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JOHNS HOPKINS
MEDICINE

Clinical Study Protocol

Sponsor: Pfizer Inc.

Protocol Title: A Phase 2a Open-Label Study to Assess the Efficacy, Safety, and Tolerability of Abrocitinib for Reducing Pruritus in Adults with Prurigo Nodularis and Chronic Pruritus of Unknown Origin

Brief Title: Efficacy of Abrocitinib for Reducing Pruritus in Adults with Prurigo Nodularis and Chronic Pruritus of Unknown Origin

NCT Number:	NCT05038982
IRB Number:	IRB00262268
IND Number:	152968
Name of Investigational Product:	Abrocitinib
Phase of Development:	2a
Indication:	Prurigo Nodularis and Chronic Pruritus of Unknown Origin
Protocol Date:	March 16, 2022
ICF Date:	March 16, 2022

JHM IRB - eForm A – Protocol

- **Use the section headings to write the JHM IRB eForm A, inserting the appropriate material in each. If a section is not applicable, leave heading in and insert N/A.**
- **When submitting JHM IRB eForm A (new or revised), enter the date submitted to the field at the top of JHM IRB eForm A.**

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1. Abstract

a. Provide no more than a one page research abstract briefly stating the problem, the research hypothesis, and the importance of the research.

Prurigo nodularis (PN) is a chronic inflammatory skin disease clinically characterized by intensely pruritic nodules on the extremities and trunk (Fostini et al., 2013; Pereira & Ständer, 2016). There are no FDA approved therapies for PN. Topical therapies such as topical corticosteroids, calcineurin inhibitors, calcipotriol, and capsaicin, systemic corticosteroids, thalidomide, systemic immunomodulatory drugs such as methotrexate and cyclosporin, antiepilectics and antidepressants, phototherapy and photochemotherapy are often tried with limited success and in some cases with unfavorable risk-benefit ratio (Qureshi et al., 2019). Emerging reports are detailing the significant disease burden and unmet need in PN patients, with a prevalence estimate of 125,000 ambulatory visits per year in the United States (Whang et al., 2020).

Chronic pruritus of unknown origin (CPUO) is defined as itch lasting for more than 6 weeks without underlying systemic or neuropathic etiologies (Kim et al., 2019). CPUO presents on multiple segments of the body, and it is unresponsive to emollients. CPUO encompasses patients without a characteristic primary dermatologic eruption and negative systemic workup. Currently, there is a poor understanding of the etiology of CPUO, with eosinophilia and immune dysregulation suggested to play a role, but studies have been limited by small sample sizes (Kim et al., 2019; Patel et al., 2019). CPUO pathophysiology is hypothesized to involve several neuroimmune mediators, including histamine, IL-31, substance P, and TRPV1 (Miranda et al., 2018).

In this study, we would like to evaluate the safety and efficacy of abrocitinib, a Jak1 inihibtor, as a treatment for PN and CPUO. We hypothesize application of abrocitinib will improve these conditions of chronic itch, ultimately leading to improved overall quality of life via blockade of key cytokines known to be associated with conditions of itch including IL-31.

2. Objectives (include all primary and secondary objectives)

Primary Objective: To assess the efficacy of abrocitinib in reducing pruritus in patients with prurigo nodularis (PN) or chronic pruritus of unknown origin (CPUO) who are experiencing moderate to severe pruritus

Secondary Objectives:

- To evaluate the effect of abrocitinib in improving quality of life in patients with prurigo nodularis or chronic pruritus of unknown origin who are experiencing moderate to severe pruritus
- To evaluate the safety and tolerability of abrocitinib in subjects with prurigo nodularis or chronic pruritus of unknown origin who are experiencing moderate to severe pruritus

Exploratory Objectives:

- To evaluate the correlation between abrocitinib responsiveness and comorbidities in prurigo nodularis and chronic pruritus of unknown origin
- To evaluate the correlation between responsiveness to abrocitinib therapy with skin and blood biomarkers of prurigo nodularis and chronic pruritus of unknown origin

3. Background (briefly describe pre-clinical and clinical data, current experience with procedures, drug or device, and any other relevant information to justify the research)

Jak1, the target of abrocitinib, plays a critical role in signaling of many cytokines. Relevant for this application, Jak1 is involved in the signaling for IL-6 family cytokines including oncostatin M and IL-31, as well as for IL-4 signaling, all of which have been linked to chronic itch and prurigo nodularis (Campion et al., 2019; Ghoreschi et al., 2009; Zhang et al., 2008). Additionally, abrocitinib has been shown to inhibit IL-22 signaling in keratinocytes as well as various cytokine signaling pathways, including IFNα (Fetter et al., 2020; Silverberg et al., 2020).

As the etiology of PN and CPUO is unknown, and there are currently no FDA approved therapies, it is extremely difficult to treat patients with PN and CPUO. Prior investigations have suggested roles for aberrant keratinocyte signaling, neuronal dysregulation, and cutaneous inflammation (Hughes et al., 2020; Kowalski et al., 2019; Zhong et al., 2019). Targeted RT-qPCR and immunohistochemical staining have demonstrated dysregulation of select neurotrophic factors and cytokines, but these results were inconsistent (Fukushi et al., 2011; Matsumura et al., 2015; Park et al., 2011; Takada et al., 2013; Wong et al., 2020; Zhong et al., 2019). Similarly, previous studies have shown conflicting evidence of immune polarization (Fukushi et al., 2011; Park et al., 2011; Wong et al., 2020; Zhong et al., 2019).

