Clinical Study Protocol

A 24 Week, Open-Label Study to Evaluate the Efficacy and Safety of Upadacitinib in Patients with Moderate-to-Severe Prurigo Nodularis

Testing Facility

Eczema Treatment Center of New Jersey
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(609) 443-4500

Study Sponsor and Principal Investigator

Jerry Bagel, MD

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PROTOCOL SYNOPSIS

Study Title	A 24 Week, Open-Label Study to Evaluate the Efficacy and Safety of Upadacitinib in Patients with Moderate-to-Severe Prurigo Nodularis
Sponsors	Jerry Bagel, MD
Study Objectives	**Primary Objective:** To explore the effectiveness of upadacitinib in patients with prurigo nodularis. **Secondary Objectives:** To explore the safety of upadacitinib in patients with prurigo nodularis.
Study Design	A single center, open-label study of 25 subjects to assess 24 weeks upadacitinib in patients with moderate-to-severe prurigo nodularis.
Study Centers	Eczema Treatment Center of New Jersey 59 One Mile Road, East Windsor, NJ 08520
Study Population	25 adult male and female subjects with moderate-to-severe prurigo nodularis
Main Inclusion Criteria	1. Male or female adult 18-64 years of age at time of screening. 2. Diagnosis of prurigo nodularis for ≥ 3 months. 3. Moderate-to-Severe prurigo nodularis as determined by at least 10 PN lesions on legs and/or arms and/or trunk at screening and baseline . 4. Failure of at least a 2-week course of medium to super potent TCS or TCS is not medically advisable for subject. 5. Females of childbearing potential must not have a positive serum pregnancy test at the Screening Visit and must have a negative urine pregnancy test at the Baseline Visit prior to study drug dosing. Note: subjects with borderline pregnancy test at Screening must have a serum pregnancy test ≥ 3 days later to determine eligibility. If female, subject must be postmenopausal OR permanently surgically sterile OR for females of childbearing potential practicing at least one protocol specified method of birth control, that is effective from the Baseline Visit through at least 30 days after the last dose of study drug. Female subject must not be pregnant, breastfeeding or considering becoming pregnant during the study or for approximately 30 days after the last dose of the study drug. 6. Subject is a candidate for systemic therapy per investigator discretion. 7. Able and willing to give written informed consent prior to performance of any study-related procedures. 8. Subject must be in general good health as judged by the Investigator, based on medical history, physical examination.

Main Exclusion Criteria	1. Presence of skin condition other than prurigo nodularis or atopic dermatitis that may interfere with study assessments. 2. Diagnosis of active atopic dermatitis at screening and baseline. 3. PN secondary to medications. 4. PN secondary to medical conditions such as neuropathy or psychiatric disease. 5. Severe concomitant illness(es) under poor control that, in the investigator's judgment, would adversely affect the patient's participation in the study. 6. Severe renal conditions (eg, patients with uremia and/or on dialysis) 7. Participants with uncontrolled thyroid disease. 8. Active tuberculosis or non-tuberculous mycobacterial infection, or a history of incompletely treated tuberculosis unless documented adequately treated. Patients with latent TB at screening may be enrolled if tuberculosis treatment is initiated prior to first dose. 9. Diagnosed active endoparasitic infections; suspected or high risk of endoparasitic infection, unless clinical and (if necessary) laboratory assessment have ruled out active infection before randomization. 10. Active chronic or acute infection (except HIV infection) requiring treatment with systemic antibiotics, antivirals, antiprotozoals, or antifungals within 2 weeks before the screening visit or during the screening period. 11. Known or suspected immunodeficiency. 12. Active malignancy or history of malignancy within 5 years before the baseline visit, except completely treated in situ carcinoma of the cervix, completely treated and resolved non-metastatic squamous or basal cell carcinoma of the skin.
Background and Hypothesis	Prurigo Nodularis (PN) is a chronic skin disorder that presents as multiple firm nodules commonly located on the extensor surfaces of the extremities. The lesions are very pruritic and commonly associated with another disorder of cutaneous hypersensitivity such as atopic dermatitis.[1] Treatment for PN varies from topical and intralesional corticosteroids for mild cases to phototherapy and systemic immunosuppressives for more severe cases.[2] Upadacitinib is a novel selective orally available JAK1 inhibitor with the potential to decrease T helper 2 cell-mediated skin inflammation and itch mediated by JAK1, while having minimal inhibitory effects on JAK2 and JAK3. This study will evaluate the safety and efficacy of upadacitinib in prurigo nodularis itch improvement as well as improvement of PN lesions. A second Phase 3 trial evaluating Dupixent® (dupilumab) in adults with uncontrolled prurigo nodularis, a chronic type 2 inflammatory skin disease, met its primary and key secondary endpoints, showing it significantly reduced itch and skin lesions compared to placebo at 24 weeks in this investigational setting. The data confirm the positive results that were previously reported from the Phase 3 PRIME2 trial and will be submitted to regulatory authorities around the world starting in the first half of this year. The impact of prurigo nodularis on quality of life is one of the highest among inflammatory skin diseases due to the extreme itch.[3] Emerging research has shown that JAK inhibitors look promising for the treatment of PN. A case report of tofacitinib for PN and the success of baricitinib for prurigo-type atopic dermatitis, both demonstrate the effectiveness of the JAK inhibitor for the treatment of PN.[4] This study aims to explore the efficacy of upadacitinib for PN.

