulsifier component is at least about 8% by weight of the emulsion.

[0280] In some embodiments:

[0281] the occlusive agent component comprises a petrolatum;

[0282] the stiffening agent component comprises one or more substances independently selected from one or more fatty alcohols;

[0283] the emollient component comprises one or more substances independently selected from mineral oils and triglycerides;

[0284] the emulsifier component comprises one or more substances independently selected from glyceryl fatty esters and sorbitan fatty esters;

[0285] the stabilizing agent component comprises one or more substances independently selected from polysaccharides; and

[0286] the solvent component comprises one or more substances independently selected from alkylene glycols and polyalkylene glycols.

[0287] In some embodiments:

[0288] the occlusive agent component comprises white petrolatum;

[0289] the stiffening agent component comprises one or more substances independently selected from cetyl alcohol and stearyl alcohol;

[0290] the emollient component comprises one or more substances independently selected from light mineral oil, medium chain triglycerides, and dimethicone;

[0291] the emulsifier component comprises one or more substances independently selected from glyceryl stearate and polysorbate 20;

[0292] the stabilizing agent component comprises xanthan gum; and

[0293] the solvent component comprises one or more substances independently selected from propylene glycol and polyethylene glycol.

[0294] In some embodiments, the emulsion further comprises an antimicrobial preservative component.

[0295] In some embodiments, the antimicrobial preservative component is present in an amount of about 0.05% to about 3% by weight of the emulsion.

[0296] In some embodiments, the antimicrobial preservative component is present in an amount of about 0.1% to about 1% by weight of the emulsion.

[0297] In some embodiments, the antimicrobial preservative component comprises one or more substances independently selected from alkyl parabens and phenoxyethanol.

[0298] In some embodiments, the antimicrobial preservative component comprises one or more substances independently selected from methyl paraben, propyl paraben, and phenoxyethanol.

[0299] In some embodiments, the emulsion further comprises a chelating agent component.

[0300] In some embodiments, the chelating agent component comprises edetate disodium.

[0301] Ruxolitinib can be prepared as described in U.S. Patent 7,598,257 and U.S. Patent Publ. No. 2009/0181959, each of which is incorporated herein by reference in its entirety. The 1:1 phosphate salt of ruxolitinib can be prepared as described in U.S. Patent Publ. No. 2008/0312259, which is incorporated herein by reference in its entirety.

[0302] As will be appreciated, some components of the cream (emulsion) described herein can possess multiple functions. For example, a given substance

may act as both an emulsifying agent component and a stabilizing agent. In some such cases, the function of a given component can be considered singular, even though its properties may allow multiple functionality. In some embodiments, each component of the formulation comprises a different substance or mixture of substances.

[0303] It is further appreciated that certain features of the disclosure, which are, for clarity, described in the context of separate embodiments, can also be provided in combination in a single embodiment. Conversely, various features of the disclosure which are, for brevity, described in the context of a single embodiment, can also be provided separately or in any suitable subcombination.

[0304] ***Combination Therapies***

[0305] 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, which can also be administered in separate formulations or combined into a single formulation.

[0306] In some embodiments, the additional therapeutic agent is a vitamin D3 analog (e.g., calcipotriol or maxacalcitol). In some embodiments, the additional therapeutic agent is calcipotriol. In some embodiments, the additional therapeutic agent is maxacalcitol. In some embodiments, the ruxolitinib, or pharmaceutically acceptable salt thereof, and the vitamin D3 analog which is calcipotriol or maxacalcitol, are administered in a single formulation. In some embodiments, the ruxolitinib, or pharmaceutically acceptable salt thereof, and the calcipotriol, are administered in a single formulation. In some embodiments, the ruxolitinib, or pharmaceutically acceptable salt thereof, and the maxacalcitol, are administered in a single formulation.

In some embodiments, the combination therapy comprises an anhydrous topical skin formulation, wherein the anhydrous topical skin formulation comprises (a) ruxolitinib, or a pharmaceutically acceptable salt thereof and (b) a vitamin D3 analog, which is calcipotriol or maxacalcitol. In some embodiments, the formulation is an anhydrous cream, an anhydrous foam, an anhydrous ointment, an anhydrous lotion, or an anhydrous gel. In some embodiments, the formulation is an anhydrous cream. In some embodiments, the formulation is an anhydrous ointment. In some embodiments, the combination therapy comprises ruxolitinib, or a pharmaceutically acceptable salt thereof, and the vitamin D3 analog is calcipotriol. In some embodiments, the combination therapy comprises ruxolitinib, or a pharmaceutically acceptable salt thereof, and the vitamin D3 analog is maxacalcitol. In some embodiments, the combination therapy comprises from about 0.5% to about 3.0%, about 0.5% to about 2.0%, or about 0.5% to about 1.5% w/w of the ruxolitinib, or a pharmaceutically acceptable salt thereof, on a free base basis. In some embodiments, the combination therapy comprises about 0.3%, about 0.35%, about 0.4%, about 0.45%, about 0.5%, about 0.55%, about 0.6%, about 0.65%, about 0.7%, about 0.75%, about 0.8%, about 0.85%, about 0.9%, about 0.95%, about 1.0%, about 1.05%, about 1.1%, about 1.15%, about 1.2%, about 1.25%, about 1.3%, about 1.35%, about 1.4%, about 1.45%, about 1.5%, about 1.55%, about 1.6%, about 1.65%, about 1.7%, about 1.75%, about 1.8%, about 1.85%, about 1.9%, about 1.95%, about 2.0%, about 2.5%, or about 3.0 by weight of the formulation on a free base basis of the ruxolitinib, or the pharmaceutically acceptable salt thereof. In some embodiments, the combination therapy comprises from about 0.0005% w/w to about 0.05%, about 0.0005% to about 0.01%, or about 0.0005% to about 0.005%, w/w of the vitamin D3 analog. In some embodiments, the combination therapy comprises about 1.5% w/w of ruxolitinib, or a

pharmaceutically acceptable salt thereof, and about 0.005% w/w of the vitamin D3 analog. In some embodiments, the combination therapy further comprises a solvent component and an oil component. In some embodiments, the combination therapy further comprises an antioxidant component.

[0307] In some embodiments, the additional therapeutic agent is a steroid. In some embodiments, the additional therapeutic agent is a corticosteroid. In some embodiments, the steroid is such as pimecrolimus, tacrolimus, triamcinolone, dexamethasone, fluocinolone, cortisone, prednisone, prednisolone, or flumetholone.

[0308] In some embodiments, the additional therapeutic agent is a topical calcineurin inhibitor. In some embodiments, the topical calcineurin inhibitor is tacrolimus ointment or pimecrolimus cream.

[0309] In some embodiments, the additional therapeutic agent is an antibiotic. In some embodiments, the antibiotic is clindamycin, doxycycline, minocycline, trimethoprim-sulfamethoxazole, erythromycin, metronidazole, rifampin, moxifloxacin, dapsone, or a combination thereof. In some embodiments, the antibiotic is clindamycin, doxycycline, minocycline, trimethoprim-sulfamethoxazole, or erythromycin in combination with metronidazole. In some embodiments, the antibiotic is a combination of rifampin, moxifloxacin, and metronidazole. In some embodiments, the antibiotic is a combination of moxifloxacin and rifampin.

[0310] In some embodiments, the additional therapeutic agent is a retinoid. In some embodiments, the retinoid is adapalene, etretinate, acitretin, or isotretinoin.

[0311] In some embodiments, the additional therapeutic agent is an immunosuppressant. In some embodiments, the immunosuppressant is methotrexate or cyclosporin A. In some embodiments, the immunosuppressant is mycophenolate mofetil or mycophenolate sodium.

[0312] **Kits**

[0313] The present application also includes pharmaceutical kits useful, for example, in the treatment and/or prevention of hidradenitis suppurativa (HS), which include one or more containers containing a pharmaceutical composition comprising a therapeutically effective amount of ruxolitinib, or a pharmaceutically acceptable salt thereof, as 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, 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

[0314] The disclosure 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 disclosure 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.

[0315] **Example 1: Preparation of Oil-In-Water Cream Formulations of Ruxolitinib (INCB018424) Phosphate**

[0316] First, 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. The results of those findings are provided in **Table 3**.

[0317] **Table 3**

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
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
C ₁₂₋₁₅ alcohol benzoate	<0.2	0.15
Caprylic triglyceride	<0.2	0.15

[0318] 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.

[0319] 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.

[0320] 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 4-6** were scaled appropriately). Some batches were subject to minor changes 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.

[0321] **Procedure**

[0322] 1. A paraben phase was prepared by mixing methyl and propyl parabens with a portion of the propylene glycol (see % in **Tables 3-6**).

[0323] 2. Next, a xanthan gum phase was prepared by mixing xanthan gum with propylene glycol (see % in **Table 3-6**).

[0324] 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 triglycerides. The phase is heated to 70-80 °C to melt and form a uniform mixture.

[0325] 4. The aqueous phase was next prepared by mixing purified water, polyethylene glycol, and disodium EDTA. The phase is heated to 70-80 °C.

[0326] 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.

[0327] 6. The xanthan gum phase from step 2 was then added to the mixture from step 5.

[0328] 7. The oil phase from step 3 was then combined under high shear mixing with the mixture from step 6 to form an emulsion.

[0329] 8. Phenoxyethanol was then added to the emulsion from step 7. Mixing was continued, and then the product was cooled under low shear mixing.

[0330] **Table 4**

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

FORMULA		Function	Percentage of Total (% w/w)	Grams/Tube
PHASE	COMPONENT			
	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
	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

[0331] Table 5

Ingredient	Kilograms	Percentage (w/w)
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

[0332] Table 6

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
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

[0333] **Table 7**

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

[0334] More consistent batches at larger scales (e.g., 140 kg) could be obtained by adding ruxolitinib phosphate gradually to the aqueous phase and then combining with the other phases. Similarly, more consistent batches could be obtained by slower cooling (e.g., by using room temperature water in the outer jacket of the reactor, rather than lower temperature water).

[0335] **Table 8** shows the 0.75% and 1.5% ruxolitinib cream formulations; the 1.5% ruxolitinib cream formulation in Table 6 is the one used in Example 2.

[0336] Table 8

Component	0.75% Cream		1.5% Cream	
	wt%	g per 60 g tube	wt%	g per 60 g tube
Ruxolitinib Phosphate	0.99 (0.751))	0.594	1.98 (1.50 ^b)	1.188
Propylene Glycol	15.0	9.00	15.0	9.00
Methylparaben	0.10	0.06	0.10	0.06
Propylparaben	0.05	0.03	0.05	0.03
Xanthan Gum	0.40	0.24	0.40	0.24
Light Mineral Oil	4.00	2.40	4.00	2.40
Glyceryl Stearate SE	3.00	1.80	3.00	1.80
Polysorbate 20	1.25	0.75	1.25	0.75
White Petrolatum	7.00	4.20	7.00	4.20
Cetyl Alcohol	3.00	1.80	3.00	1.80
Stearyl Alcohol	1.75	1.05	1.75	1.05
Dimethicone 360	1.00	0.60	1.00	0.60
Triglycerides, Medium Chain	5.00	3.00	5.00	3.00
Purified Water	49.91	29.95	48.92	29.36
Edetate Disodium	0.05	0.03	0.05	0.03
Polyethylene Glycol 200	7.00	4.20	7.00	4.20
Phenoxyethanol	0.50	0.30	0.50	0.30
Total	100%	60 g	100%	60 g

[0337] 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). The viscosity of the cream formulations (e.g., containing 0.75% or 1.5% ruxolitinib phosphate on a free base basis) had a viscosity of $\geq 17,000$ cPs on release and a shelf-life viscosity of $\geq 10,000$ cPs.

[0338] **Example 2: Phase II Study Treating Hidradenitis Suppurativa (HS) with Ruxolitinib**

[0339] This (INCB 18424-221) is a Phase 2, randomized, double-blind vehicle controlled (DBVC) study with DBVC period of 16 weeks followed by an open-labeled extension (OLE) period of 16 weeks.

[0340] Participants will be screened for up to 28 days prior to the first application of ruxolitinib 1.5% cream or vehicle cream. Key entry criteria for participants are diagnosis of HS (Hurley Stage I or II) for at least 3 months before screening visit and a total AN count of 3 to ≤ 10 with no draining tunnels at screening and baseline. The AN count of 3 may affect at least 1 distinct anatomical area; however, an AN count of > 3 to ≤ 10 must be affecting at least 2 distinct anatomical areas.

[0341] Approximately 60 eligible participants ≥ 18 of age will be randomized 1:1 to either ruxolitinib 1.5% cream or vehicle cream. Participants will be stratified by baseline AN count (≥ 3 to 4 or ≥ 5 to 10). Participants will apply either ruxolitinib 1.5% cream or vehicle cream (both BID) through Week 16 to all affected areas identified at baseline.

[0342] At Week 16, participants who meet the criteria (compliant with the Protocol and without safety concerns) will enter the 16-week OLE period. Participants randomized to vehicle BID in the DBVC period will be crossed over to ruxolitinib 1.5% cream BID and participants randomized to ruxolitinib 1.5% cream BID at baseline will remain on ruxolitinib 1.5% cream BID through Week 32 in an open-label fashion. At Week 16, the HS treatment area will be evaluated by the investigator to assess the disease and confirm whether treatment continuation is required (AN count ≥ 1 and/or Skin Pain NRS ≥ 1) during the OLE period or can otherwise (re)enter an observation/no treatment cycle (AN count = 0 and Skin Pain NRS = 0). During the OLE, participants will only treat symptomatic lesions (e.g.,

presence of lesion, pain, and/or itch) including new lesions, not exceeding a total of 20% BSA.

[0343] Treatment assignment during the DBVC period will remain blinded to investigators and participants until after all participants have completed study or discontinued and completed the safety follow-up period.