In both CPUO and PN, there is evidence of involvement of IL-31 and Oncostatin-M (Kowalski et al., 2019; Salao et al., 2020); Sonkoly et al., 2006). IL-31 signals through binding the heterodimer receptor complex of Type-1 cytokine receptor IL-31RA and sub-unit OSMRb, which activates Jak1 for signal transduction (Zhang et al., 2008). PN has been studied more extensively than CPUO, and these studies have identified Th1/2 cytokine signatures as driving pSTAT6 and pSTAT3 nuclear localization in PN epidermis (Fukushi et al., 2011). As explained previously, there is conflicting evidence of immune polarization in PN. Notably, STAT6 and STAT3 activation and subsequent

nuclear localization is mediated by Jak1 activation, which itself is mediated by extracellular cytokine binding (Seif et al., 2017).
Abrocitinib is made by Pfizer, Inc. and is currently in Phase 3 trials for treatment of atopic dermatitis. At present, there is evidence that 200mg taken orally as a single daily dose is effective at reducing atopic dermatitis and itch associated from this condition. The incidence of adverse events with abrocitinib is well characterized and known adverse events will be monitored for during the course of this trial.

4. Study Procedures

a. Study design, including the sequence and timing of study procedures (distinguish research procedures from those that are part of routine care).

- **Screening Visit**
- At the screening visit **(Visit 1),** eligibility for the study will be confirmed. This will entail:
  - Physical examination: Examination of major body organs.
  - Vital signs: Measurement of blood pressure, heart rate, respiratory rate, body temperature, height and weight.
  - Tuberculosis assessment: tuberculosis testing will be performed where indicated and as required by local health practice. This can be a skin test or a blood test.
  - Blood collection: The total amount of blood to be taken in this study for each participant is approximately 130mL (about 9 tablespoons). These samples will be used to test:
    - Complete Blood count, biochemistry (tests of kidney, thyroid and liver function).
    - IgE (immunoglobulin E) marker of inflammatory disorders
    - Hepatitis B and C test. The law requires us to report positive tests to the health department. This reporting will include information that identifies you (for example name, date of birth, home address, phone number, etc.) as required by Maryland law. The health department may use this information to contact you for further follow up and/or to help conduct health surveillance activities aimed at preventing or controlling diseases.
    - HIV screening test. You may be asked to sign a separate State of Maryland consent form for this HIV test. If the HIV test is positive it does not always mean you are infected with the HIV virus. It does mean you will need further testing and you will receive counseling about this. The law requires us to report positive tests to the health department. This reporting will include information that identifies you (for example name, date of birth, home address, phone number, etc.) as required by Maryland law. The health department may use this information to contact you for further follow up and/or to help conduct health surveillance activities aimed at preventing or controlling diseases.
      - Only for participants with known history of HIV: CD4+ T cell count and viral load will be evaluated at screening and

at the end of the study drug period. This will be approximately 10 mL (less than one tablespoon) blood in addition to total amount of blood.

- Pregnancy testing: only for women capable of having children: by blood test at the first study visit and urine sampling test every 4 weeks at site visit.

- **For Study Visits 2 through 7 (Week 0 – 16) the following procedures will be done according to the schedule above: Visits will be conducted within the specified week or within +/- 5 days of the intended week.**
  - Dispensing of Investigational Drug: All participants will receive abrocitinib beginning at visit 2. This will be taken as a daily oral dose of 200mg in tablet form. This therapy will continue for 12 weeks (through visit 6).
  - Electronic diary: Participants will be asked to complete a diary daily in the morning. This will include questionnaires to evaluate the severity of symptoms such as itch and pain and asking participants to rate their quality of sleep during the last night. The completion of the diary will take approximately 10 minutes. The study doctor or site staff will train participants on how to use the diary during Visit 1 and give you instructions on how to complete these assessments. This diary must be returned to the site at the end of study visit.
  - Questionnaires: Participants will need to complete up to 6 questionnaires on a tablet. This will provide insight into how their disease is affecting their quality of life and to provide information on symptoms and the impact of the disease on quality of life. Total duration of completion of these questionnaires will take approximately 30 minutes. Also, the study doctor will need to evaluate the severity of symptoms and complete up to 2 questionnaires at each visit. These questionnaires include:
    - PP-NRS
    - DLQI
    - PROMIS PIQ T Score
    - 5D Pruritis Score
    - SD-NRS
    - EQ-5D
    - HADS
    - PAS
    - PN-IGA
  - Physical examination: Examination of major body organs.
  - Vital sign: Measurement of blood pressure, heart rate, respiratory rate, body temperature, and weight.
  - Photographs: Digital photographs of the pruritic areas will be taken at each study visit. These photographs will avoid any identifying areas/marks including the face, tattoos or identifying birth marks.
  - Skin biopsy: A 4mm punch biopsy of the affected pruritic area will be taken at visit 2 and visit 6. This will involve injection of lidocaine and epinephrine followed by taking the biopsy. Participants will not feel pain, only pressure. A stitch will be placed and care instructions will be given. Particpants will return for suture removal 7 to 10 days after the biopsy.

