



HRP-592 - Protocol for Human Subject Research with Use of Test Article(s)

Protocol Title:

Exploratory Trial of Ruxolitinib 1.5% Cream for Early Stage Hidradenitis Suppurativa

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1.0 Objectives

1.1 Study Objectives

We hypothesize that ruxolitinib 1.5% cream is an effective therapy for **Hidradenitis Suppurativa** patients through inhibition of inflammatory activity.

We aim to:

- Demonstrate the clinical efficacy of ruxolitinib 1.5% cream in decreasing the clinical disease activity after 16 weeks of treatment.
- Investigate the impact of ruxolitinib 1.5% cream on skin inflammation through translational analyses of skin biopsy samples.

1.2 Primary Study Endpoints

The primary efficacy measure is the proportion of participants that achieve HiSCR (is the total number of abscess and inflammatory count of the participants lesions) at Week 16 with topical ruxolitinib 1.5% cream as compared to Baseline (Week 0). The HiSCR is defined as at least a 50% reduction in the total abscess and inflammatory nodule count (AN count) for all study body sites with no increase in abscess count and no increase in draining fistula count relative to Baseline. The primary efficacy analysis will be carried out on all participants who complete 16 weeks of treatment.

1.3 Secondary Study Endpoints

- Mean difference in the International Hidradenitis Suppurativa Severity Scoring System (IHS4) score from Baseline to Week 16.
- Proportion of patients who are clear or mild by IHS4 after 16 weeks of treatment.
- Mean difference in the novel clinician-reported outcome measure (HASI, investigator-supplied) score from Baseline to Week 16.
- Mean change in the Hidradenitis Suppurativa Quality Of Life (HiSQOL) instrument for 16 weeks of treatment.
- Mean change in Numerical Rating Scale (NRS) for pain (7-day) after 16 weeks of treatment.
- Proportion of participants with a 30% and at least 2-point reduction in NRS for pain (7-day) after 16 weeks of treatment.
- Mean change in Numerical Rating Scale (NRS) for pain (24-hour) after 16 weeks of treatment.
- Proportion of participants with a 30% and at least 2-point reduction in NRS for pain (24-hour) after 16 weeks of treatment.

2.0 Background

2.1 Scientific Background and Gaps

Hidradenitis suppurativa (HS) is a chronic, inflammatory skin disease of unknown etiology that causes painful swollen nodules, draining abscesses, and disfiguring scars of the skin folds that make walking, sitting, and working difficult or impossible. Malodorous drainage is humiliating and uncomfortable. HS is a devastating inflammatory condition that affects approximately 1% of adults of European descent,

similar in incidence to psoriasis, and is associated with serious comorbidities such as metabolic syndrome and diabetes.

Adalimumab, a monoclonal antibody against TNF α , is the only FDA-approved therapy and is only partially effective for 50-60% of patients. Importantly, there is only one topical medication, clindamycin, which is routinely used for the therapy of HS. This is a critical gap in the treatment of HS – there is a need for more and effective topical therapies.

Janus kinase (JAK) kinases are intracellular, non-receptor tyrosine kinases that bind to cytokine-specific receptors and, therefore, influence various aspects of the immune response. JAK1 is associated with the receptors for IFN, IL-6, and IL-10. JAK2 is mainly involved in the reaction with hematopoietic receptors as well as those for IL-12 and IL-23. JAK2 are connected with the receptors for IFN, IL-12, and IL-23. There are no published studies documenting JAK-STAT expression in HS; however, other work has shown the important role of all four kinases in other skin conditions. Importantly, IL-6 and Interferon-gamma have been shown to be elevated in HS. Topical ruxolitinib 1.5% cream, the interventional treatment in this protocol, is not available outside of a clinical study.

Some tools to measure hidradenitis suppurativa are given by administering questionnaires that specifically define how participants are feeling and how their disease affects their daily living. This includes assessing the pain level of the lesions. These are in addition to questionnaires that are obtained during clinical visits. These tools can also help to determine whether or not the assigned medication is helping the disease. The pain associated with the disease if lessened could help improve their quality of life. It is important to capture these measures prior to medication dosing. An improved quality of life could be due to the decreased amount of lesions. Additionally, clinician- reported outcomes, including counts of lesions and the HASI (scores the severity of the participants lesions) will be used to evaluate objective changes in the disease burden. The questionnaires, HiSQOL, pain scale, lesion counts and HASI will capture this for the participant.

2.2 Previous Data

The JAK family of kinases includes JAK1, JAK2, JAK3, and TYK2. The JAK-STAT (Signal Transducer and Activator of Transcription proteins (*STATs*) pathway is used by cytokines including ILs, interferons, and other molecules to transmit signals from the cell membrane to the nucleus. Upon engagement of extracellular ligands, intracellular JAK proteins, which associate with type I/II cytokine receptors, become activated and phosphorylate STAT proteins, which dimerize and then translocate into the nucleus to directly regulate gene expression. Among all JAK family members, JAK1 signaling relates primarily to cytokines involved in inflammation.

Numerous inflammatory dermatoses are driven by soluble inflammatory mediators, which rely on JAK-STAT signaling. For example, the pathogenesis of atopic dermatitis is complex but, in part, involves increased T helper cell (Th) type 2 (ie, Th2) immunity driven by JAK-STAT signaling downstream of cytokines, such as IL-4, IL-5, and IL-13. In vitiligo, JAK-STAT also serves a central role in interferon- γ -mediated

melanocyte destruction by CD8+ T cells. In psoriasis, JAK-STAT-dependent cytokines, IL-12 and IL-23, are fundamental mediators. Interleukin-23 stimulates Th17 cells to produce IL-17, another important pathogenic molecule in psoriasis. The presence of Th17 cells in HS lesional tissue suggests that although IL-17 does not rely on JAK-STAT signaling, blockade of upstream IL-23 using JAK inhibitors may indirectly result in a decrease in Th17 cell presence and IL-17 expression.

Recent literature suggests that the main cytokines involved in HS pathogenesis are IL-1 β , IL-17, IL-23, IL-10, and, to a lesser extent, TNF- α . The expression and/or activity of these cytokines is profoundly regulated by the intracellular level through JAK-STAT signaling, and is primarily mediated by JAK1. Therefore, it can be reasonably expected that interference with the transduction of intracellular signals generated by these cytokines will modify/decrease the level of inflammation seen in HS and thus moderate or control the disease activity.

2.3 Study Rationale

JAK kinases bind to cytokine-specific receptors and, therefore, influence various aspects of the immune response. JAK1 is associated with the receptors for IFN, IL-6, and IL-10. JAK2 is mainly involved in the reaction with hematopoietic receptors as well as those for IL-12 and IL-23. JAK2 are connected with the receptors for IFN, IL-12, and IL-23. There are no published studies documenting JAK-STAT expression in HS; however, other work has shown the important role of all four kinases in other inflammatory skin conditions, such as alopecia areata, psoriasis, and vitiligo. Importantly, IL-6 and Interferon-gamma have been shown to be elevated in HS. To date in dermatology, psoriasis has been the most studied indication for JAK inhibitors including tofacitinib, baricitinib, and ruxolitinib. Incyte has completed 4 clinical studies with JAK1 and JAK2 inhibitors for the treatment of psoriasis. Topical ruxolitinib has been associated with clinical improvement and benefit in patients with chronic plaque psoriasis. Given the fact that HS shares a similar inflammatory cytokine profile as that seen in psoriasis, inhibition of JAK-STAT signaling represents a promising therapeutic strategy for the treatment of HS.