[0344] During the DBVC and OLE periods, participants who are treated with HS lesional rescue medications and/or procedures, are considered nonresponsive to therapy, and will be discontinued from the study.

[0345] **Tables 9A** and **9B** summarize the schedule of activities.

[0346] Table 9A. Schedule of activities.

Visit Day (Range)	Screening		Treatment (vehicle-controlled period)						Treatment (open-label extension) ^a				Unscheduled Visit	Follow-up 30 days (+ 7) days after last application)
	Days -28 to -1	Baseline (Day 1)	Wk 2 (± 3 d)	Wk 4 (± 3 d)	Wk 8 (± 3 d)	Wk 12 (± 3 d)	Wk 16 ^a ± 3 d/ ET1	Wk 20 (± 3 d)	Wk 24 (± 3 d)	Wk 28 (± 3 d)	Wk 32 (± 3 d/ ET2)			
Administrative procedures														
Informed consent	X													
Inclusion/exclusion criteria	X	X												
Demographic, medical history	X													
Prior/concomitant medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Contact IRT	X	X	X	X	X	X	X	X	X	X	X			
Randomization		X												
Distribute eDiary	X													
Distribute reminder cards		X	X	X	X	X	X	X	X	X	X			
eDiary verification		X	X	X	X	X	X	X	X	X	X			
Apply study drug in clinic		X												
Weight/dispense study drug		X	X	X	X	X	X	X	X	X	X			
Collect/weight study drug and review study drug diary			X	X	X	X	X	X	X	X	X			
Assess study drug compliance			X	X	X	X	X	X	X	X	X	X	X	
Safety assessments														
AE assessments	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Physical examination	X ^b					X ^c					X ^b	X ^c		
Vital signs	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Height and body weight	X													
Efficacy assessments														
%BSA	X ^a	X	X	X	X	X	X	X	X	X	X	X		X

	Screening		Treatment (vehicle-controlled period)						Treatment (open-label extension) ^a				Follow-up	
	Days -28 to -1 (Day 1)	Baseline (Day 1)	Wk 2 (± 3 d)	Wk 4 (± 3 d)	Wk 8 (± 3 d)	Wk 12 (± 3 d)	Wk 16 ^b ± 3 d/ ET1	Wk 20 (± 3 d)	Wk 24 (± 3 d)	Wk 28 (± 3 d)	Wk 32 (± 3 d/ ET2)	Unscheduled visit	30 days (± 7) days after last application)	
			X	X	X	X	X	X	X	X	X			X
Visit Day (Range)														
Lesion count and assessment														
Overall Hurley Stage		X		X			X				X		X	
Patient-reported outcome														
Skin Pain NRS			Completed each evening through the last application of study drug.											
Itch NRS			Completed each evening through the last application of study drug.											
Analgesic use (nonopioid only)			Completed each evening through the last application of study drug.											
PGIC			X	X	X	X	X	X	X	X	X		X	

[0347] Table 9B: Schedule of activities (cont'd).

	Screening		Treatment (vehicle-controlled period)					Treatment (open-label extension) ^a				Follow-up	
	Days -28 to -1 (Day 1)	Baseline (Day 1)	Wk 2 (± 3 d)	Wk 4 (± 3 d)	Wk 8 (± 3 d)	Wk 12 (± 3 d)	Wk 16 ^b ± 3 d/ ET1	Wk 20 (± 3 d)	Wk 24 (± 3 d)	Wk 28 (± 3 d)	Wk 32 (± 3 d/ ET2)	Unscheduled Visit	30 days (+ 7) days after last application)
Visit Day (Range)													
Patient-reported outcome (continued)													
HISQoL		X		X	X		X		X		X		X
DLOI		X		X	X		X		X		X		X
WPAI-HS		X		X	X		X		X		X		X
EQ-5D-5L		X		X	X		X		X		X		X
Laboratory assessments													
Chemistry assessments	X	X ^c					X				X	X ^d	X
Hematology assessments	X	X ^c					X				X	X ^d	X
hsCRP		X			X		X				X		
FSH ^e	X												

	Screening	Treatment (vehicle-controlled period)						Treatment (open-label extension)*				Unscheduled Visit	Follow-up 30 days (* 7) days after last application)
		Baseline Days -28 to -1 (Day 1)	Wk 2 (± 3 d)	Wk 4 (± 3 d)	Wk 8 (± 3 d)	Wk 12 (± 3 d)	Wk 16~ ± 3 d/ ET1	Wk 20 (± 3 d)	Wk 24 (± 3 d)	Wk 28 (± 3 d)	Wk 32 (± 3 d/ ET2)		
Visit Day (Range)		X											X
Serum Pregnancy test				X	X	X	X	X	X	X	X		
Urine Pregnancy test				X	X	X	X	X	X	X	X		
HIV/Hepatitis Serology	X												
Translational assessments													
Serum biomarkers		X		X			X				X		
Photography (at selected sites)		X			X		X				X		
Drug exposure assessments													
Blood PK sampling			X	X									
Saliva PK Sampling		X	X	X	X		X						

[0348] "HS lesion count" will be assessed at each study visit and used for calculation of efficacy parameters as follows: AN counts, HiSCR, IHS4, ISH4-55, and flare incidence. Lesion count and assessment will be recorded in the lesion count worksheet, which includes assessment of anatomical regions including but are not limited to left and right axilla; or left and right inguinocrural fold or inframammary areas.

[0349] "Abscess and inflammatory nodule counts" (AN counts) will be recorded at all visits. The AN results will be used to calculate change in AN count relative to baseline, as well as AN50, AN75, AN90, and AN100, defined respectively as at least a 50%, 75%, 90%, and 100% decrease in AN count relative to baseline.

[0350] "Hidradenitis Suppurativa Clinical Response" or "HiSCR" was originally developed based on the underlying Phase 2 trial of adalimumab and validated against meaningful changes in pain score and DLQI (Kimball AB, Sobell JM, Zouboulis CC, et al. HiSCR (Hidradenitis Suppurativa Clinical Response): a novel clinical endpoint to evaluate therapeutic outcomes in patients with hidradenitis suppurativa from the placebo-controlled portion of a phase 2 adalimumab study. *J Eur Acad Dermatol Venereol* 2016;30:989-994; Sabat R, Jemec GBE, Matusiak Ł, Kimball AB, Prens E, Wolk K. Hidradenitis suppurativa. *Nat Rev Dis Primers* 2020;6:18). In this study, participants with draining fistulas (tunnels) will be excluded from the study. Should a randomized participant develop a draining tunnel during the study, the participant will be discontinued from the study.

[0351] The "Hurley classification" was originally designed for selection of the appropriate treatment modality in a certain body location (Zouboulis CC, Tzellos T, Kyrgidis A, et al. Development and validation of the International Hidradenitis

Suppurative Severity Score System (IHS4), a novel dynamic scoring system to assess HS severity. Br J Dermatol 2017;177:1401-1409): medical therapy for Stage I, local surgery for Stage II, and wide surgical excision for Stage III (see Table 2). Participants who have been diagnosed with HS, Hurley Stage I or II as per inclusion criterion, will be enrolled into the study.

[0352] The baseline Skin Pain NRS and the Itch NRS is established prior to the first dose of drug as follows: The average of the 7-day Itch NRS score prior to the baseline visit (minimum 4 out of the 7 days' data required) will be collected.

[0353] Participants are eligible to be included in the study only if all of the following criteria apply:

[0354] (1) Ability to comprehend and willingness to sign a written ICF for the study.

[0355] (2) Male or female participants age 18 years or above.

[0356] (3) Diagnosis of HS based on clinical history and physical examination for at least 3 months before screening visit.

[0357] (4) Diagnosis of HS (Hurley I or II) with the following: (a) A total AN count of 3 to $\leq$ 10, with no draining tunnels at screening and baseline visits. AND (b) The AN count at the screening AND baseline visits: AN of 3 should affect at least 1 distinct anatomical area and AN of > 3 to $\leq$ 10 should affect at least 2 distinct anatomical areas. Note: Anatomical areas include but are not limited to left and right axilla; or left and right inguinocrural fold or inframammary areas.

[0358] (5) Baseline Skin Pain or Itch NRS score $\geq$ 1. Baseline Skin Pain or Itch NRS is defined as the 7-day average of Skin Pain or Itch NRS score before Day 1 (data from a minimum of 4 out of 7 days directly prior to Day 1 is needed).

[0359] (6) Agreement to NOT use topical and systemic antibiotics for treatment of HS during the study.

[0360] (7) Agreement to NOT use a diluted beach bath or topical antiseptic washes containing chlorhexidine gluconate or benzoyl peroxide on the areas affected by HS lesions during the study.

[0361] (8) Willingness to avoid pregnancy or fathering children based on the following criteria: (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 ruxolitinib 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. (b) Female participants who are WOCBP must have a negative serum pregnancy test at screening and before the first application 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 ruxolitinib 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. (c) Female participants not considered to be of childbearing potential are eligible.

[0362] Participants are excluded from the study if any of the following criteria apply:

[0363] (1) Presence of draining tunnels at screening or at baseline visits.

[0364] (2) Total HS BSA affected (excluding scalp) is > 20%.

[0365] (3) Participants with concurrent conditions and history of other diseases: (a) Active ongoing inflammatory diseases of the skin other than HS that

might confound the evaluation of HS. (b) 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 HS AN or compromise participant safety. (c) Active tuberculosis; or current and/or history of latent tuberculosis unless adequately treated. (d) Immunocompromised (e.g., lymphoma, acquired immunodeficiency syndrome, or Wiskott-Aldrich syndrome). (e) Chronic or acute infection requiring treatment with systemic antibiotics, antivirals, antiparasitics, antiprotozoals, or antifungals within 2 weeks before baseline. (f) Active acute bacterial, fungal, or viral skin infection (e.g., herpes simplex, herpes zoster, chicken pox, clinically infected AD, or impetigo) within 2 weeks before baseline. (g) Unstable asthma or COPD requiring systemic treatment (such as intravenous steroids) or hospital admission or emergency room treatment within 3 months from baseline; or stable asthma or COPD requiring more than 720 µg/day (2 puff BID of 180-ug dose) or fluticasone more than 440 µg/day (2 puffs BID of 110-ug dose) or other equivalent inhaled corticosteroids.

[0366] (4) 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 administration of study drug and attending required study visits; pose a significant risk to the participant; or interfere with interpretation of study data. For example: (a) Clinically significant or uncontrolled cardiovascular disease, including unstable angina, acute myocardial infarction, or stroke within 6 months from Day 1 of study drug application, New York Heart Association Class III or IV congestive heart failure, and arrhythmia requiring therapy or persistent uncontrolled hypertension (blood pressure > 150/90 mmHg) unless approved by medical monitor/sponsor. (b) Any malignancies or history of malignancies within 5 years before baseline with the

exception of adequately treated or excised nonmetastatic basal cell or squamous cell cancer of the skin, or cervical carcinoma in situ. (c) History of severe anemia, severe thrombocytopenia, or severe neutropenia.

[0367] (5) Any of the following clinical laboratory test results at screening: (a) Cytopenias at screening, defined as follows: Hemoglobin < 100 g/L (i.e., 10 g/dL); ANC < $1.5 \times 10^9/L$ (i.e., 1500/ μL); and/or Platelet count < $1 \times 10^{11}/L$ (i.e., 100,000/ μL). (b) Liver function tests: AST or ALT $\geq 2.5 \times ULN$; and/or Total bilirubin > $1.5 \times ULN$ unless Gilbert's syndrome. (c) Estimated GFR < 30 mL/min/1.73 m² (using the Chronic Kidney Disease Epidemiology Collaboration equation). (d) Positive serology test results at screening for HIV antibody. (e) History or current of 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 hepatitis B vaccination can enroll. Participants who are positive for the hepatitis B surface antigen will be eligible if they are negative for HBV-DNA; participants who are positive for the anti-HCV antibody will be eligible if they are negative for HCV-RNA. (f) Any other clinically significant laboratory result that, in the opinion of the investigator, poses a significant risk to the participant.

[0368] (6) History of treatment failure (as assessed by the investigator through study participant interview) for HS or any other inflammatory condition with any systemic or topical JAK or TYK2 inhibitor (eg, abrocitinib, baricitinib, brepocitinib, deucravacitinib, filgotinib, lestaurtinib, pacritinib, ruxolitinib, tofacitinib, upadacitinib).

[0369] (7) Use of any of the following treatments within the indicated washout period before the baseline visit: (a) 12 weeks or 5 half-lives (if known), whichever is longer, for systemic immunosuppressive or immunomodulating biologic drugs (e.g., adalimumab, anakinra, bermekimab, bimekizumab, brodalumab, certolizumab,

dupilumab, etanercept, golimumab, guselkumab, infliximab, iscalimab, ixekizumab, risankizumab, rituximab, secukinumab, vilobelimab, ustekinumab, etc.). (b) 4 weeks for any topical or systemic JAK or TYK2 inhibitor (e.g., abrocitinib, baricitinib, brepocitinib, deucravacitinib, filgotinib, lestaurtinib, pacritinib, ruxolitinib, tofacitinib, upadacitinib, etc.). (c) 4 weeks – systemic corticosteroids or adrenocorticotrophic hormone analogs, cyclosporin, methotrexate, azathioprine, or other systemic immunosuppressive or immunomodulating agents (e.g., mycophenolate or tacrolimus). (d) 2 weeks or 5 half-lives, whichever is longer – strong systemic CYP3A4 inhibitors. (e) 2 weeks – systemic antibiotics and immunizations with live-attenuated vaccines, sedating antihistamines unless on a long-term stable regimen (nonsedating antihistamines are permitted). (f) weeks – topical therapy for HS (e.g., topical antiseptics, topical antibiotics, topical corticosteroids, topical calcineurin inhibitors, other topicals). (g) 2 weeks – any opioid treatment.