- Blood collection at all visits. The total amount of blood to be taken in this study for each participant is approximately 130mL (approximately 9 tablespoons). These samples will be used to test:
  - Hematology (blood count), biochemistry. Biomarker testing

Examination	**Visit 1 Screening Week (-4)**	**Visit 2 (Week 0)**	**Visit 3 (Week 2)**	**Visit 4 (Week 4)**	**Visit 5 (Week 8)**	**Visit 6 (Week 12)**	**Visit 7 (Week 16)**
Informed Consent	X						
I/E criteria – Full list above, but tests include: TSH, Hepatitis panel, HIV antibodies, CD4 count, CBC, CMP, lipid panel, PPD test, hCP test for pregnancy among WOCBP. Blood draw criteria is below.	X	X					
Demographics & Medical History	X						
Vital signs	X	X	X	X	X	X	X
Skin examination	X	X	X	X	X	X	X
PP-NRS		X	X	X	X	X	X
DLQI		X	X	X	X	X	X
PROMIS PIQ T-Score		X	X	X	X	X	X
5D Pruritus Score		X	X	X	X	X	X
SD-NRS		X	X	X	X	X	X
EQ-5D		X	X	X	X	X	X
HADS		X	X	X	X	X	X
PAS		X	X	X	X	X	X
PN-IGA		X	X	X	X	X	X
Photographs*		X	X	X	X	X	X
Dispense abrocitinib		X	X	X	X		
Adverse Event Monitoring		X	X	X	X	X	X
Itch Diary Review/compliance			X	X	X	X	X
Skin biopsy		X				X	
Plasma/PBMC isolation from blood draw		X				X	X
Labs from Blood Draw (CMP, CBC, Lipid panel, IgE)	X	X	X	**X**	**X**	X	
Patient who are HBcAB-positive and HBV DNA-negative at baseline require HBV DNA monitoring		X	X			X	

b. If your study involves data/biospecimens from participants enrolled under other research studies with a written consent or under a waiver of consent, please list the IRB application numbers for those studies. Please note: Certificate of Confidentiality (CoC) protections applied to the data in source studies funded by NIH or CDC will extend to this new study if the funding was active in 2016. If this situation applies, Section 36, question 6 in the application will need to be answered "Yes" and "Hopkins Faculty" should be selected in question 7. No other documents are required.

   N/A

c. Study duration and number of study visits required of research participants.

   Participants will be in this trial for up to 20 weeks including screening and follow-up.

d. Blinding, including justification for blinding or not blinding the trial, if applicable.

   This study will not be blinded. All participants will receive study drug therefore blinding is not applicable.

e. Justification of why participants will not receive routine care or will have current therapy stopped.

   Participants will need to stop current therapy in order to qualify for the study. In order to clearly elucidate the efficacy of abrocitinib against PN and CPUO, it is important for concurrent therapies to be halted. It is also important to note that the majority of therapies offered to these patients have poor efficacy in controlling PN and CPUO.

   Participants will continue to receive other routine care.

f. Justification for inclusion of a placebo or non-treatment group.

   There is no placebo group in this study. As this is an early phase, small study, we will not include a placebo group. If the data is suggestive of efficacy, a full blinded, and placebo-controlled study will be done.

g. Definition of treatment failure or participant removal criteria.

Discontinuation Criteria

Discontinuation from Study Treatment

Temporary Interruption of Investigational Product

In some circumstances, patients may need to temporarily interrupt treatment as a result of AEs or abnormal laboratory values that may have an unclear relationship to investigational product.

For the abnormal laboratory findings and clinical events (regardless of relatedness) listed in Table 1, specific guidance is provided for temporarily interrupting treatment and when treatment may be restarted. Retest frequency and timing of follow-up laboratory tests to monitor the abnormal finding is at the discretion of the investigator. Investigational product that was temporarily interrupted because of an AE or abnormal laboratory value not specifically covered in Table 1 may be restarted at the discretion of the investigator.

Laboratory Measure	Action	Monitoring Guidance
Lipid parameters	Patients should be managed according to international clinical guidelines for hyperlipidemia	12 weeks after initiation of treatment and thereafter according to international clinical guidelines for hyperlipidemia
Absolute Neutrophil Count (ANC)	Treatment should be interrupted if ANC < 2 x 10^9 cells/L and may be restarted once ANC return above this value	Before treatment initiation (see exclusion criteria too) and thereafter according to routine patient management
Absolute Lymphocyte Count (ALC)	Treatment should be interrupted if ALC < 0.5 x 10^9 cells/L and may be restarted once ALC return above this value	
Hemoglobin (Hb)	Treatment should be interrupted if Hb < 11 g/dL and may be restarted once Hb return above this value	
Hepatic transaminases	Treatment should be temporarily interrupted if drug-induced liver injury is suspected	

Table 1 Criteria for Temporary Interruption of Investigational Product

Hold Investigational Product if the Following Laboratory Test Results or Clinical Events Occur:	Investigational Product May be Resumed When:
Symptomatic herpes zoster	All skin lesions have crusted and are resolving
Infection that, in the opinion of the investigator, merits the IP being interrupted.	Resolution of infection that, in the opinion of the investigator, merits the IP being restarted.

Abbreviations: ALT = alanine aminotransferase; AST = aspartate aminotransferase; IP = investigational product; ULN = upper limit of normal.

1.1.2. Permanent Discontinuation from Investigational Product

Investigational product must be permanently discontinued if the patient or the patient's designee requests to discontinue investigational product.