3.0 Inclusion and Exclusion Criteria

3.1 Inclusion Criteria

1. Male or female subjects age 12 years or older
 - This inclusion criteria has been updated due to the approval of the study medication for use in this age group (12 years and older) in other indications. Additionally, Humira, an approved biologic medication for HS, is also used in this population, highlighting the need for topical breakthrough treatments for those affected by HS at younger ages. Due to the open-label nature of this medication and the anticipated benefits for any children participating, the greater than minimal risk of this study design is justified.
2. Hidradenitis suppurativa, and should be Hurley Stage I or II, defined as papules, nodules, and/or abscess formation, single or multiple, with or without sinus tracts;
3. Subjects must have a diagnosis of HS for at least 3 months (90 days) prior to Baseline;
4. Active HS lesions must be present in at least one distinct anatomic area;

5. Subject must have at least 3 total inflammatory lesions at the Baseline visit;
6. Subjects who had surgery in the treatment area, should be at least 3 months status post the procedure (this applies to deroofting/marsupialization or excision, not incision & drainage)
7. Subject has a negative TB screening assessment (including a PPD test and/or T-Spot) OR for patients with treated latent TB or negative chest x-ray (CXR posterior-anterior [PA] and lateral view within prior 90 days) at Screening with documentation of treated latent tuberculosis (90 days of treatment).
8. Medications can be continued if they have been at a stable dose for the requisite duration and the dose is not increased during the study period:
 - Biologic medication (such as TNF α , IL-12/23 or IL-17 inhibitors): Up to 30% of enrolled participants will be allowed to remain on a concurrent biologic at stable dosage if treated with a stable dose and frequency for 6 months or longer;
 - Oral antibiotic must be a stable dose and frequency for 28 days or longer;
 - Hormone-based therapy (birth control pills or spironolactone) must be a stable dose and frequency for 4 months or longer;
 - Oral retinoids must be on a stable dose and frequency for 90 days or longer;
 - Other topical therapy must be discontinued 14 days prior to the Baseline visit.
 - Childbearing potential: In addition, you must be willing to use a method of contraception during the study period and for 4 weeks after the last dose of study drug. (Note: Periodic abstinence [e.g., calendar, ovulation, symptothermal, post-ovulation methods] and withdrawal are not acceptable as abstinence.)

3.2 Exclusion Criteria

1. Non-english speaking
2. Infection(s) unrelated to HS requiring treatment with:
 - intravenous (IV) anti-infectives (antibiotics, antivirals, antifungals) within 30 days prior to Baseline or;
 - oral anti-infectives (antibiotics, antivirals, antifungals) within 14 days prior to Baseline, except as required as part of an anti-TB regimen;
3. Subject previously treated with a biologic medication but stopped due to lack of effect/sufficient effect as deemed by the investigator.
4. Any other active skin disease or condition (e.g., bacterial, fungal or viral infection) that may interfere with assessment of HS;
5. Pregnant (or considering becoming pregnant) or lactating females
Note: Nonchildbearing potential is defined as surgically sterile with a hysterectomy and/or bilateral oophorectomy OR postmenopausal (defined as amenorrhea at least 12 months before screening, confirmed by FSH levels at screening).
6. Clinically significant abnormal screening laboratory results as evaluated by the Investigator.
7. Subject does not have reliable internet access for weekly electronic surveys;
8. Subject is considered by the Study Investigator, for any reason, to be an unsuitable candidate for the study.

9. Excluded/prohibited concomitant medication and procedures include: JAK inhibitors (systemic or topical (eg, ruxolitinib, tofacitinib, baricitinib, filgotinib, lestaurtinib, and pacritinib)) within 4 weeks of Screening ; surgical, laser, or IPL intervention in area with HS lesion within 3 months of Screening, except for rescue lesional treatment; systemic corticosteroid within 4 weeks; use of topical creams, ointments, gels, and liquids except the study therapy.
10. Prolonged QT interval corrected for heart rate using Fridericia's formula (QTcF), defined as ≥ 450 msec.

3.3 Early Withdrawal of Subjects

3.3.1 Criteria for removal from study

Some possible reasons for an early withdraw might be subjects require or receive treatment that is not allowed in this study, subject becomes pregnant, subject experiences side effects from the study treatments that they find unacceptable, HS worsens according to the study doctor's assessment, or subject does not follow instructions.

3.3.2 Follow-up for withdrawn subjects

If a subject withdraws completely from the research study, no further information will be collected and his/her participation will end. All attempts will be made to conduct the last study visit and perform all early termination assessments.

4.0 Recruitment Methods

4.1 Identification of subjects

Subjects will be recruited through STUDYfinder. Dr. Zaenglein will be recruiting from her dermatology clinic. She, and other dermatology providers, will identify participants during their regularly scheduled visits (interactions during a clinic visit). Additionally, an established recruitment database of HS patients may be used.

4.2 Recruitment process

4.2.1 How potential subjects will be recruited.

Subjects will call the study line at the research site. The coordinator will call and if the subject decides to schedule an appointment, the coordinator will schedule a screening visit. The site will utilize a screening form for all potential subjects. Subjects who are identified in clinic will call the research office or stop in after their regular scheduled appointment for their screening visit at another time.

4.2.2 Where potential subjects will be recruited.

Dr. Zaenglein will be recruiting from her dermatology clinic and online resource STUDYFinder. We will also be utilizing our HS database and contacting previous

dermatology research participants who agreed for the study team to be contacted for upcoming trials.

4.2.3 When potential subjects will be recruited.

Potential subjects will be recruited during their regular scheduled HS Dermatology clinic visit by the study coordinator.

4.2.4 Describe the eligibility screening process and indicate whether the screening process will occur before or after obtaining informed consent. Screening begins when the investigator obtains information about or from a prospective participant in order to determine their eligibility. In some studies, these procedures may not take place unless HIPAA Authorization is obtained OR a waiver of HIPAA Authorization when applicable for the screening procedures is approved by the IRB. [For FDA regulated studies, consent for any screening activities would need to be obtained prior to screening unless specifically waived by the IRB.]

Subjects will call the site to be screened. If the subject decides to schedule an appointment the coordinator schedules a screening visit. If the subject declines, the telephone screening is discarded.

5.0 Consent Process and Documentation

5.1 Consent Process:

Check all applicable boxes below:

- ☒ Informed consent will be sought and documented with a written consent form
[Complete Sections 5.2 and 5.6]
- ☐ Implied or verbal consent will be obtained – subjects will not sign a consent form
(waiver of written documentation of consent) [Complete Sections 5.2, 5.3 and 5.6]
- ☐ Informed consent will be sought but some of the elements of informed consent
will be omitted or altered (e.g., deception). [Complete section 5.2, 5.4 and 5.6]
- ☐ Informed consent will not be obtained – request to completely waive the informed
consent requirement. [Complete Section 5.5]

5.2 Obtaining Informed Consent

5.2.1 Timing and Location of Consent

The consent will take place in the Dermatology Research Office, UPC II-RM 2010 in a private room by a research coordinator

5.2.2 Coercion or Undue Influence during Consent

Subjects will have ample time to read and ask questions about the study. Their involvement in the study will not affect their treatment if they are currently patients of the dermatology clinic.

5.3 Waiver of Written Documentation of Consent

5.3.1 Indicate which of the following conditions applies to this research:

☐ The research presents no more than minimal risk of harm to subjects and involves no procedures for which written consent is normally required outside of the research context.