[0370] (8) Current treatment or treatment within 30 days or 5 half-lives (whichever is longer) before the baseline visit with another investigational medication or current enrollment in another investigational drug Protocol.

[0371] (9) Participant with known allergy or reaction to any of the components of the study cream.

[0372] (10) 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 participant's ability to comply with the administration schedule and study assessments.

[0373] (11) Pregnant or lactating participants, or those considering pregnancy during the period of their study participation.

[0374] (12) Participants with inadequate venous access in nonlesional areas or in lesional areas not treated by the study drug within the last 7 days.

[0375] (13) Participants who are committed to a mental health institution by virtue of an order issued either by the judicial or the administrative authorities.

[0376] (14) Participants who, in the opinion of the investigator, are unable or unlikely to comply with the administration schedule and study evaluations.

[0377] (15) Employees of the sponsor or investigator or otherwise dependents of them.

[0378] Ruxolitinib 1.5% cream or matching vehicle cream will be applied as a thin film BID, with applications approximately 8 hours apart in the morning and in the evening at least 1 hour before bedtime.

[0379] At the baseline visit, an estimate of the %BSA ($\leq 20\%$) affected by HS (total AN count 3 to ≤ 10) to be treated (excluding scalp) will be used by the IRT system to calculate the number of tubes of study drug to be dispensed. The participant will apply a thin film of study drug in front of site staff at the baseline/Day 1 visit by applying small amounts of study drug on each nodule and the surrounding area of the nodule (≈ 1 cm). All areas identified at baseline should continue to be treated through the end of the DBVC period (Week 16) unless the participant meets criteria for stopping study drug. If there are new AN to be treated, after consultation with the investigator, study drug should be applied to these AN in addition to the areas treated at baseline (maximum total affected areas $\leq 20\%$ BSA), and the percentage of BSA to be treated will be recalculated and increased. This new estimate will be entered into the IRT system to calculate the number of tubes of study drug to be dispensed. Participants whose additional new areas to be treated in

addition to the areas identified at the baseline visit exceed 20% BSA should be discontinued from study treatment and ET assessment should be completed.

[0380] At Week 16 and starting the OLE period, participants will be evaluated by the investigator to confirm whether they: require continuation of therapy due to AN count ≥ 1 and/or the presence of pain (Skin Pain NRS ≥ 1) or, can begin an observation/no treatment cycle due to AN count = 0 and no pain [Skin Pain NRS of 0]).

[0381] At Week 16, the IRT system will dispense a prespecified number of tubes according to the assessment of total BSA to be treated.

[0382] Between OLE study visits, participants will treat all areas identified with HS lesions (total affected area not to exceed 20% BSA). If all signs and symptoms of HS resolve between study visits, the participant will contact the investigator to confirm that study drug applications should be stopped 3 days after the HS lesion (AN count = 0) have disappeared. If this 3-day window is during a study visit and the AN count = 0, Skin Pain NRS = 0, as assessed by the investigator, treatment is to be stopped at the study visit.

[0383] Multiple cycles of treatment/no treatment may be utilized as needed and treatment start/stop dates should be recorded in the eDiary. If a participant has stopped treatment during the OLE period, treatment may be restarted after consultation with the investigator if the participant has an AN count ≥ 1 and/or pain (Skin Pain NRS score ≥ 1). Approval to treat additional areas may occur via telephone during the OLE period, although the investigator, at their discretion, may ask the participant to return for an unscheduled visit.

[0384] At any time during the OLE period, if a participant's new areas to be treated in addition to the areas already identified at the previous visit exceed 20%

BSA, then the participant should be discontinued from study treatment and the ET assessment should be completed. The amount of study drug used per application will be determined by weighing a tube before and after the participant applies study drug to the affected areas. 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. **Table 10** presents the study treatment information.

[0385] **Table 10:** Study treatment information.

	Study Treatment 1	Study Treatment 2
Study treatment name:	Ruxolitinib	Vehicle
Mechanism of action:	JAK 1/2 inhibitor	Not applicable
Dosage formulation:	Cream	Cream
Treatment strength:	1.5%	Not applicable
Administration instructions:	DBVC period: Apply a thin film to affected areas identified at baseline in the morning and at least 1 hour before bedtime with applications approximately 8 hours apart for 16 weeks. OLE period: Apply a thin film to affected areas only in the morning and at least 1 hour before bedtime with applications approximately 8 hours apart as needed for 16 weeks.	
Packaging and labeling:	Ruxolitinib or vehicle cream will be provided in 60 g tubes. 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	

[0386] The primary analysis will be based on the intent-to-treat (ITT) population. The summary of primary and major/key secondary objectives and endpoints along with exploratory parameters is provided in **Tables 11** and **12**.

[0387]

[0388] **Table 11:** Primary Objective and Endpoint

Objectives	Endpoints
Primary	
To establish the efficacy of ruxolitinib 1.5% cream BID in participants with HS.	Change from baseline in abscess and inflammatory nodules (AN) count at Week 16.

[0389] **Table 12** presents the key study design elements. Further study details are presented after the table.

[0390] **Table 12: Key Study Design Elements**

Study Phase	Phase 2
Clinical Indication	Treatment of patients with hidradenitis suppurativa
Population	Men or women ≥ 18 years of age, who have been diagnosed with HS (Hurley Stage I and II) for at least 3 months; with total AN count of 3 to ≤ 10 . The AN count of 3 may affect at least 1 distinct anatomical area; however, an AN count of > 3 to ≤ 10 must be affecting at least 2 distinct anatomical areas.
Number of Participants	Approximately 60 participants will be randomized 1:1 to 1 of 2 treatment groups (ruxolitinib 1.5% cream BID or vehicle cream BID).
Study Design	This is a randomized, 16-week DBVC study followed by a 16 week OLE with an active treatment for participants who complete 16 weeks of DBVC period, followed by a 30-day post-treatment, safety follow-up visit.
Estimated Duration of Study Participation	Estimated total duration of participants is up to approximately 40 weeks, including up to 4 weeks for screening, up to 32 weeks for treatment, and 30 days for safety follow-up.
Data Safety Monitoring Board/Data Monitoring Committee	No
Coordinating Principal Investigator	To be determined

[0391] **Table 13** presents the objectives and endpoints.

Objectives	Endpoints
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Primary	
To establish the efficacy of ruxolitinib 1.5% cream BID in participants with HS.	Change from baseline in AN count at Week 16.
Secondary	
To further evaluate the treatment effect of ruxolitinib 1.5% cream BID in participants with HS.	• Proportion of participants achieving AN50, AN75, AN90, and AN100 (at least 50%, 75%, 90%, and 100% reduction respectively in AN count relative to baseline) at Week 16. • Change from baseline in the Skin Pain NRS score at Week 16. • Change from baseline in the Itch NRS score at Week 16. • Proportion of participants who achieve HiSCR at Week 16. Note: HiSCR is defined as at least 50% reduction in AN count with no increase in either abscess or draining fistula counts, relative to baseline. • Change from baseline in the International Hidradenitis Suppurativa Severity Score System (IHS4) score at Week 16. Note: IHS4 score is calculated by the number of inflammatory nodules (multiplied by 1) plus the number of abscesses (multiplied by 2) plus the number of draining tunnels (multiplied by 4).
To evaluate the safety and tolerability of ruxolitinib 1.5% cream BID in participants with HS.	The type, frequency, and severity of AEs, and changes in vital signs and hematology and serum chemistry parameters.

[0392] Approximately 60 participants will be randomized 1:1 to ruxolitinib cream 1.5% BID or vehicle BID. The sample size was not calculated based on statistical power calculations, but for demonstration of preliminary findings of clinical response. It is anticipated that a sample size of approximately 60 participants will permit sufficient data to be generated to assess whether ruxolitinib cream warrants

further investigation in HS. Also, the sample size is considered sufficient to provide enough data for an initial evaluation of the safety profile.

[0393] The primary efficacy analysis will compare ruxolitinib 1.5% cream versus vehicle cream in the mean change from baseline in AN count using a MMRM. The MMRM will include the fixed effect of treatment group (ruxolitinib 1.5% and vehicle cream), stratification factor (AN count ≥ 3 to 4 or AN count ≥ 5 to 10 at baseline), visit, and visit by treatment interaction. The variance-covariance matrix of the within-participant errors in MMRM will be modeled as unstructured.

[0394] The primary alternative hypothesis (superiority of active ruxolitinib 1.5% cream BID group compared with vehicle) will be tested at a 2 sided $\alpha = 0.1$ level using the least square mean estimate of the change from baseline in AN count at Week 16 from the MMRM specified above. Subgroup analysis by baseline characteristics will be performed.

[0395] All secondary and exploratory efficacy variables will be summarized using descriptive statistics based on the ITT population. For categorical measurements, summary statistics will include sample size, frequency, and percentages. For continuous measurements, summary statistics will include sample size, mean, median, standard deviation, standard error of the mean, minimum, and maximum. Summary statistics for continuous measures will be provided for baseline, the actual measurements at each visit, and the change and percentage change from baseline at each visit, if applicable. The Skin Pain NRS score for each visit will be determined by averaging the 7 daily Skin Pain NRS scores before the corresponding visit day. If 4 or more daily scores are missing (out of the 7), the Skin Pain NRS score at the visit will be set to missing. The Itch NRS score for each visit will be determined using a similar approach.

[0396] **Example 3: Blinded Results from Example 2: Phase II Study**

Treating Hidradenitis Suppurativa (HS) with Ruxolitinib

[0397] The clinical trial in Example 2 (a Phase 2, randomized, double-blind vehicle controlled (DBVC) study with DBVC period of 16 weeks followed by an open-labeled extension (OLE) period of 16 weeks) was conducted and blinded data were available through week 32 from the total enrollment. The preliminary blinded data are presented below.

[0398] **Tables 14, 15, and 16** summarize the demographics and baseline characteristics of the study participants, their baseline disease characteristics, and participant disposition in the DBVC period, respectively. Specifically, **Table 14** presents summary data demographics and baseline characteristics of the intent-to-treat population. **Table 15** presents a summary of the baseline disease characteristics of the intent-to-treat population. **Table 16** presents a summary of the participants disposition in the DBVC period of the intent-to-treat population.

Table 14

Variable	Total (N=69)
Age (years)	
n	69
Mean	31.7
STD	9.76
Min	18
Median	29.0
Max	59
18 to 29 (years) -n(%)	36 (52.2)
30 to 49 (years) -n(%)	29 (42.0)
50 to 65 (years) -n(%)	4 (5.8)
> 65 (years) -n(%)	0 (0.0)
Sex – n(%)	
Male	7 (10.1)
Female	62 (89.9)
Ethnicity – n(%)	
Hispanic or Latino	8 (11.6)

Not Hispanic or Latino	61 (88.4)
Not Reported	0 (0.0)
Unknown	0 (0.0)
Other	0 (0.0)
Race – n (%)	
White/Caucasian	31 (44.9)
Black/African -American	29 (42.0)
Asian	2 (2.9)
American-Indian/Alaska Native	0 (0.0)
Native Hawaiian/Pacific Islander	0 (0.0)
Not Reported	0 (0.0)
Unknown	1 (1.4)
Other	6 (8.7)
Height (cm) at baseline	
n	69
Mean	166.50
STD	6.379
Min	150.0
Median	167.00
Max	182.9
Weight (kg) at baseline	
n	69
Mean	96.61
STD	23.283
Min	51.7
Median	93.00
Max	170.1
Body Mass Index (kg/m ²) at baseline	
n	69
Mean	34.90
STD	8.374
Min	19.2
Median	19.2
Max	62.4

Table 15

Variable	Total (N=69)
Disease Duration (Months)	
n	69
Mean	88.1
STD	83.08
Min	4.6
Median	52.5
Max	457.5

Prior surgical treatment for HS – n (%)	
Yes	15 (21.7)
No	54 (78.3)
Prior therapy received for HS – n (%)	
Yes	52 (75.4)
No	17 (24.6)
HS family history – n (%)	
Yes	18 (26.1)
No	51 (73.9)
Selected comorbidities – n (%)	
Atopic dermatitis	4 (5.8)
Psoriasis	2 (2.9)
Acne	11 (15.9)
Hypertension	10 (14.5)
Diabetes	3 (4.3)
Chronic kidney disease	0 (0.0)
Malignancy	0 (0.0)
Other autoimmune disease(s)	1 (1.4)
Anxiety	17 (24.6)
Depression	16 (23.2)
Obesity	14 (20.3)
Inflammatory bowel disease	0 (0.0)
Number of anatomical areas with HS	
n	69
Mean	2.8
STD	0.99
Min	1.0
Median	3.0
Max	6.0
Days since onset of current episode of HS flare/activity	
n	69
Mean	360.8
STD	704.16
Min	18.0
Median	58.0
Max	3691.0
Number of HS flares since diagnosis	
n	69
Mean	51.1
STD	85.06
Min	1.0
Median	20.0
Max	500.0
Hurley stage – n (%)	
Stage I	35 (50.7)
Stage II	34 (49.3)
Stage III	0 (0.0)

AN count category – n (%)	
≥ 3 to 4	27 (39.1)
≥ 5 to 10	42 (60.9)
AN count	
n	69
Mean	5.4
STD	1.81
Min	3.0
Median	5.0
Max	9.0
Abscess count	
n	69
Mean	0.7
STD	1.28
Min	0.0
Median	0.0
Max	5.0
Inflammatory nodule count	
n	69
Mean	4.8
STD	2.05
Min	0.0
Median	5.0
Max	9.0
Nondraining tunnel count	
n	69
Mean	0.3
STD	0.94
Min	0.0
Median	0.0
Max	6.0
Draining tunnel count	
n	69
Mean	0.0
STD	0.00
Min	0.0
Median	0.0
Max	0.0
Skin Pain NRS Score	
n	68
Mean	4.3
STD	2.36
Min	0.0
Median	3.8
Max	9.2
Itch NRS Score	
n	68

Mean	4.1
STD	2.67
Min	0.0
Median	3.4
Max	10.0
Total BSA involvement	
n	69
Mean	2.0
STD	1.49
Min	0.2
Median	2.0
Max	7.5

Table 16

Variable	Total (N=69)
Number (%) of participants treated	69 (100.0)
Number (%) of participants with ongoing treatment	8 (11.6)
Number (%) of participants who completed treatment	50 (72.5)
Number (%) of participants who discontinued from treatment	11 (15.9)
Primary Reason for Discontinuation of Treatment	
Adverse Event	2 (2.9)
Death	0 (0.0)
Lack of Efficacy	0 (0.0)
Lost to Follow-up	5 (7.2)
Non-Compliance with Study Drug	0 (0.0)
Pregnancy	0 (0.0)
Protocol Deviation	1 (1.4)
Physician Decision	0 (0.0)
Study Terminated by the Sponsor	0 (0.0)
Withdrawal by Subject	1 (1.4)
Other	2 (2.9)
Number (%) of participants who withdrew from study	11 (15.9)
Primary Reason of Study Discontinuation	
Adverse Event	2 (2.9)
Death	0 (0.0)
Lack of Efficacy	0 (0.0)
Lost to Follow-up	5 (7.2)
Physician Decision	0 (0.0)
Protocol Deviation	1 (1.4)
Study Terminated by the Sponsor	0 (0.0)

Withdrawal by Subject	1 (1.4)
Other	2 (2.9)

[0399] **Table 17** presents a summary and analysis of participants achieving HiSCR during the study period (intent-to-treat population).