Discontinuation of the investigational product for abnormal liver tests should be considered by the investigator when a patient meets 1 of the following conditions:

- ALT or AST >2.5 x ULN
- ALT or AST >2 x ULN with the appearance of fatigue, nausea, vomiting, right upper-quadrant pain or tenderness, fever, rash, and/or eosinophilia (>5%)
- ALP >3 x ULN that is deemed to be of liver origin and drug-related
- ALP >2.5 x ULN with the appearance of fatigue, nausea, vomiting, right upper-quadrant pain or tenderness, fever, rash, and/or eosinophilia (>5%)

Investigational product should be permanently discontinued if any of the following laboratory abnormalities are observed:

- White blood cell count <1000 cells/μL (1.00 x 10^3/μL or 1.00 billion/L)
- ANC <1000 cells/μL (1.00 x 10^3/μL or 1.00 billion/L)
- Lymphocyte count <500 cells/μL (0.50 x 10^3/μL or 0.50 billion/L)
- Hemoglobin <10.0 g/dL; (<100.0 g/L)
- Platelet count <75,000/mm^3; (<75.0x10^9/L)
- Creatinine (serum) >1.5x ULN
- Total bilirubin >1.5xULN
- Diastolic: recurrent or persistent (≥ 24 hours) of symptomatic increase from baseline in the same posture, by >20 mmHg

Note: Temporary interruption rules must be followed where applicable. For laboratory values that meet permanent discontinuation thresholds, investigational product should be discontinued. However, if in the opinion of the investigator the laboratory abnormality is due to intercurrent illness such as cholelithiasis or another identified factor, laboratory tests may be repeated. Only when the laboratory value meets resumption thresholds following the resolution of the intercurrent illness or other identified factor may the investigator restart investigational product after consultation with the Pfizer-designated medical monitor. In addition, patients will be discontinued from investigational product in the following circumstances:

- Pregnancy
- Malignancy
- HBV DNA detected with a value above limit of quantitation
- Development of a VTE (DVT/PE) during the study

h. Description of what happens to participants receiving therapy when study ends or if a participant's participation in the study ends prematurely.

At the conclusion of the study, study drug will not be available to participants any longer. This drug is not yet FDA approved and no long-term extension studies are

planned. Participants will discuss with their physician regarding the proper course of future treatment for their condition.

i. If biological materials are involved, please describe all the experimental procedures and analyses in which they will be used.

Translational Component

Please note that both skin tissue and blood samples will be sent to Duke University for analysis as described below. We do intend to publish with the Duke team however it's not a straight collaboration (fee for service - no subcontract). We will send them samples for the biomarker analysis. We will pay for services done there. Duke will return any unused samples so there will be no sample ownership change. Any residual specimens will be returned to Dr. Kwatra at JHU.

Skin biomarker analysis

All patients will undergo two 4 mm punch biopsies at baseline and Week 12, the end of treatment. The 4mm biopsies will include one from lesional skin (pruritic, prurigo nodule) and one from non-lesional (non-itchy) skin at baseline and again at Week 12. Each 4 mm punch biopsy will be divided in two. One half of the 4mm biopsy samples (lesional and non-lesional) will immediately be placed in RNALater solution to be used in confirmatory qPCR. The other half of the 4mm biopsies will be stored in 10% formalin prior to preservation as FFPE cassettes. Nanostring will use the Neuroinflammatory panel with 30 custom genes specific to abrocitinib (Appendix F). Specific deliverables for publication will be a volcano plot and heat map showing differences in expression of itch-related mediators before and after treatment for lesional and non-lesional skin. In addition, ingenuity pathway analysis and gene set variation analyses of Th1, Th2, Th17, and Th22 pathways affected by abrocitinib will be displayed graphically.. Our group is already completing an investigation using these techniques in collaboration with Duke University for healthy PN patients. Nanostring data will be confirmed with targeted immunohistochemistry staining, where choices of specific targets will be based on most dysregulated mediators observed following Nanostring.

Blood biomarker analysis

Plasma will be isolated from patients before therapy at Week 0, at Week 12, and at Week 16. Plasma will be used for cytokine profiling, proteomics and metabolomics. We will perform cytokine arrays on plasma samples using the V-PLEX Human Biomarker 54-Plex Kit.. Translational work for human plasma will also include proteomics and metabolomics approaches in collaboration with Duke University.

For proteomics, we will use an untargeted LC-MS/MS approach. Using this approach, Dr. Moseley, Director of Duke's proteomics facility, has been able to detect over 400 proteins in human plasma samples.

For metabolomics, we will use the MxP Q500 assay kit from Biocrates (https://biocrates.com/mxp-quant-500-kit/). This kit includes 633 metabolites from 26 biochemical classes. We will measure each sample in triplicate.

PBMCs will be isolated from patient whole blood at the same time points above, at Week 0, at Week 12, and at Week 16. To analyze multiple immune cell populations, we will use the Maxpar Direct Immune Profiling Assay from Fluidigm, which uses Cytometry by time-of-flight (CyTOF), a novel variant of conventional flow cytometry. This kit supplies 30 metal-tagged antibodies as a dry pellet, with additional channels/metal tags allowing for additional targets. 37 immune cell populations can be characterized from PBMCs, and CyTOF technology will allow for complete protein quantification of all selected markers.

These tests will not be performed at a CLIA certified laboratory because these are not clinical grade tests and are designed only for research purposes. No results from these tests will be shared with participants as these are not intended for diagnostic purposes.

5. Inclusion/Exclusion Criteria

Inclusion Criteria:

- Males or female participants between ages 18-80 years at time of signing informed consent
- A clinical diagnosis of prurigo nodularis, defined by the presence of at least 10 pruritic nodules on at least 2 different anatomic locations (with each arm, leg, and anterior and posterior trunk considered distinct anatomic locations)
  OR
- Subject has ongoing chronic pruritus of unknown origin, which must be present on multiple segments on the body. CPUO patients must not have known dermatologic or systemic conditions, that in the opinion of the investigator, are the cause of patient's pruritus
- Subject has moderate to severe pruritus, defined as average worst itch numeric rating scale – PP-NRS $\geq$ 7 (range 0-10, higher score indicating greater degree of pruritus severity) in the 7 days prior to the Screening Visit.
- Must read and understand the informed consent approved by the institutional review board (IRB) governing the site and provide written informed consent.