Study Visits	Visit 1 (Screening) Visit 2 (Baseline) Visit 3 (Week 4) Visit 4 (Week 8) Visit 5 (Week 12) Visit 6 (Week 16) Visit 7 (Week 20) Visit 8 (Week 24)
Study Endpoints	**Primary Endpoint:**Proportion of participants with improvement (reduction) in worst-itch numeric rating scale (WI-NRS) by ≥4 from baseline to Week 12. [Time Frame: Baseline to Week 12]WI-NRS is a patient-reported outcome (PRO) comprised of a single item rated on a scale from 0 ("No itch") to 10 ("Worst imaginable itch. **Secondary Endpoints:** Proportion of patients with improvement in worst-itch numeric rating scale (WI-NRS) by ≥4 from baseline to Week 24 IGA PN-S 0 or 1 at weeks 12 & 24 IGA PN-A 0 or 1 at week 12 & 24 Percent improvement of PN-S & PN-A at week 12 & 24 DLQI improvement at weeks 12 & 24 Adverse Events
References	Tessa B. Mullins, Poonam Sharma, Christopher A. Riley, Sidharth Sonthalia. Prurigo Nodularis. StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2021 Jan. 2020 Sep 15. Eric H Kowalski, Diana Kneiber, Manuel Valdebran, Umangi Patel, Kyle T Amber. Treatment-resistant prurigo nodularis: challenges and solutions. Clin Cosmet Investig Dermatol. 2019 Feb 28;12:163-172. doi: 10.2147/CCID.S188070. eCollection 2019.

2 ETHICS AND REGULATORY OBLIGATIONS

2.1 Institutional Review Board (IRB)

Written IRB approval of this protocol must be obtained before the study is initiated. Compliance with Title 21 of the US Code of Federal Regulations (CFR), Part 56, is required in order to protect the rights and welfare of human subjects involved in this study.

2.2 Ethical Conduct of the Study

The study will be conducted in accordance with the ethical principles that have their origins in the Declaration of Helsinki and its amendments. In addition, the study will be performed in compliance with Good Clinical Practices (GCP), including the archiving of essential documents.

2.3 Subject Information and Consent

The Informed Consent Form will be reviewed and approved by the IRB. The purpose, duration and possible risks and benefits will be explained to each potential subject. Consent in writing must be obtained from the subject before enrollment into the study. Consents will be signed and dated as required by Title 21 of CFR, Part 50. The consent will also comply with the requirements of the Health Insurance Portability and Accountability Act (HIPAA). The original, signed Informed Consent Form will be retained by the Investigator. A signed copy of the Informed Consent Form will be given to the subject. Each subject will be assigned a subject number that will be used in lieu of the subject's name on further research documentation.

3 INTRODUCTION

3.1 Overview of Prurigo Nodularis and Study Rationale

Prurigo Nodularis (PN) is a chronic skin disorder that presents as multiple firm nodules commonly located on the extensor surfaces of the extremities. The lesions are very pruritic and commonly associated with another disorder of cutaneous hypersensitivity such as atopic dermatitis.[1] Treatment for PN varies from topical and intralesional corticosteroids for mild cases to phototherapy and systemic immunosuppressives for more severe cases.[2] Upadacitinib is a novel selective orally available JAK1 inhibitor with the potential to decrease T helper 2 cell-mediated skin inflammation and itch mediated by JAK1, while having minimal inhibitory effects on JAK2 and JAK3. This study will evaluate the safety and efficacy of upadacitinib in prurigo nodularis itch improvement as well as improvement of PN lesions.

4. STUDY OBJECTIVE

To explore the effectiveness and safety of upadacitinib in patients with moderate-to-severe prurigo nodularis.

5. INVESTIGATIONAL PLAN

5.1 Overall Study Design and Plan

25 subjects with prurigo nodularis with at least 10 PN lesions on arms, legs and/or trunk with moderate-to-severe itch will receive upadacitinib 15mg once daily.