Table 17

Achieving HiSCR at:	Total	Yes, n (%)
Week 2	67	15(22.4)
Week 4	66	27(40.9)
Week 8	63	38(60.3)
Week 12	58	35(60.3)
Week 16	53	33(62.3)
Early Termination DBVC	6	0(0.0)
Follow-up DBVC	4	3(75.0)
Week 20	42	30(71.4)
Week 24	29	24(82.8)
Week 28	22	17(77.3)
Week 32	15	14(93.3)
Early Termination OLE	5	3(60.0)
Follow-up OLE	3	3(100.0)

[0400] Abbreviations: HiSCR = Hidradenitis Suppurativa Clinical Response

[0401] A HiSCR responder was defined as a participant achieving $\geq 50\%$ reduction in AN count with no increase in either abscess or draining fistula counts, relative to baseline. From **Table 17**, HiSCR responders increased from Week 2 to Week 16.

[0402] **Table 18** presents a summary and analysis of AN Count during the study period.

Table 18

AN count at:	n	Mean (STD)	Median
Baseline	69	5.45 (1.811)	5.00
Week 2	67	4.45 (2.382)	5.00
Change from Baseline at Week 2	67	-1.03 (2.153)	-1.00
Percent Change from Baseline in AN Count at Week 2	67	-17.42 (42.817)	-16.67
Week 4	66	3.59 (2.320)	3.00
Change from Baseline at Week 4	66	-1.92 (2.248)	-2.00
Percent Change from Baseline in AN Count at Week 4	66	-34.52 (38.014)	-29.17
Week 8	63	2.71 (2.296)	2.00
Change from Baseline at Week 8	63	-2.79 (2.641)	-3.00
Percent Change from Baseline in AN Count at Week 8	63	-47.58 (44.838)	-57.14
Week 12	58	2.48 (2.458)	2.00
Change from Baseline at Week 12	58	-3.05 (2.481)	-3.00
Percent Change from Baseline in AN Count at Week 12	58	-56.01 (41.250)	-66.67
Week 16	53	2.45 (2.099)	2.00
Change from Baseline at Week 16	53	-3.02 (2.349)	-3.00
Percent Change from Baseline in AN Count at Week 16	53	-54.17 (38.811)	-60.00
Early Termination DBVC	6	6.33 (4.885)	5.00
Change from Baseline at Early Termination DBVC	6	0.83 (3.764)	0.00
Percent Change from Baseline in AN Count at Early Termination DBVC	6	12.50 (47.067)	0.00
Follow-up DBVC	4	2.75 (1.500)	3.00
Change from Baseline at Follow-up DBVC	4	-4.00 (2.944)	-4.50
Percent Change from Baseline in AN Count at Follow-up DBVC	4	-52.78 (38.087)	-63.89
Week 20	42	2.07 (1.827)	2.00
Change from Baseline at Week 20	42	-3.43 (2.097)	-3.00
Percent Change from Baseline in AN Count at Week 20	42	-62.55 (34.330)	-66.67
Week 24	29	1.72 (1.791)	1.00
Change from Baseline at Week 24	29	-3.69 (2.156)	-4.00

Percent Change from Baseline in AN Count at Week 24	29	-67.34 (31.150)	-75.00
Week 28	22	1.91 (1.900)	2.00
Change from Baseline at Week 28	22	-3.41 (2.085)	-4.00
Percent Change from Baseline in AN Count at Week 28	22	-64.07 (30.218)	-66.67
Week 32	15	1.00 (0.845)	1.00
Change from Baseline at Week 32	15	-4.20 (1.859)	-4.00
Percent Change from Baseline in AN Count at Week 32	15	-79.22 (18.095)	-80.00
Early Termination OLE	5	2.60 (1.949)	2.00
Change from Baseline at Early Termination OLE	5	-4.00 (2.646)	-3.00
Percent Change from Baseline in AN Count at Early Termination OLE	5	-57.79 (30.872)	-60.00
Follow-up OLE	3	1.33 (1.155)	2.00
Change from Baseline at Follow-up OLE	3	-4.67 (1.528)	-5.00
Percent Change from Baseline in AN Count at Follow-up OLE	3	-77.14 (20.603)	-71.43

[0403] Abbreviations: AN = Abscess and Inflammatory Nodule; STD = Standard Deviation.

[0404] From **Table 18**, AN count decreased from baseline to week 16.

[0405] **Table 19** presents a summary and analysis of participants achieving AN50 during the study period.

Table 19

Number (%) of Participants Achieving AN50 at:	Total	Yes, n (%)
Week 2	67	16(23.9)
Week 4	66	27(40.9)
Week 8	63	39(61.9)
Week 12	58	38(65.5)
Week 16	53	35(66.0)
Early Termination at DBVC	6	0(0.0)
Follow-up DBVC	4	3(75.0)
Week 20	42	32(76.2)

Week 24	29	25(86.2)
Week 28	22	18(81.8)
Week 32	15	14(93.3)
Early Termination at OLE	5	3(60.0)
Follow-up OLE	3	3(100.0)

[0406] Abbreviations: AN = Abscess and Inflammatory Nodule.

[0407] An AN50 responder was defined as a participant achieving $\geq 50\%$ reduction in AN count relative to baseline. From **Table 19**, AN50 responders increased from baseline to week 16.

[0408] **Table 20** presents a summary and analysis of participants achieving AN75 during the study period.

Table 20

Number (%) of Participants Achieving AN75 at:	Total	Yes, n (%)
Week 2	67	4(6.0)
Week 4	66	16(24.2)
Week 8	63	20(31.7)
Week 12	58	23(39.7)
Week 16	53	20(37.7)
Early Termination at DBVC	6	0(0.0)
Follow-up DBVC	4	2(50.0)
Week 20	42	18(42.9)
Week 24	29	15(51.7)
Week 28	22	9(40.9)
Week 32	15	11(73.3)
Early Termination at OLE	5	1(20.0)
Follow-up OLE	3	1(33.3)

[0409] Abbreviations: AN = Abscess and Inflammatory Nodule.

[0410] An AN75 responder was defined as a participant achieving $\geq 75\%$ reduction in AN count relative to baseline. From **Table 20**, AN75 responders increased from baseline to week 16.

[0411] **Table 21** presents a summary and analysis of participants achieving AN90 during the study period.

Table 21

Number (%) of Participants Achieving AN90 at:	Total	Yes, n (%)
Week 2	67	3(4.5)
Week 4	66	5(7.6)
Week 8	63	10(15.9)
Week 12	58	13(22.4)
Week 16	53	10(18.9)
Early Termination at DBVC	6	0(0.0)
Follow-up DBVC	4	0(0.0)
Week 20	42	11(26.2)
Week 24	29	5(17.2)
Week 28	22	4(18.2)
Week 32	15	4(26.7)
Early Termination at OLE	5	1(20.0)
Follow-up OLE	3	1(33.3)

[0412] Abbreviations: AN = Abscess and Inflammatory Nodule.

[0413] An AN90 responder was defined as a participant achieving $\geq 90\%$ reduction in AN count relative to baseline. From **Table 21**, AN90 responders increased from baseline to week 16.

[0414] **Table 22** presents a summary and analysis of participants achieving AN100 during the study period.

Table 22

Number (%) of Participants Achieving AN100 at:	Total	Yes, n (%)
Week 2	67	3(4.5)
Week 4	66	5(7.6)
Week 8	63	10(15.9)
Week 12	58	13(22.4)
Week 16	53	10(18.9)
Early Termination at DBVC	6	0(0.0)
Follow-up DBVC	4	0(0.0)
Week 20	42	11(26.2)
Week 24	29	5(17.2)

Week 28	22	4(18.2)
Week 32	15	4(26.7)
Early Termination at OLE	5	1(20.0)
Follow-up OLE	3	1(33.3)

[0415] Abbreviations: AN = Abscess and Inflammatory Nodule.

[0416] An AN100 responder was defined as a participant achieving 100% reduction in AN count relative to baseline. From **Table 22**, AN100 responders increased from baseline to week 16.

[0417] **Table 23** presents a summary and analysis of by-visit Skin Pain NRS score during the study period.

Table 23

By visit Skin Pain NRS score at:	n	Mean (STD)	Median
Baseline	68	4.33 (2.362)	3.79
Week 2	53	3.18 (2.459)	2.83
Change from Baseline at Week 2	52	-0.93 (1.908)	-0.80
Week 4	54	2.55 (2.181)	2.15
Change from Baseline at Week 4	53	-1.38 (2.088)	-1.29
Week 8	49	2.21 (2.088)	2.00
Change from Baseline at Week 8	48	-1.95 (2.318)	-1.82
Week 12	52	2.16 (2.379)	1.75
Change from Baseline at Week 12	51	-1.97 (2.883)	-1.58
Week 16	43	1.91 (2.512)	1.00
Change from Baseline at Week 16	42	-2.35 (2.973)	-2.29
Early Termination at DBVC	3	5.72 (0.948)	6.00
Change from Baseline at Early Termination at DBVC	3	-1.33 (1.024)	-1.36
Week 20	34	1.96 (2.601)	1.08
Change from Baseline at Week 20	33	-2.22 (2.990)	-2.49
Week 24	23	1.88 (2.143)	1.75

Change from Baseline at Week 24	23	-2.39 (2.519)	-2.02
Week 28	13	1.83 (1.709)	1.75
Change from Baseline at Week 28	13	-2.19 (2.814)	-1.11
Week 32	7	0.55 (0.712)	0.00
Change from Baseline at Week 32	7	-2.68 (2.915)	-2.33
Early Termination OLE	2	5.70 (4.101)	5.70
Change from Baseline at Early Termination OLE	2	2.60 (5.940)	2.60
Follow-up OLE	1	0.00 (NA)	0.00
Change from Baseline at Follow-up OLE	1	-7.86 (NA)	-7.86

[0418] Abbreviations: NRS = Numeric Rating Scale; STD = Standard Deviation.

[0419] From **Table 23**, Skin Pain NRS score decreased from baseline to week 16.

[0420] **Table 24** presents a summary and analysis of by-visit Itch NRS score during the study period.

Table 24

By visit Skin Pain NRS score at:	n	Mean (STD)	Median
Baseline	68	4.06 (2.674)	3.43
Week 2	53	3.16 (2.568)	2.60
Change from Baseline at Week 2	52	-0.72 (1.628)	-0.66
Week 4	54	2.61 (2.293)	2.18
Change from Baseline at Week 4	53	-1.10 (2.169)	-0.90
Week 8	49	2.01 (2.144)	1.50
Change from Baseline at Week 8	48	-1.88 (2.305)	-1.40
Week 12	52	2.14 (2.300)	1.55
Change from Baseline at Week 12	51	-1.84 (2.877)	-1.40
Week 16	43	1.93 (2.392)	1.00

Change from Baseline at Week 16	42	-2.13 (3.005)	-1.56
Early Termination at DBVC	3	4.34 (1.645)	4.86
Change from Baseline at Early Termination at DBVC	3	-2.61 (2.401)	-1.57
Week 20	33	2.18 (2.453)	1.40
Change from Baseline at Week 20	32	-1.72 (2.782)	-1.49
Week 24	23	1.73 (2.477)	1.00
Change from Baseline at Week 24	23	-2.48 (2.846)	-2.14
Week 28	13	1.74 (2.102)	1.25
Change from Baseline at Week 28	13	-2.16 (2.800)	-1.50
Week 32	7	0.76 (0.990)	0.00
Change from Baseline at Week 32	7	-2.08 (2.530)	-1.40
Early Termination OLE	2	5.10 (4.101)	5.10
Change from Baseline at Early Termination OLE	2	4.40 (3.111)	4.40
Follow-up OLE	1	0.00 (NA)	0.00
Change from Baseline at Follow-up OLE	1	-6.00 (NA)	-6.00

[0421] Abbreviations: NRS = Numeric Rating Scale; STD = Standard Deviation.

[0422] From **Table 24**, Itch NRS score decreased from baseline to week 16.