OR

☐ The only record linking the subject and the research would be the consent document and the principal risk would be potential harm resulting from a breach of confidentiality. Each subject will be asked whether the subject wants documentation linking the subject with the research, and the subject's wishes will govern. *(Note: This condition is not applicable for FDA-regulated research. If this category is chosen, include copies of a consent form and /or parental permission form for participants who want written documentation linking them to the research.)*

OR

☐ If the subjects or legally authorized representatives are members of a distinct cultural group or community in which signing forms is not the norm, that the research presents no more than minimal risk of harm to subjects and provided there is an appropriate alternative mechanism for documenting that informed consent was obtained. *(Note: This condition is not applicable for FDA-regulated research.)*

Describe the alternative mechanism for documenting that informed consent was obtained:

Each consented participant will have ICF process documented on their source.

5.3.2 Indicate what materials, if any, will be used to inform potential subjects about the research (e.g., a letter accompanying a questionnaire, verbal script, implied consent form, or summary explanation of the research)

Coordinator will complete a screening form for each potential participant

5.4 Informed consent will be sought but some of the elements of informed consent will be omitted or altered (e.g., deception).

5.4.1 Indicate the elements of informed consent to be omitted or altered

NA

5.4.2 Indicate why the research could not practicably be carried out without the omission or alteration of consent elements

NA

5.4.3 Describe why the research involves no more than minimal risk to subjects.

NA

5.4.4 Describe why the alteration/omission will not adversely affect the rights and welfare of subjects.

NA

5.4.5 If the research involves using identifiable private information or identifiable biospecimens, describe why the research could not be practicably be carried out without using such information or biospecimens in an identifiable format.

NA

5.4.6 Debriefing

NA

5.5 Informed consent will not be obtained – request to completely waive the informed consent requirement

5.5.1 Indicate why the research could not practicably be carried out without the waiver of consent

NA

5.5.2 Describe why the research involves no more than minimal risk to subjects.

NA

5.5.3 Describe why the alteration/omission will not adversely affect the rights and welfare of subjects.

NA

5.5.4 If the research involves using identifiable private information or identifiable biospecimens, describe why the research could not be practicably be carried out without using such information or biospecimens in an identifiable format.

NA

5.5.5 Additional pertinent information after participation

NA

5.6 Consent – Other Considerations

5.6.1 Non-English-Speaking Subjects

NA

5.6.2 Cognitively Impaired Adults

5.6.2.1 Capability of Providing Consent

NA

5.6.2.2 Adults Unable to Consent

NA

5.6.2.3 Assent of Adults Unable to Consent

NA

5.6.3 Subjects who are not yet adults (infants, children, teenagers)

5.6.3.1 Parental Permission

For all subjects under the age of 18, parental/legal guardian permission will be obtained using an informed consent form. The consent process will be documented in the subject's research records and a copy of the signed ICF will be provided.

5.6.3.2 Assent of subjects who are not yet adults

The Information Sheet will be provided to all potential participants ages 12-17. They will be given ample time to review the document in a private room. All questions will be answered by study team members prior to providing assent.

Assent will be obtained and documented for all children participants in this study, as subjects will be at least 12 years of age. Assent will be documented in the ICF and in the subject's research chart.

6.0 HIPAA Research Authorization and/or Waiver or Alteration of Authorization

6.1 Authorization and/or Waiver or Alteration of Authorization for the Uses and Disclosures of PHI

Check all that apply:

- ☐ **Not applicable, no identifiable protected health information (PHI) is accessed, used or disclosed in this study.** *[Mark all parts of sections 6.2 and 6.3 as not applicable]*
- ☒ **Authorization will be obtained and documented as part of the consent process.** *[If this is the only box checked, mark sections 6.2 and 6.3 as not applicable]*
- ☒ **Partial waiver is requested for recruitment purposes only (Check this box if patients' medical records will be accessed to determine eligibility before consent/authorization has been obtained).** *[Complete all parts of sections 6.2 and 6.3]*
- ☐ **Full waiver is requested for entire research study (e.g., medical record review studies).** *[Complete all parts of sections 6.2 and 6.3]*
- ☐ **Alteration is requested to waive requirement for written documentation of authorization (verbal authorization will be obtained).** *[Complete all parts of sections 6.2 and 6.3]*

6.2 Waiver or Alteration of Authorization for the Uses and Disclosures of PHI

6.2.1 Access, use or disclosure of PHI representing no more than a minimal risk to the privacy of the individual

6.2.1.1 Plan to protect PHI from improper use or disclosure

Information is included in the “Confidentiality, Privacy and Data Management” section of this protocol.

6.2.1.2 Plan to destroy identifiers or a justification for retaining identifiers

All study materials that have identifiable information will be kept until notified by the sponsor. If a subject has a phone screen conducted and does not schedule an appointment or if they do not want their information kept for future studies the phone screening is shredded.

6.2.2 Explanation for why the research could not practicably be conducted without access to and use of PHI

Research needs to use PHI to ensure subject meets eligibility criteria.

6.2.3 Explanation for why the research could not practicably be conducted without the waiver or alteration of authorization

Participants are screened prior to scheduling them for their research appointment to help determine if the patient is potentially eligible for the study. This helps sift through candidates for appointments so patient’s time is not wasted.

6.3 Waiver or alteration of authorization statements of agreement

Protected health information obtained as part of this research will not be reused or disclosed to any other person or entity, except as required by law, for authorized oversight of the research study, or for other permitted uses and disclosures according to federal regulations.

The research team will collect only information essential to the study and in accord with the ‘Minimum Necessary’ standard (information reasonably necessary to accomplish the objectives of the research) per federal regulations.

Access to the information will be limited, to the greatest extent possible, within the research team. All disclosures or releases of identifiable information granted under this waiver will be accounted for and documented.

7.0 Study Design and Procedures

7.1 Study Design

This is a prospective interventional study of topical ruxolitinib 1.5% cream twice a day for the treatment of early stage (stage I and II) HS.

7.2 Study Procedures**7.2.1 Screening visit**

Informed consent	Laboratory screening obtained* <ul style="list-style-type: none"> • Hepatitis B and Hepatitis C surface and core antibodies • Interferon-releasing assay for tuberculosis (or chest x-ray for those with a history of positive PPD) • Complete blood count (CBC) with differential • Hepatic panel (AST, ALT, Alk phos) • Fasting lipid panel (total, high-density, and low density cholesterol and triglycerides) • Pregnancy testing for women of child bearing potential (WOCBP)**
Inclusion/exclusion criteria reviewed	
Complete physical exam	
Clinician assessments (Lesion count, Hurley stage, HASI)	
Clinical photography of all lesions (do not include face)- kept in research files	
ECG	
Alcohol intake and recreational drug use	
Begin weekly surveys (more details below)	

*All blood will be obtained at Penn State Health outpatient laboratory.

**If subjects are postmenopausal, (defined as amenorrhea at least 12 months before screening) this will be confirmed by FSH levels drawn at the clinical site (approx. 2 teaspoons of blood)

Begin weekly surveys – These will be completed by the participants weekly through the end of Week 16 through REDCap. The weekly instruments will include patient-reported measures: NRS pain with 24-hour recall, NRS pain with 7-day recall, Hidradenitis suppurativa Quality of Life instrument (HiSQOL); medication use (assessing use of rescue medications or other potentially modifying medications or interventions).

7.2.2 Week 0, Baseline visit (28 ±5 days)- Can be combined with Screening Visit

Subjects will have a combined Screening/Baseline visit if all Inclusion/Exclusion criteria is met at the Screening visit.