Sex

a) Female participants are eligible for the study if they are not pregnant, planning to become pregnant or breastfeeding during the study and one of the following applies:
   - Female participant is not a WOCBP: Female patients of non–child-bearing potential are not required to use birth control and they are defined as:
   - Women who are infertile due to surgical sterilization (hysterectomy, bilateral oophorectomy, or tubal ligation)
   - Post-menopausal – defined either as
     - A woman at least 50 years of age with an intact uterus, not on hormone therapy, who has either
       - Cessation of menses for at least 1 year
       - At least 6 months of spontaneous menorrhea with follicle-stimulating hormone >40 mIU/mL
     - Women aged 55 years or older who are not on hormone therapy, and who have had at least 6 months of spontaneous amenorrhea
     - Women aged 55 years or older who have a diagnosis of menopause

OR

- If female participant is a WOCBP:

a. Female patients of child-bearing potential who are abstinent (if this is complete abstinence, as their preferred and usual lifestyle) or in a same-sex relationship (as part of their preferred and usual lifestyle) must agree to either remain abstinent or stay in a same-sex relationship without sexual relationships with the opposite sex.

b. Total abstinence is defined as refraining from intercourse during the entirety of the study and for at least 1 week following the last dose of investigational product. Periodic abstinence such as calendar, ovulation, symptothermal, post-ovulation methods and withdrawal are not acceptable methods of contraception.

c. Otherwise, female patients of childbearing potential must agree to use 2 effective methods of contraception, where at least 1 form is highly effective, for the entirety of the study and for at least 1 week following the last dose of investigational product.

d. The following contraception methods are considered acceptable (the patient should choose 2, and 1 must be highly effective [defined as less than 1% failure rate per year when used consistently and correctly]):

- Highly effective birth control methods:
  - Combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation: oral, intravaginal, or transdermal
  - Progestogen- only containing hormonal contraception associated with inhibition of ovulation: oral, intravaginal, or transdermal
  - intrauterine device (IUD)/intrauterine hormone-releasing system (IUS)
  - vasectomized male (with appropriate post-vasectomy documentation of the absence of sperm in the ejaculate).
- Effective birth control methods:
  - Male or female condom with spermicide. It should be noted that the use of male and female condoms as a double barrier method is not considered acceptable due to the high failure rate when these methods are combined.

- Diaphragm with spermicide
- Cervical sponge
- Cervical cap with spermicide

Note: When local guidelines concerning highly effective or effective methods of birth control differ from the above, the local guidelines must be followed. Contraceptive use by women should be consistent with local regulations regarding the methods of contraception for those participating in clinical studies.

Exclusion Criteria:

- Has less than 75% compliance with the daily PP-NRS during 14 days of screening period prior to medication initiation unless approved by the Primary Investigator
- History of chronic urticaria with active lesions in past 3 months
- Subject is on hemodialysis or peritoneal dialysis
- Have experienced any of the following within 12 weeks of screening: VTE (DVT/pulmonary embolism [PE]), myocardial infarction (MI), unstable ischemic heart disease, stroke, or New York Heart Association Stage III/IV heart failure.
- Have a history of recurrent (≥ 2) VTE (DVT/PE).
- Have a history or presence of cardiovascular, respiratory, hepatic, gastrointestinal, endocrine, hematological, neurological, or neuropsychiatric disorders or any other serious and/or unstable illness that in the opinion of the investigator, could constitute an unacceptable risk when taking investigational product or interfere with the interpretation of data.
- Have a history of lymphoproliferative disease; have signs or symptoms suggestive of possible lymphoproliferative disease, including lymphadenopathy or splenomegaly; have active primary or recurrent malignant disease; or have been in remission from clinically significant malignancy for <5 years prior to randomization.
    - The following may be exempted:
      a. Patients with cervical carcinoma in situ that has been resected with no evidence of recurrence or metastatic disease for at least 3 years may participate in the study.

      b. Patients with basal cell or squamous epithelial skin cancers that have been completely resected with no evidence of recurrence for at least 3 years may participate in the study.
- Have a current or recent (<4 weeks prior to randomization) clinically serious viral, bacterial, fungal, or parasitic infection or any other active or recent infection that in the opinion of the investigator, would pose an unacceptable risk to the patient if participating in the study.
  Note: For example, a recent viral upper respiratory tract infection or uncomplicated urinary tract infection need not be considered clinically serious.
- Have symptomatic herpes simplex at the time of randomization.
- Have had symptomatic herpes zoster infection within 12 weeks prior to randomization.

- Have a history of disseminated/complicated herpes zoster (for example, ophthalmic zoster or CNS involvement).

- Have a positive test for hepatitis B virus (HBV) defined as:
  a. positive for hepatitis B surface antigen (HBsAg), or
  b. positive for hepatitis B core antibody (HBcAb) and positive for hepatitis B virus deoxyribonucleic acid (HBV DNA)
  Note: Patients who are HBcAb-positive and HBV DNA-negative may be enrolled in the study but will require additional HBV DNA monitoring during the study.