Example 4: Unblinded Results from Example 2: Phase II Study Treating

Hidradenitis Suppurativa (HS) with Ruxolitinib

[0423] The clinical trial in Example 2 (a Phase 2, randomized, double-blind vehicle controlled (DBVC) study with DBVC period of 16 weeks followed by an open-labeled extension (OLE) period of 16 weeks) was conducted, blinded data were available through week 32 from the total enrollment (Example 3), and now, unblinded

data is available after completion of the DBVC period. The unblinded data are presented below.

[0424] As provided in **Table 25**, the primary endpoint (i.e., to establish the efficacy of ruxolitinib 1.5% cream BID in participants with HS) based on a change from baseline in AN count at week 16 was achieved. **Table 25** presents a summary and analysis of AN Count during the study period.

Table 25

AN count at:	Vehicle BID (N=35)			Ruxolitinib 1.5% BID (N=34)		
	n	Mean (STD)	Median	n	Mean (STD)	Median
Baseline	35	5.34 (1.814)	5.00	34	5.56 (1.829)	5.50
Week 2	35	4.63 (2.462)	4.00	32	4.31 (2.278)	5.00
Change from Baseline at Week 2		-0.71 (2.283)	-1.00		-1.31 (1.991)	-1.00
Percent Change from Baseline in AN Count at Week 2		-11.00 (47.964)	-12.50		-22.89 (35.750)	-15.48
Week 4	35	3.57 (1.899)	3.00	31	3.71 (2.710)	3.00
Change from Baseline at Week 4		-1.77 (2.129)	-2.00		-2.00 (2.338)	-2.00
Percent Change from Baseline in AN Count at Week 4		-30.65 (35.396)	-25.00		-37.27 (40.081)	-42.86
Week 8	34	3.03 (2.736)	2.00	29	2.31 (1.561)	2.00
Change from Baseline at Week 8		-2.32 (3.002)	-3.00		-3.38 (2.007)	-3.00
Percent Change from Baseline in AN Count at Week 8		-39.17 (54.408)	-55.00		-58.12 (26.614)	-57.14
Week 12	34	2.79 (2.761)	2.00	26	2.15 (2.053)	1.50
Change from Baseline at Week 12		-2.56 (2.584)	-3.00		-3.73 (2.426)	-3.50

Percent Change from Baseline in AN Count at Week 12		-50.25 (45.909)	-66.67		-62.12 (35.402)	-73.21
Week 16	32	2.91 (2.053)	3.00	24	1.83 (1.857)	1.00
Change from Baseline at Week 16		-2.38 (2.196)	-2.00		-4.04 (2.156)	-4.00
Percent Change from Baseline in AN Count at Week 16		-44.17 (40.093)	-50.00		-68.69 (28.684)	-75.00
Week 20	29	2.45 (1.804)	2.00	22	2.14 (2.054)	2.00
Change from Baseline at Week 20		-2.69 (2.089)	-3.00		-3.59 (2.364)	-4.00
Percent Change from Baseline in AN Count at Week 20		-51.68 (34.390)	-60.00		-61.85 (43.233)	-69.05
Week 24	21	1.67 (1.983)	1.00	16	1.19 (1.223)	1.00
Change from Baseline at Week 24		-3.38 (2.376)	-3.00		-4.50 (1.713)	-4.00
Percent Change from Baseline in AN Count at Week 24		-65.95 (35.525)	-66.67		-80.23 (18.904)	-83.33
Week 28	18	1.89 (2.111)	2.00	12	1.92 (1.676)	1.50
Change from Baseline at Week 28		-3.28 (2.321)	-3.00		-4.08 (2.353)	-4.00
Percent Change from Baseline in AN Count at Week 28		-63.61 (32.986)	-66.67		-66.29 (29.122)	-73.33
Week 32	16	1.31 (1.302)	1.00	8	1.50 (1.069)	1.00
Change from Baseline at Week 32		-4.19 (2.105)	-4.50		-4.25 (1.389)	-4.00
Percent Change from Baseline in AN Count at Week 32		-74.48 (25.499)	-79.17		-74.21 (14.232)	-77.50

[0425] Abbreviations: AN = Abscess and Inflammatory Nodule; STD = Standard Deviation.

[0426] **FIG. 1** plots the mean and standard error of the AN count during the treatment period from baseline to week 32.

[0427] Below **Table 26** presents a summary and analysis of participants achieving AN50 during the study period (intent-to-treat population). An AN50 responder was defined as a participant achieving $\geq 50\%$ reduction in AN count relative to baseline.

Table 26

Number (%) of Participants Achieving AN50 at:	Vehicle BID (N=35)		Ruxolitinib 1.5% BID (N=34)	
	Total	Yes, n (%)	Total	Yes, n (%)
Week 2	35	6(17.1)	32	9(28.1)
Week 4	35	12(34.3)	31	14(45.2)
Week 8	34	21(61.8)	29	18(62.1)
Week 12	34	22(64.7)	26	16(61.5)
Week 16	32	18(56.3)	24	19(79.2)
Week 20	29	19(65.5)	22	17(77.3)
Week 24	21	18(85.7)	16	15(93.8)
Week 28	18	14(77.8)	12	10(83.3)
Week 32	16	14(87.5)	8	7(87.5)

[0428] **FIG. 2** plots the number of participants at each visit versus the proportion of AN50 responses (%). From **Table 26** and **FIG. 2**, AN50 responders increased from baseline to week 16 with ruxolitinib 1.5% BID.

[0429] Below **Table 27** presents a summary and analysis of participants achieving AN75 during the study period (intent-to-treat population). An AN75 responder was defined as a participant achieving $\geq 75\%$ reduction in AN count relative to baseline.

Table 27

Number (%) of Participants Achieving AN75 at:	Vehicle BID (N=35)		Ruxolitinib 1.5% BID (N=34)	
	Total	Yes, n (%)	Total	Yes, n (%)
Week 2	35	1(2.9)	32	3(9.4)
Week 4	35	7(20.0)	31	8(25.8)
Week 8	34	10(29.4)	29	10(34.5)
Week 12	34	11(32.4)	26	13(50.0)
Week 16	32	8(25.0)	24	13(54.2)
Week 20	29	9(31.0)	22	10(45.5)
Week 24	21	10(47.6)	16	12(75.0)
Week 28	18	6(33.3)	12	6(50.0)
Week 32	16	9(56.3)	8	6(75.0)

[0430] **FIG. 3** plots the number of participants at each visit versus the proportion of AN75 responses (%). From **Table 27** and **FIG. 3**, AN75 responders increased from baseline to week 16 with ruxolitinib 1.5% BID.

[0431] Below **Table 28** presents a summary and analysis of participants achieving HiSCR during the study period (intent-to-treat population).

Table 28

Achieving HiSCR at:	Vehicle BID (N=35)		Ruxolitinib 1.5% BID (N=34)	
	n	Yes, n (%)	n	Yes, n (%)
Week 2	35	6(17.1)	32	9(28.1)
Week 4	35	12(34.3)	31	14(45.2)
Week 8	34	20(58.8)	29	18(62.1)
Week 12	34	19(55.9)	26	16(61.5)
Week 16	32	16(50.0)	24	19(79.2)
Week 20	29	17(58.6)	22	17(77.3)
Week 24	21	17(81.0)	16	15(93.8)
Week 28	18	13(72.2)	12	9(75.0)
Week 32	16	14(87.5)	8	7(87.5)

[0432] Abbreviations: HiSCR = Hidradenitis Suppurativa Clinical Response

[0433] **FIG. 4** is a bar graph illustrating those patients achieving HiSCR during the treatment period from week 2 to week 32. From **Table 28** and the bar graph of **FIG. 4**, the treatment group of ruxolitinib 1.5% BID shows a significant proportion of HiSCR responses at week 16.

[0434] Below **Table 29** presents a summary and analysis of participants achieving modified HiSCR (mHiSCR) during the study period (intent-to-treat population). As used herein, “modified Hidradenitis Suppurativa Clinical Response” or “mHiSCR” is defined as at least 50% reduction in inflammatory nodule count with no increase in either abscess or draining fistula counts, relative to baseline. Further, “an inflammatory nodule” refers to as nontender, nonerythematous nodule. All participants applied ruxolitinib 1.5% cream BID after Week 16.

Table 29

	Vehicle BID (N=35)		Ruxolitinib 1.5% BID (N=34)	
Achieving HiSCR at:	n	Yes, n (%)	n	Yes, n (%)
Week 2	34	6(17.6)	31	8(25.8)
Week 4	34	13(38.2)	30	14(46.7)
Week 8	33	19(57.6)	28	18(64.3)
Week 12	33	18(54.5)	26	17(65.4)
Week 16	31	15(48.4)	24	18(75.0)
Early Termination DBVC	2	0(0.0)	5	0(0.0)
Follow-up DBVC	2	1(50.0)	3	1(33.3)
Week 20	28	16(57.1)	22	17(77.3)
Week 24	20	16(80.0)	16	14(87.5)
Week 28	17	12(70.6)	12	8(66.7)
Week 32	15	12(80.0)	8	7(87.5)

Early Termination OLE	3	1(33.3)	2	2(100.0)
Follow-up OLE	10	8(80.0)	6	3(50.0)

[0435] From **Table 29**, the treatment group of ruxolitinib 1.5% BID shows a significant proportion of mHiSCR responses at week 16.

[0436] Below **Table 30** presents a summary and analysis of by-visit Skin Pain NRS score during the study period.

Table 30

By visit Skin Pain NRS score at:	Vehicle BID (N=35)			Ruxolitinib 1.5% BID (N=34)		
	n	Mean (STD)	Median	n	Mean (STD)	Median
Baseline	34	4.24 (2.369)	4.01	34	4.42 (2.386)	3.69
Week 2	30	3.04 (2.224)	3.00	23	3.36 (2.777)	2.67
Change from Baseline at Week 2		-1.21 (1.763)	-0.83		-0.57 (2.059)	-0.80
Week 4	30	2.46 (2.069)	2.17	24	2.67 (2.354)	2.08
Change from Baseline at Week 4		-1.69 (2.210)	-1.29		-1.00 (1.909)	-1.77
Week 8	25	2.33 (2.177)	1.50	24	2.09 (2.029)	2.00
Change from Baseline at Week 8		-2.08 (2.596)	-1.71		-1.82 (2.051)	-1.96
Week 12	31	2.32 (2.210)	2.00	23	2.27 (2.764)	1.67
Change from Baseline at Week 12		-2.06 (2.634)	-1.21		-1.51 (3.302)	-1.67
Week 16	23	1.83 (2.092)	2.00	23	2.05 (2.784)	1.00
Change from Baseline at Week 16		-2.61 (2.458)	-2.08		-1.85 (3.289)	-2.00
Week 20	23	2.17 (2.159)	2.00	20	2.27 (2.962)	1.20
Change from Baseline at Week 20		-2.26 (2.545)	-2.50		-1.74 (3.310)	-2.19

Week 24	17	1.50 (1.439)	1.14	14	1.37 (2.571)	0.00
Change from Baseline at Week 24		-2.15 (2.403)	-2.02		-2.66 (2.135)	-2.50
Week 28	13	1.59 (1.694)	1.33	9	0.82 (1.101)	0.25
Change from Baseline at Week 28		-2.38 (2.721)	-1.81		-2.54 (2.207)	-1.75
Week 32	10	1.75 (2.536)	0.50	4	0.52 (0.790)	0.20
Change from Baseline at Week 32		-2.20 (3.503)	-2.38		-2.23 (3.048)	-1.20

[0437] Abbreviations: NRS = Numeric Rating Scale; STD = Standard

Deviation

[0438] **FIG. 5** plots the mean and standard error by visit of Skin Pain NRS during the treatment period from baseline to week 32.

[0439] Below **Table 31** presents a summary and analysis of by-visit Itch NRS score during the study period.

Table 31

By visit Skin Pain NRS score at:	Vehicle BID (N=35)			Ruxolitinib 1.5% BID (N=34)		
	n	Mean (STD)	Median	n	Mean (STD)	Median
Baseline	34	4.14 (2.798)	3.76	34	3.98 (2.585)	3.00
Week 2	30	3.28 (2.427)	3.10	23	3.01 (2.789)	2.14
Change from Baseline at Week 2		-1.07 (1.644)	-0.86		-0.29 (1.534)	-0.57
Week 4	30	2.51 (1.990)	2.20	24	2.74 (2.663)	2.07
Change from Baseline at Week 4		-1.56 (2.331)	-1.07		-0.53 (1.847)	-0.65
Week 8	25	2.20 (2.187)	1.50	24	1.80 (2.125)	1.34

Change from Baseline at Week 8		-2.04 (2.845)	-1.87		-1.72 (1.646)	-1.22
Week 12	31	2.10 (2.011)	2.00	23	2.19 (2.658)	1.25
Change from Baseline at Week 12		-2.25 (2.757)	-1.69		-1.23 (2.933)	-0.97
Week 16	23	1.73 (1.762)	1.00	23	2.14 (2.792)	1.00
Change from Baseline at Week 16		-2.75 (2.884)	-1.89		-1.42 (2.906)	-1.20
Week 20	22	2.42 (2.159)	2.20	20	2.05 (2.696)	1.14
Change from Baseline at Week 20		-2.02 (2.471)	-1.61		-1.59 (2.789)	-1.39
Week 24	17	1.32 (1.924)	1.00	14	1.58 (2.600)	0.71
Change from Baseline at Week 24		-2.56 (2.789)	-2.14		-2.12 (2.121)	-1.93
Week 28	13	1.50 (2.144)	0.43	9	0.69 (0.944)	0.17
Change from Baseline at Week 28		-3.12 (2.984)	-2.29		-1.90 (2.162)	-1.20
Week 32	10	1.66 (1.944)	1.00	4	0.38 (0.750)	0.00
Change from Baseline at Week 32		-2.51 (3.474)	-1.91		-2.26 (2.995)	-1.77

[0440] Abbreviations: NRS = Numeric Rating Scale; STD = Standard

Deviation

[0441] **FIG. 6** plots the mean and standard error by visit of Itch NRS during the treatment period from baseline to week 32.