Complete physical exam	Patient reported measures- collected electronically
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Clinician reported measures collected	WOCBP only- urine sample for pregnancy
Clinical photography	Dispense and start treatment with topical ruxolitinib 1.5% cream. Study coordinator will provide instructions for twice daily application.
Target lesion evaluated	Tissue sample collected (details below)

Tissue sample of Target Lesion: We will collect a full-thickness skin punch biopsy (4-6mm) from an active inflammatory lesion from each subject as a mandatory part of the study. Gelfoam will be immediately applied to the area after the biopsy procedure. Vaseline will be placed where the biopsy was taken to help the healing process. We are collecting lesional HS skin only. One punch biopsy will be collected at Week 0 of the target lesion/area.

For all full-thickness skin punch biopsies, skin punch will be immediately placed in sterile specimen cup and transported on ice to Dr. Nelson's laboratory (C7801 BMR) for storage and analysis. Biopsy will be bisected and portions will be formalin-fixed paraffin-embedded for planned immunohistochemistry analyses. Remaining biopsy portion will be placed in RNALater and stored at -80C. Total RNA will be isolated from the skin punch and may be subjected to RNA-sequencing in future studies.

7.2.3 Week 4 (± 5 days)

Clinical photography	Target lesion evaluated
Patient reported measures- collected electronically	All used/ unused study medication returned
Clinician reported measures	New study medication dispensed
Complete physical exam	WOCBP only- urine sample for pregnancy

7.2.4 Week 8 (± 5 days)

Clinical photography	Target lesion evaluated
Patient reported measures- collected electronically	All used/ unused study medication returned
Clinician reported measures	New study medication dispensed
Complete physical exam	WOCBP only- urine sample for pregnancy

7.2.5 Week 16/Early Termination (± 5 days)

Clinical photography	Laboratory Testing (approx. 8 tsp blood):
Complete physical exam	<ul style="list-style-type: none"> • CBC with differential • Hepatic panel (AST, ALT, Alk phos) • Fasting lipid panel (Total, high-density, and low density cholesterol, and triglycerides) • WOCBP only- urine sample for pregnancy
Patient reported measures-completed electronically	
Clinician reported measures	
Tissue sample collected (details below)	
Target lesion evaluated	
All dispensed medication (used and unused) will be returned to the research office	

Tissue sample of Target lesion identified at the baseline visit (whether active or resolved): We will collect a full-thickness skin punch biopsy (4-6mm) from the target lesion.

For all full-thickness skin punch biopsies, skin punch will be immediately placed in sterile specimen cup and transported on ice to Dr. Nelson's laboratory (C7801 BMR) for storage and analysis.

Biopsy will be bisected and portions will be formalin-fixed paraffin-embedded for planned immunohistochemistry analyses.

Remaining biopsy portion will be placed in RNALater and stored at -80C. Total RNA will be isolated from the skin punch and may be subjected to RNA-sequencing in future studies.

7.2.6 F/U Telephone Call (30 days post last dose of study medication) (+7 days)

Coordinator will call participant and discuss any new A/E's or changes in medication since the last dose of study medication.

7.3 Duration of Participation

During the study, participants will have scheduled visits in the Dermatology Research Office at Screening, Baseline/Week 0 (can be combined with Screening), Week 4, Week 8, and Week 16. Each of these visits is expected to last for up to 60 minutes.

Participation will be up to 24 weeks long, including the screening and follow up periods.

7.4 Test Article(s) (Study Drug(s) and/or Study Device(s))

7.4.1 Description

Topical ruxolitinib 1.5% cream is an investigational treatment for hidradenitis suppurativa. The drug molecule, ruxolitinib, is FDA-approved to treat myelofibrosis and polycythemia vera. Ruxolitinib inhibits janus-associated kinases (JAK) 1 and 2. Which leads to disruption of cytokine and growth factor signaling pathways. Topical ruxolitinib 1.5% cream is not FDA-approved for any

indication, so an IND will be obtained from the FDA for use. The cream will be supplied by the company, Incyte.

7.4.2 Treatment Regimen

A thin layer of Topical ruxolitinib 1.5% cream will be applied to areas of hidradenitis suppurativa on the skin twice a day.

7.4.3 Method for Assigning Subject to Treatment Groups

NA

7.4.4 Subject Compliance Monitoring

Tubes of the study medication will be weighed at every study visit. Study team will re-educate subjects for dosing administration at all study visits.

7.4.5 Blinding of the Test Article

NA

7.4.6 Receiving, Storage, Dispensing and Return

7.4.6.1 Receipt of Test Article

Tubes of ruxolitinib 1.5% cream will be obtained from Incyte, the sponsor. The IP will each be dispensed in 60g tubes. Labeling will include instructions that the product is for external use only, to use the IP twice daily on the skin at sites of HS.

7.4.6.2 Storage

The IP cream can be stored at ambient temperature (15°C-30°C/59°F-86°F). IP will be stored in our Investigational Drug Services Pharmacy. Temperatures will be monitored and recorded by the SensoScientific Temperature monitoring system.

7.4.6.3 Preparation and Dispensing

Topical ruxolitinib 1.5% cream will be provided by Incyte, so no preparation is needed. The amount of tubes dispensed to each participant depends on their lesion count. The investigator (or designee) is responsible for study treatment accountability, reconciliation, and record maintenance (i.e., receipt, reconciliation, and final disposition records). Inventory and accountability records will be maintained and readily available for inspection by the study monitor and are open to inspection at any time.

by any applicable regulatory authorities. The participant will administer the topical cream after teaching by the investigator (or designee).

The investigator or designee will maintain records that document:

- Delivery of study drug to the study site.
- Inventory of study drug at the site.
- Participant use of the study drug including tube weights from each supply dispensed.
- Return of study drug to the investigator or designee by participants.

The investigational product will be used only in accordance with the Protocol. The investigator will also maintain records adequately documenting that the participants were provided the specified study drug, including the dates, quantities, and any available batch or serial numbers or unique code numbers assigned to the investigational product and study participants. All IP will be maintained by Investigational Drug Service.

7.4.6.4 Return or Destruction of the Test Article

The investigator (or designee) will be expected to collect and document all used, unused, and partially used containers of study drug dispensed to subjects. Once the returns have been accounted for by 2 members of the IDS pharmacy team, the medications will be destroyed as per the Investigational Drug Service Destruction Policy. Expired study medications will be destroyed as per the Drug Services Pharmacy Policies. At the conclusion of the study, any remaining study drug will be destroyed as per the Investigational Pharmacy Policies. Accountability records documenting the destruction will be available for review by the study monitor.

7.4.6.5 Prior and Concomitant Therapy

All concomitant medications and treatments (including over-the-counter or prescription medicines, vitamins, vaccines, and/or herbal supplements) will be recorded on electronic study forms in REDCap. Any addition, deletion, or change in the dose of these medications will also be recorded. Concomitant treatments/procedures that are required to manage a participant's medical condition during the study will also be recorded in the REDCap study forms.

Any prior medication received up to 28 days before the first dose of study treatment and 30 days after the last dose of

study treatment will be recorded in the REDCap study forms. A detailed history of prior medications use related to HS in the year before screening will be also be collected, as well as response to each treatment and reason for discontinuation.

Excluded/prohibited concomitant medication and procedures include: JAK inhibitors (systemic or topical (eg, ruxolitinib, tofacitinib, baricitinib, filgotinib, lestaurtinib, and pacritinib)) in the 4 weeks prior to screening; surgical, laser, or IPL intervention in area with HS lesion in prior 3 months and except for rescue lesional treatment (see below); topical use of creams, ointments, gels, and liquids except the study therapy.