- Have hepatitis C virus (HCV) infection (hepatitis C antibody-positive and HCV ribonucleic acid [RNA]-positive).
  Note: Patients who have documented anti-HCV treatment for a past HCV infection AND are HCV RNA-negative may be enrolled in the study.

- Have evidence of HIV infection and/or positive HIV antibodies

- Patients with uncontrolled HIV defined as reported CD4+ counts of $\leq$250

- Have had household contact with a person with active TB and did not receive appropriate and documented prophylaxis for TB.

- Have evidence of active TB or latent TB

  a.) Have evidence of active TB, defined in this study as the following:
  - Positive purified protein derivative (PPD) test ($\geq$5 mm induration between approximately 2 and 3 days after application, regardless of vaccination history), medical history, clinical features, and abnormal chest x-ray at screening.
  - QuantiFERON®-TB Gold test or T-SPOT®.TB test (as available and if compliant with local TB guidelines) may be used instead of the PPD test. Patients are excluded from the study if the test is not negative and there is clinical evidence of active TB.

- Have received any of the following medications:
  a. Biologic treatments for immunologic disease such as etanercept, infliximab, certolizumab, adalimumab, golimumab, tocilizumab, abatacept, ustekinumab, ixekizumab, secukinumab, or anakinra within 8 weeks of screening.

  b. Cyclophosphamide (or any other cytotoxic agent), belimumab, or anifrolumab (or another anti-IFN therapy) within 12 weeks of screening.

  c. Rituximab, any other B cell depleting therapies, or intravenous immunoglobulin (IVIg) within 24 weeks of screening.

- Treatment with any other JAK inhibitors within the past 12 weeks

- Treatment with the following agents within 4 weeks prior to planned treatment with abrocitinib:
  - Systemic immunomodulating agents (including but not limited to cyclosporine, methotrexate, mycophenolate mofetil, azathioprine, thalidomide, phototherapy, tanning salon use)
  - Systemic neuromodulating therapies (including but not limited to gabapentin, pregabalin, mu-opioid receptor antagonists (e.g. naltrexone or naloxone), kappa opioid receptor agonists (e.g. butorphanol), cannabinoids, H1 antihistamines, selective serotonin reuptake inhibitors (e.g. paroxetine, fluvoxamine), amitriptyline or other tricyclic antidepressants

        - SSRIs and SNRIs, are allowable if taken at a stable dose for at least 3 months before screening
        - Gabapentinoids are excluded unless used at a stable dose for at least 6 months or used for non-prurigo conditions
        - Oral antihistamines are allowable if taken at a stable dose for 3 months prior to screening
    - Topical anti-pruritic therapies (topical steroids, pramoxine, camphor, menthol, polidocanol, capsaicin)
    - Intralesional corticosteroids
    - Phototherapy
    - Herbal medications with unknown properties, or known beneficial effects for PN
    - Regular use of a tanning booth (more than 2 visits per week)

- Have been treated with probenecid that cannot be discontinued for the duration of the study.

- Have been exposed to a live vaccine within 6 weeks of randomization or are expected to need/receive a live vaccine during the course of the study (with the exception of herpes zoster vaccination).

  Note: All patients who have not previously received the herpes zoster vaccine by screening will be encouraged (per local guidelines) to do so prior to randomization; vaccination with live herpes zoster vaccine must occur >4 weeks prior to randomization and start of investigational product. Patients will not be randomized if they were exposed to a live herpes zoster vaccination within 4 weeks of planned randomization. Investigators should review the vaccination status of their patients and follow the local guidelines for vaccination of patients ≥18 years of age with nonlive vaccines intended to prevent infectious disease prior to entering patients into the study.

- Are currently enrolled in or have discontinued within 4 weeks of screening from any other clinical trial involving an investigational product or nonapproved use of a drug or device or any other type of medical research judged not to be scientifically or medically compatible with this study.

- Have had any major surgery within 8 weeks prior to screening or will require major surgery during the study that, in the opinion of the investigator would pose an unacceptable risk to the patient.

- Planning travel that would interfere with study visits.

- Are largely or wholly incapacitated permitting little or no self-care, such as being bedridden or confined to wheelchair.

- In the opinion of the investigator, are at an unacceptable risk for participating in the study.

- Have donated more than a single unit of blood within 4 weeks prior to screening or intend to donate blood during the course of the study.

- Have a history of intravenous drug abuse, other illicit drug abuse, or chronic alcohol abuse within the 2 years prior to screening or are concurrently using, or expected to use during the study, illicit drugs (including marijuana).

- Are unable or unwilling to make themselves available for the duration of the study and/or are unwilling to follow study restrictions/procedures.

- Are investigator site personnel directly affiliated with this study and/or their immediate families. Immediate family is defined as a spouse, parent, child, or sibling, whether biological or legally adopted.

- Have screening laboratory test values, including thyroid-stimulating hormone (TSH), outside the reference range for the population that, in the opinion of the investigator, pose an unacceptable risk for the patient's

participation in the study. Patients who are receiving thyroxine as replacement therapy may participate in the study, provided stable therapy has been administered for ≥12 weeks and TSH is within the laboratory's reference range. Patients who have TSH marginally outside the laboratory's normal reference range and are receiving stable thyroxine replacement therapy may participate if the treating physician has documented that the thyroxine replacement therapy is adequate for the patient.