5.2 Study Population Criteria

Males and females 18-64 years of age with moderate-to-severe prurigo nodularis

5.2.1 Inclusion Criteria

Patients who meet all of the following criteria will be enrolled in the study:

1. Male or female adult 18- 64 years of age at time of screening.

2. Diagnosis of prurigo nodularis for ≥ 3 months

3. Moderate-to-Severe prurigo nodularis as determined by at least 10 PN lesions on legs and/or arms and/or trunk at screening and baseline.

4. Failure of at least a 2 week course of medium to super potent TCS or TCS is not medically advisable for subject.

5. Females of childbearing potential must not have a positive serum pregnancy test at the Screening Visit and must have a negative urine pregnancy test at the Baseline Visit prior to study drug dosing. Note: subjects with borderline pregnancy test at Screening must have a serum pregnancy test ≥ 3 days later to determine eligibility.
If female, subject must be postmenopausal OR permanently surgically sterile OR for females of childbearing potential practicing at least one protocol specified method of birth control, that is effective from the Baseline Visit through at least 30 days after the last dose of study drug. Female subject must not be pregnant, breastfeeding or considering becoming pregnant during the study or for approximately 30 days after the last dose of the study drug.

6. Subject is a candidate for systemic therapy

7. Able and willing to give written informed consent prior to performance of any study-related procedures.

8. Subject must be in general good health as judged by the Investigator, based on medical history, physical examination.

5.2.2 Exclusion Criteria

Patients will NOT be enrolled in this study if they meet any of the following criteria:

1. Presence of skin condition other than prurigo nodularis or atopic dermatitis that may interfere with study assessments.

2. Diagnosis of active atopic dermatitis at screening and baseline.

3. PN secondary to medications.

4. PN secondary to medical conditions such as neuropathy or psychiatric disease.

5. Severe concomitant illness(es) under poor control that, in the investigator's judgment, would adversely affect the patient's participation in the study

6. Severe renal conditions (eg, patients with uremia and/or on dialysis)

7. Participants with uncontrolled thyroid disease.

8.Active tuberculosis or non-tuberculous mycobacterial infection, or a history of incompletely treated tuberculosis unless documented adequately treated. Patients with latent TB at screening may be enrolled if tuberculosis treatment is initiated prior to first dose.

9. Diagnosed active endoparasitic infections; suspected or high risk of endoparasitic infection, unless clinical and (if necessary) laboratory assessment have ruled out active infection before randomization.

10. Active chronic or acute infection (except HIV infection) requiring treatment with systemic antibiotics, antivirals, antiprotozoals, or antifungals within 2 weeks before the screening visit or during the screening period.

11. Known or suspected immunodeficiency.

12. Active malignancy or history of malignancy within 5 years before the baseline visit, except completely treated in situ carcinoma of the cervix, completely treated and resolved non-metastatic squamous or basal cell carcinoma of the skin.

13. Use of oral systemic medications or phototherapy for the treatment of prurigo nodularis within 4 weeks.

14. Patient received UVB phototherapy within 2 weeks of Baseline.

15. Patient used topical therapies within 1 week of the Baseline Visit.

16. Patient has used dupilumab within 12 weeks of Baseline Visit.

17.. Patient has a known hypersensitivity to the excipients of upadacitinib.

18.Presence of significant lab abnormality or uncontrolled medical condition that in the opinion of the investigator would affect patient safety during the trial.

19. . Prior use of upadacitinib.

5.3 Source of Subjects and Recruitment Methods

The Investigator will manage the recruitment of subjects upon approval of the study by the Institutional Review Board. Subjects may be recruited from internal patient lists from the investigator's clinic and external IRB approved advertisements. The study site will manage recruitment campaigns with IRB approved documents.

5.4 Subject Enrollment and Treatment Assignment

25 adult subjects of either gender with moderate-to-severe prurigo nodularis will receive upadacitinib 15mg once daily. Dosage will be increased to 30mg QD at week 8 based on subject response. See dosage adjustments below. IP will be managed by site personnel and stored in a temperature controlled limited access area at the study site. Accountability records will be maintained by site personnel for all IP receipt, dispensation and returns.

5.5 STUDY TREATMENT

5.5.1 Upadacitinib Description

Upadacitinib is an oral selective and reversible inhibitor of Janus kinase (JAK) 1, which blocks signaling of many inflammatory cytokines including interleukin (IL)-6, IL-2, IL-7, and IL-15. A growing body of evidence suggests that JAK inhibition is an effective therapy for the treatment of signs and symptoms of multiple immune-mediated inflammatory diseases in humans.[5]

5.5.1.1 Upadacitinib Dosing Schedule

Subjects will be instructed to take Upadacitinib 15mg once daily starting at the baseline visit. Study drug should be taken approximately the same time each day. Study drug can be taken with or without food. If a subject forgets to take their dose at the regularly scheduled time they should take it immediately, unless it is within 10 hours of the next scheduled dose. If the next dose is expected within 10 hours than the forgotten dose

should be considered missed and the next dose should be taken at the regularly scheduled time.