All medications used by the patient will be reconciled at entry into the study and through electronic surveys or in-person study visits throughout the entire study duration.

If a participant experiences significant pain after baseline, one of the following analgesic regimens may be initiated at any time: Ibuprofen (at a dose of up to 800 mg orally every 6 hours) not to exceed 3200 mg/24 hours OR acetaminophen not to exceed 4 g/24 hours. Participants can use one of the permitted antiseptic therapies. Permitted antiseptic washes are limited to one of the following: chlorhexidine gluconate, triclosan, benzoyl peroxide, or diluted bleach in bathwater. Participants can use wound care dressings on HS wounds. Options are limited to alginates, hydrocolloids, and hydrogels.

In the event of an acutely painful lesion that requires immediate intervention, the investigator and participant will have the option to perform protocol-allowed interventions. Two types of interventions are permitted: injection with intralesional triamcinolone acetonide suspension (up to 40 mg in total at the same visit) and/or incision and drainage. New systemic and topical therapies following incision and drainage, including antibiotics, are prohibited. Participants should continue using the topical study therapy. From Day 1 through Week 16, an intervention can occur on a maximum of 2 different lesions at the same visit or on the same lesion at 2 different study visits. The same lesion cannot be treated 2 times during the same visit. If participants require more than 3 interventions before Week 16, then the study drug will be discontinued for those participants. Study procedures must be performed before any interventions. Any lesion undergoing an intervention will be documented in the lesion count worksheet.

8.0 Subject Numbers and Statistical Plan

8.1 Number of Subjects

We aim to enroll at least 18 subjects to complete the interventional study to assess the primary endpoint. Anticipating screen failures and loss-to-follow-up we anticipate screening and enrolling approximately 24 people with hidradenitis suppurativa. No additional participants with *any* biologic use will be enrolled after 30% of participants with stable dosage and frequency of a biologic are enrolled.

8.2 Sample size determination

Based on the placebo and effect responses for adalimumab in the PIONEER trials (Kimball, 2016) for moderate-to-severe HS, the HiSCR response rate in the placebo group was approximately 27% (26.0% and 27.6%) and HiSCR rates of 42-59% for adalimumab. In mild-to-moderate and moderate-only HS treated with apremilast, the placebo HiSCR rate was 0% and in the response rate in the intervention groups was 53-55% (Kerdel 2019, Vossen 2019).

With a sample size of at least 18 participants, we will have sufficient power to determine if the HiSCR response rate for topical ruxolitinib 1.5% cream is 55% and significantly different from a 20% (or lower) placebo response rate with a power of 80% and risk of type I error of 5%. Typically, in a Simon's two-stage design, 11 patients would be accrued in the first stage and 7 additional in the second phase; however, we will accrue all in one cohort of at least 18 completed participants. The null hypothesis will be rejected if 5 or more responses are observed in 18 completed participants.

8.3 Statistical methods

The PI cannot be involved in the primary data analysis, but can maintain involvement in the data interpretation required for authorship. The primary statistical analysis to evaluate the null hypothesis that the proportion of participants that achieve HiSCR at Week 16. P-values ≤ 0.05 will be considered significant. The primary efficacy analysis will be carried out in the ITT Population, defined as all patients who complete the study. Last-observation-carried-forward will be used for missing data.

Secondary endpoints include the mean change in the AN count at Week 16; mean change in DLQI score from Baseline to Week 16; mean change in the novel clinician-reported outcome measure (HASI, investigator-supplied) score from Baseline to Week 16; mean change in novel HS patient-reported outcome measure (HiSQOL, Investigator-supplied) from Baseline to Week 16. Secondary efficacy variables will be summarized in the ITT Population. Statistical tests from laboratory assays will be done with the assistance of Penn State biostatisticians. Analyses can include paired t-tests, repeated measure ANOVA and regression-based analyses depending on the number of replicates, samples and repeated measures captured during each assay.

9.0 Data and Safety Monitoring Plan

9.1 Periodic evaluation of data

Data will be entered in REDCap for each participant's visit. Data reported entered into the REDCap data capture forms will be transcribed from source documents

and must be consistent with the source documents or the discrepancies will be explained. Patient Reported Outcomes will be reviewed at each scheduled visit. Safety data will be reviewed on an ongoing basis. Endpoint data will be reviewed periodically and at the end of the study. The Penn State College of Medicine Department of Public Health Sciences Clinical Trial Monitoring unit will oversee study monitoring according to the established Monitoring Plan.

9.2 Data that are reviewed

The PI, Sub-Is, and study team will review and identify adverse events. The sponsor will also review any identified AEs. Study team members will input all data into RedCap and will review input Patient Reported Outcomes. PI and Sub-Is will evaluate eligibility and ensure the integrity of all clinician assessments. Study statisticians may conduct reviews of study data periodically to evaluate the endpoints or perform data quality checks.

The PI will conduct a regular review of the ongoing study with study staff members.

9.3 Method of collection of safety information

Adverse events will be monitored from the time the participant signs the informed consent form up until the end of the study period. Adverse events that begin or worsen after informed consent will be recorded on the Adverse Event Form in the REDCap study forms regardless of the assumption of a causal relationship with the study drug. Conditions that were already present at the time of informed consent should be recorded on the Medical History in the REDCap study forms. Adverse effects and safety information will be collected at study visits with subjects.

9.4 Frequency of data collection

Adverse events will be monitored at study visits from the time the participant signs the informed consent form up until the end of the study period. Study visits will occur at Screening, Baseline (Week 0), 4, 8, and 16. If there is a potential clinically significant abnormality in laboratory assessments, then an unscheduled visit the following week will be scheduled to repeat laboratory assessments is required.

9.5 Individuals reviewing the data

Data will be reviewed first by study team members for safety and integrity, and then by staff from the Penn State College of Medicine Department of Public Health Sciences Clinical Trial Monitoring unit.

9.6 Frequency of review of cumulative data

Cumulative data will be reviewed once after data is collected on all participants.

9.7 Statistical tests

A treatment-emergent adverse event is any adverse event (AE) either reported for the first time or worsening of a pre-existing event after first use of the study drug.

Analysis of AEs will be limited to treatment-emergent AEs, but data listings will include all AEs regardless of their timing to study drug administration. Adverse events will be coded using MedDRA and tabulated by preferred term and system organ class. Severity of AEs will be based on the CTCAE v4.03 using Grades 1 through 5. The subset of AEs considered by the investigator to have a relationship to study drug will be considered to be treatment-related AEs. If the investigator does not specify the relationship of the AE to study drug, then the AE will be considered treatment-related. The incidence of AEs and treatment-related AEs will be tabulated.

Actual values and changes from baseline in clinical laboratory test results will be summarized using descriptive statistics. Laboratory test values outside the normal range will be assessed for severity based on the normal ranges for the clinical reference laboratory. The incidence of abnormal laboratory values will be tabulated. Laboratory data will be classified into Grades 1 through 4 using CTCAE v4.03. The number and percentage of participants with worst post-baseline CTCAE grade (regardless of baseline value) will be summarized. Each participant will be counted only for the worst grade observed post-baseline. Shift tables from baseline to the worst post-baseline value using CTCAE grade. For laboratory parameters where CTCAE grades are not defined, shift tables to the worst post-baseline value using the low/normal/high classifications based on laboratory reference ranges will be provided.