- Untreated thyroid, adrenal, or pituitary disease or nodules, or history of thyroid malignancy
- Use of an excluded therapy during the 4-week washout period
- Have any of the following specific abnormalities on screening laboratory tests from the central or local laboratory:

a.) ALT or AST >2 x upper limits of normal (ULN) ((Treatment should be temporarily interrupted if drug-induced liver injury is suspected) See below for discontinuations.

b.) alkaline phosphatase (ALP) ≥2 x ULN

c.) total bilirubin ≥1.5 x ULN

d.) hemoglobin <10 g/dL (100.0 g/L) (Treatment should be interrupted if Hb < 8 g/dL and may be restarted once Hb return above this value)

e. total white blood cell count <3000 cells/μL (<3.00 x 10^3/μL or <3.00 billion/L)

f. neutropenia (absolute neutrophil count [ANC] <2500 cells/μL) (<2.50 x 10^3/μL or <2.50 billion/L) (Treatment should be interrupted if ANC < 2 x 10^9 cells/L and may be restarted once ANC return above this value)

g. lymphopenia (lymphocyte count <500 cells/μL) (<0.50 x 10^3/μL or <0.50 billion/L) (Treatment should be interrupted if ALC < 0.25 x 10^9 cells/L and may be restarted once ALC return above this value)

h. thrombocytopenia (platelets <100,000 cells/μL) (<100 x 10^3/μL or <100 billion/L)

i. eGFR <40 mL/min/1.73 m^2 (Bedside Schwartz formula 2009) or serum creatinine > 1.5 times the ULN

In the case of any of the aforementioned laboratory abnormalities, the tests may be repeated once during screening, and values resulting from repeat testing may be accepted for enrollment eligibility if they meet the eligibility criterion

6. Drugs/ Substances/ Devices

a. The rationale for choosing the drug and dose or for choosing the device to be used.

Drugs:

Abrocitinib 200mg oral tablet – This drug is a study drug that was selected due to its targeting of the Jak1 pathway. 200mg is the dose that has been through Phase 3 trials for treatment of atopic dermatitis and there is significant data available regarding the safety and availability of the drug at this dose.

Tuberculin PPD – This drug is used as part of a tuberculin PPD test as performed by injecting .1mL of purified tuberculin PPD subcutaneously in the skin. This is the standard dosing for a test to determine if a patient is infected with Mycobacterium tuberculosis.

Lidocaine/epinephrine – 3 mL injection at the biopsy site. Lidocaine-HCL 1% w/ epinephrine (1:100,000)

b. Justification and safety information if FDA approved drugs will be administered for non-FDA approved indications or if doses or routes of administration or participant populations are changed.

N/A

c. Justification and safety information if non-FDA approved drugs without an IND will be administered.

N/A An IND has been given approval to proceed.

7. Study Statistics

a. Primary outcome variable.
Percent PP-NRS reduction between baseline and week 12.

b. Secondary outcome variables.

Analysis of PN-IGA, PROMIS Itch Questionnaire, PAS, 5D Pruritus Score, DLQI, HADS, and EQ-5D and detect differences between baseline through Week 12. An ordinal regression will be used because these are non-parametric, ordinal scales.

c. Statistical plan including sample size justification and interim data analysis.

The trial arms of PN and CPUO will be used to conduct subsequent analyses of treatment efficacy. We will treat a p-value of <0.05 as statistically significant, and all tests will be two-tailed. For the primary endpoint, ANOVA will be used to analyze differences in percent PP-NRS reduction (baseline and week 12) with the inclusion of other covariates. We will use a Least-Square means to account for missing data or unbalanced design. We will conduct a two-way analysis of the response variable (PP-NRS percent reduction) by classification variables: specifically, whether the patient has PN or CPUO, and week of treatment. We can derive all LS-means differences from every permutation of week or diagnosis, relative to Week 0 (baseline, prior to treatment). We will incorporate a 95% confidence limit for a significant difference in LS-mean difference between the control group and other groups.

Unlike the primary efficacy endpoint, the secondary endpoints do not have explicit, clinically meaningful changes outlined in the literature. As such, we will look for significant downregulation in itch assessments, and significant improvements in quality of life and sleep measures.

Secondary aims will be analyzed using appropriate statistical tests as outlined below, and missing data will be corrected with Multiple Imputation (MI) and we will assume that missing data is Missing at Random (MAR).

For secondary analyses, a multivariable logistic regression will be used to calculate the odds ratios of different study arms (PN and CPUO) achieving a 4-point reduction in PP-NRS and in SD NRS.

To analyze the PN-IGA, PROMIS Itch Questionnaire, PAS, 5D Pruritus Score, DLQI, HADS, and EQ-5D and detect differences between baseline through Week 12, an ordinal regression will be used because these are non-parametric, ordinal scales.

IgA for PN is not validated in the US, so we are using it as an additional secondary efficacy measure. Appendix D has a simplified version we are applying to this study. Eczema and psoriasis IgA are similarly qualitative. Analysis of PN/CPUO IgA will be an ordinal scale based on qualitative scaling determined at the site visit. We will analyze IgA with an ordinal regression, same as other scales mentioned above.

Atopy will be defined as a binary variable where patients have 2 out of 3: underlying history of atopic dermatitis, history of seasonal allergies, or asthma.
Among PN patients taking 200 mg of abrocitinib, we will use a linear regression to compare PP-NRS reduction from baseline with week 12, among PN patients with atopy and PN patients without atopy.

d. Early stopping rules.

Patients may withdraw at any time or they will be asked to end participation if the physician determines that discontinuation is in the patient's best interest. Data collected may be used if any endpoints are reached.

8. Risks

a. Medical risks, listing all procedures, their major and minor risks and expected frequency.