[0442] Below **Table 32** presents a summary and analysis of International Hidradenitis Suppurativa Severity Score System (IHS4) during the study period.

Table 32

By visit IHS4 score at:	Vehicle BID (N=35)			Ruxolitinib 1.5% BID (N=34)		
	n	Mean (STD)	Median	n	Mean (STD)	Median
Baseline	35	6.06 (2.388)	6.00	34	6.18 (2.393)	6.00
Week 2	35	5.34 (3.171)	5.00	32	4.91 (2.644)	5.00
Change from Baseline at Week 2		-0.71 (2.383)	-1.00		-1.38 (2.575)	-1.00
Percent Change from Baseline at Week 2		-11.52 (43.131)	-10.00		-19.96 (39.969)	-13.39
Week 4	35	4.11 (2.336)	4.00	31	4.90 (4.915)	4.00
Change from Baseline at Week 4		-1.94 (2.461)	-2.00		-1.48 (5.131)	-2.00
Percent Change from Baseline at Week 4		-28.57 (41.894)	-20.00		-18.85 (112.445)	-42.86
Week 8	34	3.50 (3.107)	2.50	29	2.79 (2.177)	2.00
Change from Baseline at Week 8		-2.59 (3.192)	-3.00		-3.59 (2.922)	-3.00
Percent Change from Baseline at Week 8		-38.08 (56.080)	-52.27		-54.10 (39.285)	-57.14
Week 12	34	3.21 (3.073)	2.00	26	2.38 (2.299)	1.50
Change from Baseline at Week 12		-2.88 (2.858)	-3.00		-4.12 (3.115)	-4.00
Percent Change from Baseline at Week 12		-49.72 (44.041)	-66.67		-61.38 (37.171)	-75.71
Week 16	32	3.28 (2.359)	3.00	24	2.00 (2.147)	1.00

Change from Baseline at Week 16		-2.66 (2.535)	-3.00		-4.46 (2.587)	-4.00
Percent Change from Baseline at Week 16		-42.81 (42.393)	-45.00		-69.59 (27.654)	-75.00
Week 20		2.97 (2.353)	2.00		2.36 (2.610)	2.00
Change from Baseline at Week 20	29	-2.83 (2.465)	-3.00	22	-4.00 (2.878)	-4.00
Percent Change from Baseline at Week 20		-49.06 (35.948)	-50.00		-63.48 (42.644)	-69.05
Week 24		2.05 (2.578)	1.00		1.38 (1.668)	1.00
Change from Baseline at Week 24	21	-3.86 (2.726)	-3.00	16	-4.88 (1.893)	-4.50
Percent Change from Baseline at Week 24		-67.03 (32.700)	-75.00		-80.83 (19.842)	-83.33
Week 28		2.28 (2.608)	2.00		2.42 (2.392)	2.00
Change from Baseline at Week 28	18	-3.89 (2.654)	-4.00	12	-4.33 (2.605)	-4.00
Percent Change from Baseline at Week 28		-64.55 (32.312)	-66.67		-64.79 (29.168)	-66.67
Week 32		1.63 (1.746)	1.00		1.63 (1.408)	1.00
Change from Baseline at Week 32	16	-5.00 (2.221)	-5.00	8	-4.50 (1.195)	-4.00
Percent Change from Baseline at Week 32		-76.54 (24.509)	-81.67		-75.03 (13.878)	-80.00

[0443] **FIG. 7** graphically illustrates the mean and standard error of IHS4 score during the treatment period. IHS4 is a weighted scale using the number of inflammatory nodules, the number of abscesses, and the number of draining tunnels (fistulas or sinuses), with respective weight factors of 1, 2, and 4 (Example: IHS4 score equals the number of inflammatory nodules [multiplied by 1] plus the number of abscesses [multiplied by 2] plus the number of draining tunnels [multiplied by 4]). From **Table 31** and **FIG. 7**, the IHS4 score decreased with ruxolitinib 1.5% BID from baseline to week 16 demonstrating treating HS.

[0444] The number of treatment emergent adverse events were similar between the ruxolitinib cream and vehicle groups. Only one patient on ruxolitinib cream had site application site pain.

[0445] **Example 5: Phase III Studies Treating Hidradenitis Suppurativa (HS) with Ruxolitinib**

[0446] This is a Phase 3, double-blind, randomized, vehicle-controlled (DBVC) study in participants at least 12 years of age with a confirmed diagnosis of HS. The study will consist of a 16-week DBVC period followed by a 36-week open label extension (OLE) period. The primary purpose of this study is to assess the efficacy and safety of ruxolitinib 1.5% cream BID in participants with mild to moderate HS (Hurley Stage I or II) with no draining tunnels.

[0447] Participants will be screened for up to 28 days prior to the first field application treatment with ruxolitinib 1.5% cream or vehicle cream. Field treatment is defined as study cream applied to the entire anatomical area(s) containing an abscess and/or inflammatory nodule. Key entry criteria for participants are diagnosis of HS (Hurley Stage I or II) for at least 6 months, a total AN count of ≥ 4 affecting at least 2 distinct anatomical areas, and no draining tunnels at screening or baseline.

[0448] Approximately 400 eligible participants at least 12 years of age will be randomized 1:1 to either ruxolitinib 1.5% cream or vehicle cream. Participants will be stratified by baseline geographic region (North America vs Europe) and prior HS therapy (prior HS therapy vs no prior HS therapy). Participants with prior HS therapy will make up approximately 60% of the study population.

[0449] Starting at the Day 1 visit of the DBVC period, participants will field-treat all affected anatomical areas identified at baseline through Week 16, even if the HS resolves completely. If new body sites develop ANs post Day 1, participants should contact the investigator, and as long as total affected areas remain $\leq 20\%$ BSA, then new body sites will be treated in addition to the areas identified and treated since baseline. The participant should be instructed not to use more than one 60-gram tube per week. If BSA exceeds 20%, then the participant will be withdrawn from the study. Scheduled study visits in the DBVC period will be conducted at Week 2 postbaseline and every 4 weeks for subsequent visits (i.e., Weeks 4, 8, 12, and 16).

[0450] During the DBVC period, participants who develop draining tunnels will be considered ineligible and withdrawn from the study.

[0451] At Week 16, participants who meet the criteria (ie, compliant with the Protocol and without safety concerns) will enter the 16-week OLE period. Scheduled study visits will be conducted at Weeks 20, 28, 36, 44, and 52 and scheduled telephone calls will be conducted at Weeks 24, 32, 40, and 48. Participants randomized to vehicle cream BID in the DBVC period will cross over to ruxolitinib 1.5% cream BID, and participants randomized to ruxolitinib 1.5% cream BID at baseline will remain on ruxolitinib 1.5% cream BID through Week 52 in an open-label fashion. Beginning with the visit at Week 16, the HS treatment area will be evaluated

by the investigator to assess the disease and confirm whether treatment continuation is required (ie, AN count ≥ 1) during the OLE period or if the participant can otherwise (re)enter an observation/no-treatment cycle (i.e., AN count = 0). During the OLE period, participants will only field-treat body sites with active lesions (e.g., presence of AN lesion(s)), with the total treated BSA not exceeding 20% (the actual %BSA will be entered for IRT cream dispensation). If new body sites develop ANs during the OLE, participants should contact the investigator, and as long as total affected areas remain $\leq 20\%$ BSA, the body sites will be treated. Through Week 52 of the study, the %BSA entered into IRT at the preceding visit will be utilized for IRT cream dispensation. The participant should be instructed not to use more than one 60-gram tube per week. Any participant whose total area to be treated exceeds 20% BSA should be discontinued from study treatment.

[0452] During the DBVC and OLE periods, participants who develop draining tunnels or are treated with HS lesional rescue medications and/or procedures, are considered nonresponsive to therapy, and will be discontinued from the study.

[0453] Participants who develop draining tunnels will be withdrawn from the study. Starting at Week 20 through Week 52 of the OLE, a participant who experiences worsening (defined as a 2.5X or more increase in AN count relative to baseline) of their HS disease without developing draining tunnels, will be eligible for one rescue treatment. These participants will be considered nonresponders. Participants may withdraw from the study at any time for any reason, in which case they would be able to use alternative conventional therapy for their HS. This information will be captured in EDC.

[0454] Treatment assignment during the DBVC period will remain blinded to investigators and participants until after the last visit of the last participant in the study.

[0455] The safety follow-up period should occur 30 days (+ 7-day visit window) after the Week 52 /EOT2 or ET visit (or 30 days after the last application of study cream if the Week 52/EOT2 or ET visit was not performed). If the participant is in the OLE period and has been in an observation/no-treatment cycle with an AN count = 0 for at least 30 days prior to the Week 52 /EOT2 visit, then the Week 52/EOT2 visit will also count as the safety follow-up visit.

[0456] The study begins when the first participant signs the study ICF. It is estimated that an individual will participate for approximately 60 weeks, including up to 28 days for screening, 16 weeks for treatment during the DBVC period, 36 weeks for treatment during the OLE period, and up to 30 days for follow-up after the last application of study treatment.

[0457] The end of the study is defined as the date of the last visit of the last participant in the study. A participant is considered to have completed the study if they have completed all study visits, including the safety follow-up visit.

[0458] The primary analysis will be based on the intent-to-treat (ITT) population. The summary of endpoints, i.e., primary, key secondary, and secondary objectives and endpoints, is provided in **Table 33**.

[0459] **Table 33**

Objectives	Endpoints
Primary	
To establish the efficacy of ruxolitinib 1.5% cream BID in participants with HS	The binary response status of HiSCR75 (defined as $\geq 75\%$ reduction from baseline in total AN count with no increase from baseline in abscess or draining tunnel count) at Week 16.
Key Secondary	
To evaluate the treatment effect of ruxolitinib 1.5% cream BID in participants with HS	• The binary response status of ≥ 1 HS flare (defined as $\geq 25\%$ increase in total AN count with a minimum increase in AN of 2 relative to baseline) at Week 16. • The binary response status of IHS4-55 (defined as $\geq 55\%$ reduction from baseline in the weighted count of AN and draining tunnels [calculated as the number of inflammatory nodules multiplied by 1, plus the number of abscesses multiplied by 2, plus the number of draining tunnels multiplied by 4]) at Week 16.
Secondary	

To further evaluate the treatment effect of ruxolitinib 1.5% cream BID in participants with HS	• The binary response status of HiSCR50/90/100 (defined as $\geq 50\%/90\%/100\%$ reduction from baseline in total AN count with no increase from baseline in abscess or draining tunnel count) at each scheduled postbaseline visit. • The binary response status of ≥ 1 HS flare during the OLE period. • Change from baseline in IHS4 score at each scheduled postbaseline visit. • The categorical outcome of participants in each of the IHS4 disease categories (described as follows: a total score of 0-3 signifies mild, 4-10 signifies moderate, and 11 or higher signifies severe disease) at each visit. • Change and percentage change from baseline in total AN count at each scheduled postbaseline visit. • The binary response status of participants with baseline Skin Pain NRS score ≥ 3 who achieve Skin Pain NRS30 (defined as $\geq 30\%$ and ≥ 1-unit reductions from baseline in Skin Pain NRS score) at each scheduled postbaseline visit. • The binary response status of Itch NRS score ≥ 3 at baseline who achieve Itch NRS30 (defined as $\geq 30\%$ and ≥ 1-unit reductions from baseline in Itch NRS score) at each scheduled postbaseline visit. • PGIC score at each scheduled postbaseline visit. • The binary response status of PGIC response at each scheduled postbaseline visit. • Change from baseline in PGIS at each scheduled postbaseline visit. • The binary response status of DLQI4 (defined with ≥ 4-point reduction in DLQI score relative to baseline) at each scheduled postbaseline visit.
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	• The binary response status of CDLQI6 (defined with ≥ 6-point reduction in CDLQI score relative to baseline) at each scheduled postbaseline visit. • Change and percentage change from baseline in HiSQoL at each scheduled postbaseline visit. • Change and percentage change from baseline in HiSQoL-AA at each scheduled postbaseline visit. • Change from baseline in EQ-5D-5L score at each scheduled postbaseline visit.
To evaluate the safety and tolerability of ruxolitinib 1.5% cream BID in participants with HS	• AEs, assessed by changes in vital signs and through clinical laboratory sample evaluations.

[0460] Participants are eligible to be included in the study only if all of the following criteria apply:

[0461] (1) Ability to comprehend and willingness to sign a written informed consent form for the study.

[0462] (2) Age 12 years or older at screening.

[0463] (3) Diagnosis of HS for at least 6 months before screening visit based on clinical history and physical examination, as performed by a dermatologist.

[0464] (4) Diagnosis of mild to moderate HS (Hurley Stage I or II) with a total abscess and inflammatory nodule count of at least 4, with no draining tunnels, and affecting at least 2 distinct anatomical areas at screening and Day 1 visits.

[0465] Note: Anatomical areas include but are not limited to the left or right axilla, left or right inguinocrural fold, and left or right inframammary areas.

[0466] (5) Agreement to NOT use topical or systemic antibiotics for treatment of HS during the DBVC period and Weeks 16 through 20 of the OLE period of the study.

[0467] (6) Agreement to NOT use topical antiseptics, including washes and leave-on products, with ingredients such as chlorhexidine gluconate, povidone iodine, sodium hypochlorite, diluted bleach, or benzoyl peroxide on the areas affected by HS lesions during the DBVC period and Weeks 16 through 20 of the OLE period of the study.

[0468] Note: Soap and water are allowed.

[0469] (7) Willingness to avoid pregnancy or fathering children based on the criteria below.