9.8 Suspension of research

The research will be suspended if it is found by the IRB that it is not being conducted in accordance with regulations or IRB requirements, or that has been associated with unexpected serious harm to human subjects, or where suspension or termination has been initiated by a sponsor or other outside entity.

10.0 Risks

Potential Risk of Clinical Significance	Summary of Data Available/ Rationale for Risk	Mitigation Strategy
Universal risks to participation in an HS clinical trial		
Aggravation of HS	Worsening of HS may occur either as a spontaneous event or due to insufficient efficacy of the study medication.	Participants can receive up to 2 lesional rescue interventions or, in the event of superinfection, a short course of antibiotic treatment Participants may also withdraw from the study at any time for any reason (see Section Error! Reference source not found.), in which case, they would be able to use alternative conventional treatments for their HS.
Loss of Confidentiality	Identifiable or private information about the subject becomes lost or known to others	Study data will be stored in locked offices, password protected files, and encrypted when appropriate for the type of data. Only the study staff and Clinical trial monitoring staff will be given access.

Risks associated with <u>topical</u> administration of ruxolitinib		
There have been no serious adverse reactions for ruxolitinib cream.		
Drug reactions	With low systemic exposure for topical application of ruxolitinib cream, it is unlikely that meaningful levels of plasma metabolites, active or otherwise will be present.	No precautions needed for concomitant use with other medications.
Prenatal and postnatal exposure	There is inadequate data related to the effect of topical ruxolitinib in a developing fetus or whether it passes into breastmilk.	Pregnant or breastfeeding women will not be included in the trial. Women will be asked to use a contraceptive method.
Photo-induced skin reaction	There is a theoretical risk of a skin reaction with topical ruxolitinib use and ultraviolet light (UV) exposure.	Participants will be counselled to avoid UV light exposure or use a standard method of protection such as sunscreen or UV-protective clothing.
Risks associated with <u>systemic</u> administration of ruxolitinib		
No clinically meaningful systemic adverse events have been found to be associated with the use of ruxolitinib cream in its clinical studies performed to date in alopecia areata, psoriasis, atopic dermatitis, and vitiligo.		
Risk of systemic infections	Longer-term oral treatment with ruxolitinib can cause immunosuppression, allowing secondary infections.	Participants will be tested at the study entry for latent TB infection, chronic hepatitis,, and monitored for any signs and symptoms of infection throughout the study (eg, clinical laboratory tests, vital signs, and AE monitoring). In the event of an infection necessitating such steps, study medication can be withheld or stopped and appropriate anti-infective therapy instituted.
Headaches	Mild to moderate headaches were observed in a proportion of healthy volunteers exposed to ruxolitinib.	Possible headaches will be captured by routine AE monitoring. Analgesics may be used to relieve headache, if appropriate.

11.0 Potential Benefits to Subjects and Others

11.1 Potential Benefits to Subjects

Participants may experience clinically meaningful improvements in their HS lesions during the study and may additionally benefit from the comprehensive safety assessments conducted as part of the study (eg, clinical laboratory tests, physical examinations). They may also feel a psychological benefit from contributing to the process of studying a therapy for HS, a disease with high unmet need that is severely debilitating to participants' well-being and daily functioning.

11.2 Potential Benefits to Others

This may also contribute to the process of developing a novel anti-inflammatory agent for HS, a disease with high unmet need that is severely debilitating to participants' well-being and daily functioning.

12.0 Sharing Results with Subjects

Sharing individual's laboratory study results is not planned. If a subject requests results then a paper copy will be given directly to the subject at the time of the study visit. If the investigator feels it is important to share a result with a subject's primary care provider, then the result will be faxed, using a cover sheet, to the provider's office fax machine.

Results from research laboratory studies will not be shared with subjects.

13.0 Subject Payment and/or Travel Reimbursements

Subjects will receive \$50.00 per study visit for their participation in this research study for up to a total of \$250.00 . If they do not complete the study for any reason, they will be paid for the visits that were completed. The payment will be provided by Greenphire clincard.

14.0 Economic Burden to Subjects

14.1 Costs

No cost to subjects for participating.

14.2 Compensation for research-related injury

It is the policy of the institution to provide neither financial compensation nor free medical treatment for research-related injury. In the event of injury resulting from this research, medical treatment is available but will be provided at the usual charge. Such charges may be paid by the study sponsor as outlined in the research agreement and explained in the consent form.

15.0 Resources Available

15.1 Facilities and locations

The research will be conducted at the Penn State College of Medicine Department of Dermatology clinical trials unit.

15.2 Feasibility of recruiting the required number of subjects

There are over 1,200 patients with the diagnosis of hidradenitis suppurativa in the Penn State Health medical system. It is not possible to determine what number of these people have mild or moderate disease. We aim to recruit at least 18 total people, which is approximately 2% of the potential population of people with HS in the Penn State system.

15.3 PI Time devoted to conducting the research

PI has set amount of time each week indicated for research time only. Dr. Kirby has 75% effort dedicated to research.

15.4 Availability of medical or psychological resources

Medical and psychological resources are available at the Penn State Milton S. Hershey Medical Center, at the same site as the clinical trial if needed.

15.5 Process for informing Study Team

All study team members will attend the SIV. If not available to attend they will be trained by reviewing the protocol and ICF. All training will be documented on a training log.

16.0 Other Approvals

16.1 Other Approvals from External Entities

Approval from the Penn State College of Medicine IRB and Incyte will be obtained prior to conducting the research.

16.2 Internal PSU Committee Approvals

Check all that apply:

- ☒ Anatomic Pathology – **Penn State Health only** – Research involves the collection of tissues or use of pathologic specimens. Upload a copy of “HRP-902 - Human Tissue For Research Form” in CATS IRB.
- ☐ Animal Care and Use – **All campuses** – Human research involves animals and humans or the use of human tissues in animals
- ☒ Biosafety – **All campuses** – Research involves biohazardous materials (human biological specimens in a PSU research lab, biological toxins, carcinogens, infectious agents, recombinant viruses or DNA or gene therapy).
- ☒ Clinical Laboratories – **Penn State Health only** – Collection, processing and/or storage of extra tubes of body fluid specimens for research purposes by the Clinical

Laboratories; and/or use of body fluids that had been collected for clinical purposes but are no longer needed for clinical use. Upload a copy of “HRP-901 - Human Body Fluids for Research Form” in CATS IRB.

- ☐ Clinical Research Center (CRC) Advisory Committee – **All campuses** – Research involves the use of CRC services in any way.
- ☒ Conflict of Interest Review – **All campuses** – Research has one or more of study team members indicated as having a financial interest.
- ☒ Radiation Safety – **Penn State Health only** – Research involves research-related radiation procedures. All research involving radiation procedures (standard of care and/or research-related) must upload a copy of “HRP-903 - Radiation Review Form” in CATS IRB.
- ☒ IND/IDE Audit – **All campuses** – Research in which the PSU researcher holds the IND or IDE or intends to hold the IND or IDE.
- ☐ Scientific Review – **Penn State Health only** – All investigator-written research studies requiring review by the convened IRB must provide documentation of scientific review with the IRB submission. The scientific review requirement may be fulfilled by one of the following: (1) external peer-review process; (2) department/institute scientific review committee; or (3) scientific review by the Clinical Research Center Advisory committee. NOTE: Review by the Penn State Health Cancer Institute (PSCI) Protocol Review Committee or the PSCI Disease Team is required if the study involves cancer prevention studies or cancer patients, records and/or tissues. For more information about this requirement see the IRB website.