Foreseeable and known risks of study drug

There is a risk that participants might experience discomfort or side effects with the use of the study drug or procedures. Some of them are still unknown at this stage. In some cases, **side effects can be serious, long-lasting, permanent, or life-threatening**. The study doctor is trained to take the appropriate measures to reduce risks and limit any discomforts you may experience.

Side Effects:

- The most commonly reported side effects are:
  - Nausea (1 in 7 people)
  - Nasopharyngitis (1 in 8 people)
  - Headache (1 in 25 people)
- Rare but serious side effects include:
  - Serious infection (less than 1 in 100 people)
  - Vomiting (1 in 85 people)
  - Decreased platelet counts (1 in 75 people)
-

Skin Biopsy

- Small risk of bleeding
- A scar may form, but is likely to fade over time
- All procedures have a small risk of infection

Blood Draw

Taking blood may cause discomfort, bleeding, or bruising where the needle enters the body. In rare cases, it may result in fainting. There is a small risk of infection.

Interviews or questionnaires

Participants may get tired or bored when we are asking you questions or they are completing questionnaires. Participants do not have to answer any question they do not want to answer.

Identifiable private information

There is the risk that information about about participants may become known to people outside this study.

b. Steps taken to minimize the risks.

Participants will be screened for conditions that may increase risk of study drug or skin biopsy.

All participant data will be deidentified and stored on a secure server in order to protect privacy to the utmost degree.

c. Plan for reporting unanticipated problems or study deviations.

All unanticipated problems and study deviations will be reported to the primary investigator, Shawn Kwatra, as well as the IRB immediately upon discovery.

d. Legal risks such as the risks that would be associated with breach of confidentiality.

As this study involves personal health information, there is a risk of breach of confidentiality. Additionally, as there are genetic studies planned as part of this study, there is a risk that this information could be disclosed with a breach of confidentiality.

e. Financial risks to the participants.

There is a small financial risk to participants if they suffer from severe side effects that impact their day-to-day life and require additional medical care or potentially missing work. These are not anticipated to be significant risks for this study.

9. Benefits

a. Description of the probable benefits for the participant and for society.

There is potential benefit to the participant if abrocitinib shows efficacy in improvement for conditions of chronic itch. There is also benefit for society of contributing to the understanding of these chronic itch conditions for which no approved therapies currently exist.

10. Payment and Remuneration

a. Detail compensation for participants including possible total compensation, proposed bonus, and any proposed reductions or penalties for not completing the protocol.

Participants will receive up to $400 for successful completion of the study. They will receive $50 for completion of study visits 1, 3, 4, 5, and 7 and $75 for completion of study visits 2 and 6. Participants will receive a check at the end of the study visit or a check will be mailed to their home address.

Participants will also receive reimbursement for parking costs.

11. Costs

a. Detail costs of study procedure(s) or drug (s) or substance(s) to participants and identify who will pay for them.

There are no costs to participate in the study.

12. Transfer of Materials

Transfer of biospecimens from Johns Hopkins to another organization for research purposes and receipt of biospecimens from an outside organization for your research must adhere to JHU policies for material transfer (https://ventures.jhu.edu/faculty-inventors/forms-policies/) and biospecimen transfer (https://hpo.johnshopkins.edu/enterprise/policies/176/39187/policy_39187.pdf?_=0.622324232879).

Please complete this section if your research involves transfer or receipt of biospecimens.

a. Will you **receive** biospecimens from an external entity for this research? [Yes/No].
If "Yes", please confirm you will secure an MTA/research agreement from the appropriate office (JHTV/ORA) prior to transfer.
See: https://ventures.jhu.edu/technology-transfer/material-transfer-agreements/ .

b. Will you **transfer** biospecimens to an external entity as part of this research? [Yes/No]
If "Yes", please address each of the following:
1) Describe the nature of the research collaboration with the external entity and the rationale for the transfer. (Include an explanation of your intellectual contribution to the design of the research study, resulting data and sharing, and participation in the planned publications.)

2) Please confirm you will secure an MTA through the appropriate office (JHTV or ORA) prior to transfer.
(See: https://ventures.jhu.edu/technology-transfer/material-transfer-agreements/.)
Already obtained: please see page 23, section 4.

3) If the biospecimens you intend to transfer were obtained through clinical or research procedures at Johns Hopkins and "Other" is selected in Item 4, Section 23, please submit the following items in that Section:

   a. A pdf version of a completed JHTV Online "Material Transfer Agreement Request Form for Outbound Material" https://ventures.jhu.edu/technology-transfer/material-transfer-agreements/ **OR** a copy of the COEUS PD (Proposal Development Summary).
   Already obtained: please see page 23, section 4

   b. A completed Biospecimen Transfer Information Sheet https://www.hopkinsmedicine.org/institutional_review_board/forms/.
   Already obtained: please see page 23, section 4

   c. A signed and dated "De-identified Human Subject Certification" https://www.hopkinsmedicine.org/institutional_review_board/forms/
   Already obtained: please see page 23, section 4

   d. Approval documents from recipient site, if applicable.
   N/A

   e. Copies of the consent forms associated with the IRB protocols under which the biospecimens were collected, with language appropriate to this transfer highlighted.
   Already obtained: please see page 23, section 4

   f. The name of the specialist you are working with in ORA to complete a contract/MTA.
   Already obtained: please see page 23, section 4
   Kathleen Maltbie

Please see the following website for more information about transferring human biospecimens to outside entities:
https://www.hopkinsmedicine.org/institutional_review_board/news/announcement_transfer_human_biospecimens_outside_entities.html/ .