[0470] (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.

[0471] (b) Female participants who are WOCBP must have a negative serum pregnancy test at screening and a negative urine pregnancy test before the first application 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.

[0472] (c) Female participants not considered to be of childbearing potential are eligible.

[0473] Participants are excluded from the study if any of the following criteria apply:

[0474] (1) Body areas to be treated exceed 20% BSA at screening or baseline.

[0475] (2) An acute abscess requiring, incision and drainage or intralesional corticosteroid injection at screening or baseline.

[0476] (3) Presence of any draining tunnel(s) at screening or baseline.

[0477] (4) Any of the following conditions:

[0478] (a) Presence of any skin condition(s) other than HS that might confound the evaluation of HS.

[0479] (b) Any other concomitant skin disorder that may interfere with and confound the evaluation of HS or compromise participant safety.

[0480] (c) Active tuberculosis; or current and/or history of latent tuberculosis unless adequately treated.

[0481] Note: Medical history related to tuberculosis will be collected in EDC.

[0482] (d) Immunocompromised (eg, lymphoma, immunosuppression associated with organ transplantation, Wiskott-Aldrich syndrome).

[0483] (e) Chronic or acute infection requiring treatment with systemic antibiotics, antivirals, antiparasitics, antiprotozoals, or antifungals within 2 weeks before Day 1.

[0484] (f) Active acute bacterial, fungal, or viral skin infection (eg, herpes simplex, herpes zoster, chicken pox, clinically infected AD, impetigo) within 2 weeks before Day 1.

[0485] (5) Current or history of any of the following conditions:

[0486] (a) Clinically uncontrolled or history of cardiovascular disease, including unstable angina, myocardial infarction, coronary artery disease, ischemic heart disease, or New York Heart Association Class III or IV congestive heart failure,

as well as uncontrolled arrhythmia or arrhythmia requiring therapy or uncontrolled hypertension (including elevated blood pressure (> 150 mmHg systolic or > 100 mmHg diastolic at screening and/or Day 1) unless approved by the medical monitor/sponsor.

[0487] (b) Venous and arterial thrombosis, deep vein thrombosis, pulmonary embolism, or stroke.

[0488] (c) Current or history of severe anemia, severe thrombocytopenia, or severe neutropenia.

[0489] (d) Any malignancies or history of malignancies within 5 years before Day 1 with the exception of adequately treated or excised nonmetastatic basal cell or squamous cell cancer of the skin or cervical carcinoma in situ.

[0490] (e) Unstable asthma or COPD requiring systemic treatment (such as intravenous corticosteroids) or hospital admission or emergency department treatment within 3 months before Day 1; or stable asthma or COPD requiring budesonide more than $720\text{ }\mu\text{g/day}$ (eg, 2 puffs BID of a $180\text{-}\mu\text{g}$ dose) or fluticasone more than $440\text{ }\mu\text{g/day}$ (eg, 2 puffs BID of a $110\text{-}\mu\text{g}$ dose) or other equivalent inhaled corticosteroids.

[0491] (f) Any serious illness or medical, physical, or psychiatric condition 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 the interpretation of study data. When in doubt, the investigator should consult with the medical monitor to clarify eligibility.

[0492] (6) Any of the following clinical laboratory test results at screening:

[0493] Exclusionary lab values:

Laboratory Parameter		Exclusion Criterion
Hematology		
a	Platelets	$< 100 \times 10^9/L$
b	Hemoglobin	$< 9 \text{ g/dL}$
c	Absolute neutrophil count (ANC)	$< 1.5 \times 10^9/L$
Hepatic		
f	ALT	$> 2.5 \times \text{ULN}$
g	AST	$> 2.5 \times \text{ULN}$
h	Total bilirubin	$> 1.5 \times \text{ULN}$ (Note: Participants with clinical diagnosis of Gilbert syndrome may have a direct bilirubin measured and would be eligible provided the direct bilirubin is $< \text{ULN}$)
Renal		
i	Estimated glomerular filtration rate	Estimated glomerular filtration rate $< 30 \text{ mL/min/1.73 m}^2$ (using the Chronic Kidney Disease Epidemiology Collaboration equation).

[0494] (a) Positive for HIV antibody.

[0495] (b) Current, 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 hepatitis B vaccination can enroll. Participants who are positive for HBsAg will be eligible if they are negative for HBV DNA; participants who are positive for the anti-HCV antibody will be eligible if they are negative for HCV RNA.

[0496] (c) Any other clinically significant laboratory result that, in the opinion of the investigator, poses a significant risk to the participant.

[0497] (7) History of treatment failure (as assessed by the investigator through participant interview) for HS (or any other inflammatory condition) with any

systemic or topical JAK or TYK2 inhibitor (eg, abrocitinib, baricitinib, brepocitinib, deucravacitinib, filgotinib, lestaurtinib, pacritinib, ruxolitinib, tofacitinib, upadacitinib).

[0498] (8) Use of any of the following treatments within the indicated washout period before Day 1:

[0499] (a) 12 weeks or 5 half-lives (if known), whichever is longer, for systemic immunosuppressive or immunomodulating biologic drugs (eg, adalimumab, anakinra, bermekimab, bimekizumab, brodalumab, certolizumab, dupilumab, etanercept, golimumab, guselkumab, infliximab, iscalimab, ixekizumab, risankizumab, rituximab, secukinumab, vilobelimab, ustekinumab).

[0500] (b) 4 weeks for any topical or systemic JAK or TYK2 inhibitor (eg, abrocitinib, baricitinib, brepocitinib, delgocitinib, deucravacitinib, filgotinib, lestaurtinib, pacritinib, ruxolitinib, tofacitinib, upadacitinib).

[0501] (c) 4 weeks for systemic corticosteroids or adrenocorticotrophic hormone analogs, cyclosporin, methotrexate, azathioprine, or other systemic immunosuppressive or immunomodulating agents (eg, mycophenolate, tacrolimus).

[0502] Note 1: Use of corticosteroid inhalers and intranasal sprays is allowed.

[0503] Note 2: Use of oral corticosteroids for nondermatologic conditions (eg, asthma exacerbation, bronchitis) is allowed for no longer than 7 days if deemed acceptable by the investigator and the sponsor (or designee).

[0504] (d) 4 weeks for surgical, laser, or any phototherapy intervention in areas with HS lesions.

[0505] (e) 2 weeks for other systemic therapies for HS (eg, retinoids, antihypertensive, antihyperglycemics, and antiandrogens such as acitretin,

isotretinoin, metformin, spironolactone, and finasteride) with potential therapeutic impact.

[0506] (f) 2 weeks for systemic anti-infectives for HS treatment (eg, antibiotics, antivirals, antifungals).

[0507] (g) 2 weeks for intralesional therapy for HS.

[0508] (h) 2 weeks for any topical therapy for HS (eg, topical antiseptics such as chlorhexidine, benzoyl peroxide, sodium hypochlorite, povidone iodine, or benzoyl peroxide; topical antibiotics; topical corticosteroids; topical calcineurin inhibitors; other topicals).

[0509] (i) 2 weeks or 5 half-lives, whichever is longer, for strong systemic CYP3A4 inhibitors.

[0510] (j) 2 weeks for immunizations with live-attenuated vaccines.

[0511] Note: Inactive/killed vaccinations are allowed (eg, flu, COVID-19, etc.).

[0512] (k) 2 weeks for any opioid treatment.

[0513] (l) Current treatment or treatment within 30 days or 5 half-lives (whichever is longer) before Day 1 with another investigational medication, or current enrollment in another investigational drug study.

[0514] (9) Undergone significant trauma or major surgery for HS or any other indication (per investigator's assessment) within 30 days preceding the screening visit.

[0515] (10) Known allergy or reaction to any of the components of the study cream formulation and/or products in the same class.

[0516] (11) History of active 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 participant's ability to comply with the administration schedule and study assessments.

[0517] (12) Pregnant or lactating.

[0518] (13) Currently hospitalized or history of hospitalization for mental health indication within 12 months.

[0519] (14) In the opinion of the investigator, unable or unlikely to comply with the application schedule, study evaluations, or procedures (eg, eDiary compliance).

[0520] (15) In the EU, participants considered incapacitated according to CTR Article 31.

[0521] (16) Employees of the sponsor or investigator or otherwise dependents of them.

[0522] Study Treatments Administered

[0523] Ruxolitinib 1.5% cream or matching vehicle cream will be applied as a thin film BID, with applications approximately 8 hours apart in the morning and in the evening at least 30 minutes before bedtime.

[0524] During clinic visits, the amount of study cream used per application will be determined by weighing a tube before and after the participant applies study cream to the affected areas. 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. Participants should be instructed not to exceed a 60-gram tube per week.

[0525] Efficacy Assessments

[0526] Although clinical trial endpoints have not been established in adolescents, the efficacy endpoints investigated in this study are applicable to both

populations (adolescents and adults) since the clinical manifestations of HS are conserved across adolescents and adults.

[0527] Lesions Counts

[0528] Hidradenitis suppurativa lesion counts will be assessed at each study visit by the investigator and used for the calculation of efficacy parameters as follows: HiSCR and HiSCR75, AN counts, and IHS4.

[0529] Lesion count and assessment will be recorded in the lesion count worksheet and includes assessment of anatomical regions including but not limited to the left and right axilla, left and right inguinocrural fold, and left and right inframammary areas.

[0530] Hidradenitis Suppurativa Clinical Response

[0531] The HiSCR was originally developed based on the underlying Phase 2 study of adalimumab and validated against meaningful changes in pain scores and DLQI. The achievement of HiSCR is defined as at least a 50% reduction in AN count with no increase in either abscess or draining fistula (tunnel) counts, relative to baseline. In this study, the HiSCR75, a higher threshold of improvement, will be used for the primary endpoint. For this study, participants with draining tunnels will be excluded. Should a randomized participant develop a draining tunnel during the study, the participant will be withdrawn from the study.

[0532] Abscess and Inflammatory Nodule Counts

[0533] Abscess and inflammatory nodule counts will be recorded at all visits. The counts will be used to calculate change in AN count relative to baseline as well as AN50, AN75, AN90, and AN100, defined respectively as at least a 50%, 75%, 90%, and 100% reduction in AN count relative to baseline.

[0534] International Hidradenitis Suppurativa Severity Score System

[0535] The IHS4 is a composite, dynamic score, and validated tool used to determine HS severity. It employs a weighted scale using the number of inflammatory nodules, the number of abscesses, and the number of draining tunnels (fistulas or sinuses), with respective weight factors of 1, 2, and 4 (e.g., IHS4 score equals the number of inflammatory nodules [multiplied by 1] plus the number of abscesses [multiplied by 2] plus the number of draining tunnels [multiplied by 4]).

[0536] Flare Incidence

[0537] The measurement of flares is an important component of treatment and its incidence is correlated with the deterioration of a patient's quality of life.

[0538] In this study, the definition of flare is outlined below, as proposed by Zouboulis et al:

[0539] At least 25% increase in the total abscess and inflammatory nodule count, relative to baseline; and

[0540] An increase of at least 2 in the total abscess and inflammatory nodule count, relative to baseline

[0541] The proportion of participants with incidence of flares will be evaluated during this study.

[0542] Hurley Stages of Hidradenitis Suppurativa

[0543] The Hurley classification is a static score and was originally designed for selection of the appropriate treatment modality in a certain body location: medical therapy for Stage I, local surgery for Stage II, and wide surgical excision for Stage III. Participants who have been diagnosed with HS (Hurley Stage I or II) as per inclusion criterion, will be enrolled into the study. Due to the heterogeneity of Hurley Stage II, participants with scarring are eligible for the study, while those with draining tunnels

will be excluded. The investigator (or designee) will determine the Hurley stage in each affected anatomical region at the visits designated in **Table 34**.

[0544] **Table 34**

Hurley Stage	Description
I	Abscess formation, single or multiple, without sinus tunnels and cicatrization/scarring.
II	One or more widely separated recurrent abscesses with tunnel (draining or nondraining) formation and cicatrization/scarring.
III	Multiple interconnected tunnels (draining or nondraining) and abscesses across the entire area, with diffuse or near diffuse involvement.

[0545] **Body Surface Area**

[0546] The total %BSA affected by HS and requiring field treatment will be used to determine the number of tubes of study cream dispensed at each visit. Total %BSA affected will be estimated at each visit as outlined in the SoA. Body surface area assessment of the body sites to receive field treatment will be approximated to the nearest 0.5% using the palmar method as a guide, with the palm plus 5 digits, with fingers together and thumb tucked to the side (handprint), considered as 1% BSA and the thumb as 0.1% BSA.

[0547] **Patient-Reported Outcomes**

[0548] Patient-reported outcomes will be collected and assessed as outlined in the SoA.

[0549] All PROs will be collected electronically. The Itch NRS and Skin Pain NRS will be collected daily via an eDiary; other PROs will be collected during site visits. For the PROs to be collected at site visits, in order to avoid bias in the participants' responses to the questionnaires, assessments should be completed

before any other evaluations or study procedures and prior to treatment-related discussions with the investigator or study site staff.

[0550] eDiary Assessments: Skin Pain and Itch Numeric Rating Scales

[0551] The participant will be instructed to complete and record the Skin Pain NRS and Itch NRS via an eDiary every evening beginning on the day of screening to the Week 52 or ET visit.

[0552] The participants will rate the following based on a 24-hour recall period:

[0553] Skin Pain NRS: Worst level of skin pain due to HS from 0 (no pain) to 10 (worst skin pain imaginable).

[0554] Itch NRS: Worst level of itch due to HS from 0 (no itch) to 10 (worst itch imaginable).

[0555] The baseline Skin Pain NRS and Itch NRS will be established prior to the first application of study cream as the average of the 7-day NRS score prior to the baseline visit (minimum 4 out of the 7 days' data required).