17.0 Multi-Site Study

- 17.1 **Other sites**
Not applicable
- 17.2 **Communication Plans**
Not applicable
- 17.3 **Data Submission and Security Plan**
Not applicable
- 17.4 **Subject Enrollment**
Not applicable
- 17.5 **Reporting of Adverse Events and New Information**
Not applicable

17.6 Audit and Monitoring Plans
Not applicable

18.0 Adverse Event Reporting

18.1 Adverse Event Definitions

For drug studies, incorporate the following definitions into the below responses, as written:	
Adverse event	Any untoward medical occurrence associated with the use of the drug in humans, whether or not considered drug related
Adverse reaction	Any adverse event caused by a drug
Suspected adverse reaction	Any adverse event for which there is a reasonable possibility that the drug caused the adverse event. Suspected adverse reaction implies a lesser degree of certainty about causality than “adverse reaction”. <ul style="list-style-type: none"> • <i>Reasonable possibility.</i> For the purpose of IND safety reporting, “reasonable possibility” means there is evidence to suggest a causal relationship between the drug and the adverse event.
Serious adverse event or Serious suspected adverse reaction	Serious adverse event or Serious suspected adverse reaction: An adverse event or suspected adverse reaction that in the view of either the investigator or sponsor, it results in any of the following outcomes: Death, a life-threatening adverse event, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions, or a congenital anomaly/birth defect. Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.
Life-threatening adverse event or life-threatening suspected adverse reaction	An adverse event or suspected adverse reaction is considered “life-threatening” if, in the view of either the Investigator (i.e., the study site principal investigator) or Sponsor, its occurrence places the patient or research subject at immediate risk of death. It does not include an adverse event or suspected adverse reaction that had it occurred in a more severe form, might have caused death.
Unexpected adverse event or Unexpected suspected adverse reaction.	An adverse event or suspected adverse reaction is considered “unexpected” if it is not listed in the investigator brochure, general investigational plan, clinical protocol, or elsewhere in the current IND application; or is not listed at the specificity or severity that has been previously observed and/or specified.

18.2 Recording and Reporting of Adverse Events

Research subjects will be routinely questioned about adverse events at study visits. All adverse events (serious or non-serious) and abnormal test findings observed or reported to study team believed to be associated with the study drug(s) or device(s) will be followed until the event (or its sequelae) or the abnormal test finding resolves or stabilizes at a level acceptable to the investigator. Adverse events will be monitored from the time the participant signs the ICF up until the end of the 24-week study period. Adverse events (including laboratory abnormalities that constitute AEs) will be described using a diagnosis whenever possible rather than by underlying signs and symptoms.

An abnormal test finding will be classified as an adverse event if one or more of the following criteria are met:

- The test finding is accompanied by clinical symptoms
- The test finding necessitates additional diagnostic evaluation(s) or medical/surgical intervention; including significant additional concomitant drug treatment or other therapy
- The test finding leads to a change in study drug dosing or discontinuation of subject participation in the clinical research study
- The test finding is considered an adverse event by the investigator.

SAE Reporting to Incyte

The Principal Investigator (PI) must report all Serious Adverse Events (SAEs) to Incyte within 24 hours of learning of an event, regardless of the PI's causality assessment. This notification should be provided on a completed Serious Adverse Event (SAE) form. SAE reporting for each subject begins the day the informed consent is signed by the patient and within 30 days after subject has completed or discontinued from the study or has taken last dose of the study drug, or as described in the protocol.

SAEs, occurring using Incyte study drug, are reported in accordance with the effective protocol. SAEs occurring with any other commercial drug are reported to the manufacturer of that drug in accordance with regulations and protocol.

Initial SAEs and/or subsequent follow-up reports should be reported via email to SafetyReporting@Incyte.com or fax (+) 1-866-981-2057. SAE reports should be for a single subject. SAE forms should be sent with a cover sheet and any additional attachments.

All adverse event information is reported to Incyte on the Principal Investigator's/Institution's Adverse Event Report Form, or a CIOMS-I or MedWatch Form FDA 3500A, or on an Adverse Event Report Form which may be provided by Incyte upon request. The Principal Investigator does not provide medical records (e.g., discharge summary) to Incyte, unless specifically requested.

Specifically, if there is a pregnancy during the study, an “Initial Pregnancy Report” or equivalent must be completed in full and emailed to SafetyReporting@Incyte.com or faxed to (+) 1-866-981-2057 within 24 hours of discovery of a pregnancy of a subject who has taken the Incyte product or the pregnancy of a partner for a subject who has taken the Incyte product. The “Follow-up Pregnancy Report Form” or equivalent must be completed and emailed to SafetyReporting@Incyte.com or faxed to (+) 1-866-981-2057 within 30 days after delivery, so that Incyte is provided with information regarding the outcome of the pregnancy. If the pregnancy results in any events which meet the serious criteria (i.e., miscarriage or termination), the SAE reporting process needs to be followed and the timelines associated with a SAE should be followed.

Guidelines for Interrupting, Restarting, and Discontinuing Study Drug in the event of an adverse event possibly related to the use of the ruxolitinib cream

ADVERSE EVENT	ACTION TAKEN
AST and/or ALT $> 3.0 \times \text{ULN}$	Subject will no longer be on study drug. Unscheduled blood draws will be completed, at intervals determined by PI, until lab values return to $\leq 3.0 \times \text{ULN}$
AST and/or ALT $> 5.0 \times \text{ULN}$	Subject will no longer be on study drug. Unscheduled blood draws will be completed at intervals determined by PI.
Platelet counts 50 to $< 100 \times 10^9/\text{L}$ or $\geq 50\%$ decrease from baseline	Subject will no longer be on study drug. Unscheduled blood draws will be completed, at intervals determined by PI, until the toxicity has resolved to $\geq 100 \times 10^9/\text{L}$.
ANC 0.5 to $< 1.0 \times 10^9/\text{L}$	Subject will no longer be on study drug. Unscheduled blood draws will be completed, at intervals determined by PI, until the toxicity has resolved to $\geq 1 \times 10^9/\text{L}$ or the baseline value.
Hemoglobin 8 to $< 10 \text{ g/dL}$ or $> 2 \text{ g/dL}$ decrease from baseline	Subject will no longer be on study drug. Unscheduled blood draws will be completed, at intervals determined by PI, until the toxicity has resolved $\geq 10 \text{ g/dL}$ or $\leq 2 \text{ g/dL}$ decrease from baseline.
Platelet count $< 50 \times 10^9/\text{L}$ ANC $< 0.5 \times 10^9/\text{L}$ ANC $< 1.0 \times 10^9/\text{L}$ with an oral temperature of at least 38.5°C OR with $\geq \text{Grade 3}$ infection Hemoglobin $< 8 \text{ g/dL}$	Subject will no longer be on study drug. Unscheduled blood draws will be completed, at intervals determined by PI.
Other adverse events that could be related to study drug use	
Any Grade 1 or Grade 2 severity	The subject will no longer be on study drug. At the discretion of the PI, unscheduled blood draws may be completed to monitor.
Any Grade 3 severity except those defined in Error! Reference source	Subject will no longer be on study drug. Unscheduled blood draws will be completed, at intervals determined by PI, until severity resolves to $\leq \text{Grade 1}$.

not found. (exception for any \geq Grade 3 nonhematologic severity)	
Any other Grade 4 severity	Subject will no longer be on study drug. Unscheduled blood draws will be completed, at intervals determined by PI.

18.3 Causality and Severity Assessments

The investigator will promptly review documented adverse events and abnormal test findings to determine 1) if the abnormal test finding should be classified as an adverse event; 2) if there is a reasonable possibility that the adverse event was caused by the study drug(s) or device(s); and 3) if the adverse event meets the criteria for a serious adverse event.

If the investigator's final determination of causality is "unknown and of questionable relationship to the study drug(s) or device(s)", the adverse event will be classified as associated with the use of the study drug(s) or device(s) for reporting purposes. If the investigator's final determination of causality is "unknown but not related to the study drug(s) or device(s)", this determination and the rationale for the determination will be documented in the respective subject's case history.

18.4 Reporting of Adverse Reactions and Unanticipated Problems to the FDA

18.4.1 Written IND/IDE Safety Reports

The Sponsor-Investigator will submit a written IND Safety Report (i.e., completed FDA Form 3500A) to the responsible new drug review division of the FDA for any observed or volunteered adverse event that is determined to be a serious and unexpected, suspected adverse reaction. Each IND Safety Report will be prominently labeled, "IND Safety Report", and a copy will be provided to all participating investigators (if applicable) and sub-investigators.

Written IND Safety Reports will be submitted to the FDA as soon as possible and, in no event, later than 15 calendar days following the Sponsor-Investigator's receipt of the respective adverse event information and determination that it meets the respective criteria for reporting.

For each written IND Safety Report, the Sponsor-Investigator will identify all previously submitted IND Safety Reports that addressed a similar suspected adverse reaction experience and will provide an analysis of the significance of newly reported, suspected adverse reaction in light of the previous, similar report(s) or any other relevant information.

Relevant follow-up information to an IND Safety Report will be submitted to the applicable review division of the FDA as soon as the information is available and will be identified as such (i.e., "Follow-up IND Safety Report").

If the results of the Sponsor-Investigator's follow-up investigation show that an adverse event that was initially determined to not require a written IND Safety Report does, in fact, meet the requirements for reporting; the Sponsor-Investigator will submit a written IND Safety Report as soon as possible, but in no event later than 15 calendar days, after the determination was made.

18.4.2 Telephoned IND Safety Reports – Fatal or Life-threatening Suspected Adverse Reactions

In addition to the subsequent submission of a written IND Safety Report (i.e., completed FDA Form 3500A), the Sponsor-Investigator will notify the responsible review division of the FDA by telephone or facsimile transmission of any unexpected, fatal or life-threatening suspected adverse reaction.

The telephone or facsimile transmission of applicable IND Safety Reports will be made as soon as possible but in no event later than 7 calendar days after the Sponsor-Investigator's receipt of the respective adverse event information and determination that it meets the respective criteria for reporting.

18.5 Reporting Adverse Reactions and Unanticipated Problems to the Responsible IRB

In accordance with applicable policies of The Pennsylvania State University Institutional Review Board (IRB), the investigator will report, to the IRB, any observed or reported harm (adverse event) experienced by a subject or other individual, which in the opinion of the investigator is determined to be (1) unexpected; and (2) probably related to the research procedures. Harms (adverse events) will be submitted to the IRB in accordance with the IRB policies and procedures.

18.6 Unblinding Procedures NA

18.7 Stopping Rules

This study does not have a primary safety endpoint nor does it pose a high risk to study subjects, so no stopping rules are planned.

19.0 Study Monitoring, Auditing and Inspecting

19.1 Study Monitoring Plan

19.1.1 Quality Assurance and Quality Control

The study will be monitored by the Clinical Trial Monitoring Team from the Department of Health Sciences at Penn State Hershey College of Medicine. The monitors will provide an independent review of the regulatory and subject records and

the data collected to assure compliance with the protocol, GCP, and applicable federal regulations. The monitoring will occur at regular intervals after the enrollment of the first subject and the times will be predetermined by the monitoring plan developed by the Clinical Trial Monitoring Team.

The investigator and department research staff will be responsible for:

- Verifying that data entries are accurate and correct.
- Maintaining accurate documentation that are securely filed at the investigator's site.
- Permitting study-related monitoring, audits, IRB/IEC review, and regulatory inspections by providing direct access to source data and other relevant clinical study documents.

19.1.2 Safety Monitoring

The **Principal Investigator** will confirm that all adverse events (AE) are correctly entered into the AE case report forms by the coordinator; be available to answer any questions that the coordinators may have concerning AEs; and will notify the IRB, FDA, sponsor and/or DSMB of all applicable AEs as appropriate. All assessments of AEs will be made by a licensed medical professional who is an investigator on the research.

The **Research Coordinator** will complete the appropriate report form and logs; assist the PI to prepare reports and notify the IRB, FDA and/or DSMB of all Unanticipated Problems/SAE's.

The **Monitor** will confirm that the AEs are correctly entered into the case report forms. The Monitor will also confirm that the adverse events are consistent with the source documents and are reported to the appropriate regulatory bodies as required.

20.0 Future Undetermined Research: Data and Specimen Banking

20.1 Data and/or specimens being stored

Skin punch biopsies will be formalin-fixed and paraffin-embedded. Isolated RNA from each skin sample will also be stored.

Laboratory data associated with each specimen (e.g., results from immunohistochemistry analyses and sequencing results) will be stored with each

sample. Clinical and demographic data collected at the time of sample collection will also be associated with each sample.

20.2 Location of storage

Isolated RNA and Paraffin blocks will be stored within Dr. Nelson's research laboratory (C7801 BMR). Research results and information will be stored electronically within the HMC secure servers. Clinical and Demographic information associated with each sample will be stored in the Dermatology Clinical Research Office (UPC 2010).

20.3 Duration of storage

Blocks will be stored for a period of 10 years and potentially used for undetermined research. Data/results generated from the use of these samples will be stored electronically indefinitely.

20.4 Access to data and/or specimens

Dermatologists will have access to patient medical information through the medical record. Dr. Nelson will only have access to the medical information requested (disease severity, duration, past/current medications, etc.). Clinical and Research Team will have access to study specimens and study information to complete all data analyses.

20.5 Procedures to release data or specimens

At the completion of this study, de-identified data will be published within a peer-reviewed journal. Any requests for access to specimens such as tissue blocks would need to be requested to Dr. Nelson in writing and if acceptable, the respective parties would work with their respective offices of technology transfer to arrange material transfer agreements.

20.6 Process for returning results

NA

21.0 References

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22.0 Confidentiality, Privacy and Data Management

IMPORTANT: The following section is required for all locations EXCEPT Penn State Health and the College of Medicine. Penn State Health and College of Medicine should skip this section and complete “HRP-598 Research Data Plan Review Form.” In order to avoid redundancy, for

this section state “See the Research Data Plan Review Form” if you are conducting Penn State Health research. Delete all other sub-sections of section 22.

For research being conducted at Penn State Health or by Penn State Health researchers only: The research data security and integrity plan is submitted using “HRP-598 – Research Data Plan Review Form Application Supplement.”

Refer to Penn State College of Medicine IRB’s “Standard Operating Procedure Addendum: Security and Integrity of Human Research Data,” which is available on the IRB’s website. In order to avoid redundancy, for this section state “See the Research Data Plan Review Form” if you are conducting Penn State Health research. Delete all sub-sections of section 22.

For all other research: complete the following section. Please refer to [PSU Policy AD95](#) for information regarding information classification and security standards and requirements. It is recommended that you work with local IT staff when planning to store, process, or access data electronically to ensure that your plan can be carried out locally and meets applicable requirements. If you have questions about Penn State’s Policy AD95 or standards or need a consultation regarding data security, please contact security@psu.edu.

“See the Research Data Plan Review Form”