[0556] Analgesic Treatment

[0557] Participants will answer the analgesic (nonopioid only) use questionnaire via an eDiary every evening beginning on the day of screening to the Week 52 or ET visit.

[0558] Hidradenitis Suppurativa Quality of Life

[0559] An assessment of quality of life will be performed using the HiSQoL, and adult participants will complete a questionnaire at the visits designated. The HiSQoL is a 17-item, HS-specific, health-related, quality-of-life instrument with a 7-day recall period used to assess HS symptoms and the impact of HS problems on quality of life.

[0560] Hidradenitis Suppurativa Quality of Life – Adolescent

[0561] An assessment of quality of life will be performed using the HiSQoL-AA. Adolescent (12-<18 years of age) participants will complete a questionnaire at the visits. The HiSQoL-AA is a 15-item with a 7-day recall period used to assess HS symptoms and experiences of HS in adolescent patients.

[0562] Dermatology Life Quality Index

[0563] The DLQI is a simple, 10-question, validated questionnaire to measure how much a skin problem has affected the adult participant over the previous 7 days, across symptoms and feelings, daily activities, leisure, work and school, personal relationships, and treatment. Adult participants will complete the DLQI at the study visits.

[0564] Children's Dermatology Life Quality Index

[0565] The CDLQI is a 10-question, validated questionnaire to measure the impact of skin disease on the lives of children over the previous 7 days. This measure will be collected from participants who are adolescents at the visits.

[0566] Patient Global Impression of Severity

[0567] The PGIS is a single-item, self-reporting measure in which the participant rates the severity of their condition based on a 7-point scale: (1) not present, (2) very mild, (3) mild, (4) moderate, (5) moderately severe, (6) severe, and (7) extremely severe. Participants will complete the PGIS at the visits.

[0568] Patient Global Impression of Change

[0569] The PGIC is a self-reporting measure that reflects the participant's belief about the efficacy of treatment since the start of the study. The PGIC is a 7-point scale ((1) very much improved, (2) much improved, (3) minimally improved, (4) no change, (5) minimally worse, (6) much worse, and (7) very much worse) depicting

a participant's rating of overall improvement and will be captured during site visits as outlined in the SoA.

[0570] EQ-5D-5L

[0571] All participants will complete the EQ-5D-5L questionnaire at the visits.

These measures will provide data for use in economic models and analyses including developing health utilities or quality-adjusted life-years.

[0572] Work Productivity and Activity Impairment – Hidradenitis Suppurativa

[0573] Participants will complete the WPAI-HS questionnaire at the visits.

The WPAI-HS questionnaire is an instrument to measure impairments in both paid work and unpaid work. It measures absenteeism and presenteeism as well as impairments in unpaid activity because of HS and other health problems during the past 7 days. A minimal clinically important difference is defined as a one-half standard deviation of the total population's baseline score. Absenteeism, presenteeism, and overall work impairment will be assessed only for employed participants.

WHAT IS CLAIMED IS:

1. A method for treating hidradenitis suppurativa (HS) in a human patient in need thereof, comprising:

topically administering to an affected skin area of the patient a topical formulation comprising 1.5% (w/w) on a free base basis of ruxolitinib, or a pharmaceutically acceptable salt thereof, wherein the patient has no draining tunnels.

2. The method of claim 1, wherein the formulation is administered twice per day.

3. The method of claim 1 or 2, wherein the ruxolitinib, or the pharmaceutically acceptable salt thereof, is ruxolitinib phosphate.

4. The method of any one of claims 1-3, wherein the topical formulation is a cream formulation.

5. The method of any one of claims 1-4, wherein the patient has Hurley I or Hurley II HS.

6. The method of any one of claims 1-5, wherein the patient has a total abscess and inflammatory nodule counts (AN count) of less than 10.

7. The method of any one of claims 1-6, wherein the body surface area (BSA) involvement of the HS is $\leq 20\%$.

8. The method of any one of claims 1-4, wherein at baseline, the patient is diagnosed with HS and has a total abscess and inflammatory nodule (AN) count of 3 to ≤ 10 with no draining tunnels.

9. The method of any one of claims 1-8, wherein after at least 2, 4, 8, 12,

or 16 weeks of administering, the patient has a change in baseline in the total AN count.

10. The method of any one of claims 1-9, wherein after at least 16 weeks of administering, the patient has a reduction in the total AN count.

11. The method of claim 10, wherein the reduction in total AN count from baseline to week 16 is at least 2.

12. The method of claim 10, wherein the reduction in total AN count from baseline to week 16 is at least 3.

13. The method of any one of claims 1-12, wherein at baseline, the patient has a Pain-NRS score of ≥ 1 at baseline.

14. The method of any one of claims 1-13, wherein after at least 2, 4, 8, 12, or 16 weeks of administering, the patient has a change in the Pain-NRS score from baseline.

15. The method of any one of claims 1-13, wherein after at least 16 weeks of administering, the patient has a reduction in the Pain-NRS score from baseline.

16. The method of claim 14 or 15, wherein the reduction in the Pain-NRS score from baseline is at least about 1.

17. The method of claim 14 or 15, wherein the reduction in the Pain-NRS score from baseline is at least about 2.

18. The method of any one of claims 1-17, wherein at baseline, the patient has an Itch-NRS score of ≥ 1 at baseline.

19. The method of any one of claims 1-18, wherein after at least 2, 4, 8, 12,

or 16 weeks of administering, the patient has a change in the Itch-NRS score from baseline.

20. The method of any one of claims 1-19, wherein after at least 16 weeks of administering, the patient has a reduction in the Itch-NRS score from baseline.

21. The method of claim 20, wherein the reduction in the Itch-NRS score from baseline is at least about 1.

22. The method of any one of claims 1-21, wherein the topical formulation is administered for at least 16 weeks.

23. The method of any one of claims 1-22, wherein the patient is aged 18 or older.

24. The method of any one of claims 1-23, wherein the patient achieves a Hidradenitis Suppurativa Clinical Response (HiSCR) and/or a modified Hidradenitis Suppurativa Clinical Response (mHiSCR), by week 2, 4, 8, 12, or 16 of administration.

25. The method of any one of claims 1-24, wherein the patient achieves AN50 by at least week 16 of administration.

26. The method of any one of claims 1-24, wherein the patient achieves AN75 by at least week 16 of administration.

27. The method of any one of claims 1-26, wherein the patient achieves International Hidradenitis Suppurativa Severity Score System (IHS4) score by at least week 16 of administration.

28. The method of any one of claims 1-26, wherein the patient achieves International Hidradenitis Suppurativa Severity Score System with a $\geq 55\%$ reduction (IHS4-55) from baseline of a total IHS4 score by at least week 16 of administration.

29. The method of any one of claims 1-26, wherein the patient achieves IHS4-55 by at least week 32 of administration.

30. The method of any one of claims 1-29, wherein after at least one of 2, 4, 8, 12, or 16 weeks of administering, the patient has a reduction in abscesses from baseline.

31. The method of claim 30, wherein after 12, or 16 weeks of administering, the patient has a reduction in abscesses from baseline.

32. The method of any one of claims 1-29, wherein after at least one of 2, 4, 8, 12, or 16 weeks of administering, the patient has a reduction in inflammatory nodules from baseline.

33. The method of claim 32, wherein after 12 or 16 weeks, the patient has a reduction in inflammatory nodules from baseline.

34. The method of any one of claims 1-29, wherein after at least one of 2, 4, 8, 12, or 16 weeks of administering, the patient has a reduction in abscesses and inflammatory nodules from baseline.

35. The method of claim 34, wherein after 12 or 16 weeks, the patient has a reduction in abscesses and inflammatory nodules from baseline.

36. A method for treating hidradenitis suppurativa (HS) in a human patient in need thereof, comprising:

topically administering to an affected skin area of the patient a topical formulation comprising 0.75% to 1.5% (w/w) on a free base basis of ruxolitinib, or a pharmaceutically acceptable salt thereof, wherein the patient has no draining tunnels.

37. The method of claim 36, wherein the ruxolitinib, or the pharmaceutically

acceptable salt thereof, comprises about 0.75% of the ruxolitinib, or the pharmaceutically acceptable salt thereof, on a free base basis.

38. The method of claim 36 or 37, wherein the formulation is administered twice per day.

39. The method of any one of claims 36-38, wherein the ruxolitinib, or the pharmaceutically acceptable salt thereof, is ruxolitinib phosphate.

40. The method of any one of claims 36-38, wherein the topical formulation is a cream formulation.

41. The method of any one of claims 36-40, wherein the patient has Hurley I or Hurley II HS.

42. The method of any one of claims 36-41, wherein the patient has a total abscess and inflammatory nodule counts (AN count) of less than 10.

43. The method of any one of claims 36-41, wherein the body surface area (BSA) involvement of the HS is $\leq 20\%$.

44. The method of any one of claims 36-43, wherein the patient achieves AN50 by at least week 16 of administration.

45. The method of any one of claims 36-43, wherein the patient achieves AN75 by at least week 16 of administration.

46. The method of any one of claims 36-45, wherein the patient achieves IHS4 by at least week 16 of administration.

47. The method of any one of claims 36-45, wherein the patient achieves International Hidradenitis Suppurativa Severity Score System with a $\geq 55\%$ reduction

(IHS4-55) from baseline of a total ISH4 score by at least week 16 of administration.

48. The method of any one of claims 36-45, wherein the patient achieves IHS4-55 by at least week 32 of administration.

49. The method of any one of claims 36-48, wherein after at least one of 2, 4, 8, 12, or 16 weeks of administering, the patient has a reduction in abscesses from baseline.

50. The method of claim 49, wherein after 12 or 16 weeks of administering, the patient has a reduction in abscesses from baseline.

51. The method of any one of claims 36-48, wherein after at least one of 2, 4, 8, 12, or 16 weeks of administering, the patient has a reduction in inflammatory nodules from baseline.

52. The method of claim 51, wherein after 12 or 16 weeks, the patient has a reduction in inflammatory nodules from baseline.

53. The method of any one of claims 36-48, wherein after at least one of 2, 4, 8, 12, or 16 weeks of administering, the patient has a reduction in abscesses and inflammatory nodules from baseline.

54. The method of claim 53, wherein after 12 or 16 weeks, the patient has a reduction in abscesses and inflammatory nodules from baseline.

55. A method for reducing pain from hidradenitis suppurativa (HS) in a human patient in need thereof, comprising:

topically administering to an affected skin area of the patient a topical formulation comprising 1.5% (w/w) on a free base basis of ruxolitinib, or a pharmaceutically acceptable salt thereof,

wherein the patient has no draining tunnels, and

wherein the patient is ≥ 18 years of age and has a reduction in AN count from baseline after 16 weeks of administering.

56. A method for reducing pain from hidradenitis suppurativa (HS) in a human patient in need thereof, comprising:

topically administering to an affected skin area of the patient, two times per day, a topical formulation comprising 1.5% (w/w) on a free base basis of ruxolitinib, or a pharmaceutically acceptable salt thereof,

wherein the patient has no draining tunnels, and

wherein the patient is ≥ 18 years of age and at baseline, the patient has a Pain-NRS score of ≥ 1 at baseline and after at least 2, 4, 8, 12, or 16 weeks of topically administering, the patient has a change in the Pain-NRS score from baseline.

57. A method for reducing itch from hidradenitis suppurativa (HS) in a human patient in need thereof, comprising:

topically administering to an affected skin area of the patient, two times per day, a topical formulation comprising 1.5% (w/w) on a free base basis of ruxolitinib, or a pharmaceutically acceptable salt thereof,

wherein the patient has no draining tunnels, and

wherein the patient achieves AN50 by at least week 16.

58. A method for treating hidradenitis suppurativa (HS) in a human patient in need thereof, comprising:

topically administering to an affected skin area of the patient, two times per day,

a topical formulation comprising 1.5% (w/w) on a free base basis of ruxolitinib, or a pharmaceutically acceptable salt thereof,

wherein the patient has no draining tunnels,

wherein the patient is ≥ 18 years of age and at baseline, and

wherein the patient achieves a Hidradenitis Suppurativa Clinical Response (HiSCR) and/or a modified Hidradenitis Suppurativa Clinical Response (mHiSCR), after at least 2, 4, 8, 12, or 16 weeks of administering.

59. A method for treating hidradenitis suppurativa (HS) in a human patient in need thereof, comprising:

topically administering to an affected skin area of the patient, two times per day, a topical formulation comprising 1.5% (w/w) on a free base basis of ruxolitinib, or a pharmaceutically acceptable salt thereof,

wherein the patient has no draining tunnels,

wherein the patient is ≥ 18 years of age and at baseline, and

wherein after at least one of 2, 4, 8, 12, or 16 weeks of administering, the patient has a reduction in abscesses and/or inflammatory nodules from baseline.

60. A method for treating hidradenitis suppurativa (HS) in a human patient in need thereof, comprising:

topically administering to an affected skin area of the patient a topical formulation comprising 1.5% (w/w) on a free base basis of ruxolitinib, or a pharmaceutically acceptable salt thereof,

wherein the patient achieves International Hidradenitis Suppurativa Severity

Score System with a $\geq 55\%$ reduction (IHS4-55) from baseline of a total ISH4 score.

61. The method according to claim 60, wherein the ISH4-55 score is about 60%, about 65%, about 70%, about 75%, about 80%, or about 85% reduction from baseline in the total ISH4 score.

62. The method according to claim 61, wherein the patient achieves a decrease in IHS4-55 score by at least week 2, 4, 8, 12, 16, 20, 24, 28, or 32.

63. The method according to claim 60, wherein the patient achieves the decrease in IHS4-55 score by at least 16 weeks.

64. The method according to claim 60, wherein the patient achieves the decrease in IHS4-55 score by at least 32 weeks.