5.5.1.2 Upadacitinib Dispensing

Subjects will return all unused upadacitinib tablets to the study site. Site personnel will keep a record of upadacitinib dispensed to and returned by each subject and note any missed doses.

5.5.1.3 Upadacitinib Dosage Adjustments

Upadacitinib will be dispensed and administered as 15mg QD at baseline. For subjects who do not achieve ≤ 2-point reduction in itch at week 8, upadacitinib dosage will be increased to 30mg QD. The investigator may reduce the dose to 15mg QD after week 16 per investigator discretion. If an SAE or an adverse event that is thought to be related to study drug and is not alleviated by symptomatic intervention, study drug will be discontinued. Subjects who permanently discontinue study drug under this protocol should receive standard care of prurigo nodularis treatment as prescribed by their physician.

5.5.3 Permitted Concomitant Therapy and Rescue Therapy

Starting from the screening visit, subjects will be instructed to use a daily non-medicated moisturizer through the end of study participation. Appropriate interventions (e.g., prescribed medications) may be performed as the investigator deems necessary to treat concomitant illnesses and/or safeguard the subjects' wellbeing. No investigational product or device may be used during the study

5.6 Study Procedures

This protocol will consist of a Screening Period (0-30 days), followed by open label treatment period of upadacitinib 15mg-30mg QD for 24 weeks. To date, Dupixent is the first and only medication to demonstrate positive results in prurigo nodularis at week 24 and receive regulatory approval for PN. This study will explore efficacy over a 24-week period to evaluate clinical response.

This Study will be conducted in compliance with CFR Title 21, Part 50 (Informed Consent of Human Subjects). Informed consent will be obtained from each subject in writing before participation in the Study. A signed copy of the Informed Consent Form will be provided to each subject. A provision to obtain a signed authorization to provide protected health information to the study sponsor, internal quality assurance agencies, health

insurance agencies, and other parties as specified in the Federal Health Insurance Portability and Accountability Act (HIPAA) privacy regulation will be included in the Informed Consent Document. HIPAA authorization is voluntary. However, since the use and release of health information is critical to the conduct of the study, subjects who do not provide authorization to use and disclose their health information will not be enrolled into the study. Subjects who withdraw their authorization to use and release health information during study participation will be formally discontinued from the study. The investigator may use and release at any time all the information collected prior to a subject's withdrawal of the authorization to all authorized parties to satisfy scientific, regulatory, and financial concerns.

5.6.1 Inclusion and Exclusion Criteria

Subjects' eligibility to participate in the study will be determined according to the Inclusion and Exclusion Criteria during the screening period (0 – 30 days prior to the first dose of the study drug). Subjects who ultimately do not satisfy the eligibility criteria except changing treatments and undergoing a washout period, will not be enrolled into the study. Subjects who need to meet eligibility requirements will be asked to make the necessary changes. Subjects who agree and comply will be re-evaluated prior to Baseline.

5.6.2 Demographics and Medical History

The following information will be obtained for each subject during screening: date of birth, sex, race/ ethnic origin, relevant medical and surgical history, including year of diagnosis of prurigo nodularis, and current and previous prurigo nodularis treatments for the last 6 months. All current therapies for other medical conditions will be documented. Medical history will be reviewed and updated at the Baseline Visit to ensure that the patient remains eligible to participate in the study.

5.6.3 Pregnancy Testing

Serum Pregnancy testing (urine β-human chorionic gonadotrophin [β-HCG]) will be conducted in all female subjects, except those without childbearing potential at Screening (-30 to -1). Urine pregnancy tests will be conducted at Baseline (prior to first dose of upadacitinib) and at each visit through week 24. An interim urine pregnancy test may be performed if there is reason to believe the subject may have become pregnant during the study. Subjects with a positive pregnancy test will not be eligible to participate or to continue to receive study treatment.

Contraception Requirements for Females

A female who is permanently surgically sterile or postmenopausal is not considered to be a female of childbearing potential and is not required to follow contraception recommendations.

Surgically sterile is defined as:

•bilateral oophorectomy (surgical removal of both ovaries); or
•bilateral salpingectomy (surgical removal of both fallopian tubes); or
•hysterectomy (surgical removal of uterus)

Postmenopausal is defined as:

•Age ≥ 55 years with no menses for 12 or more months without an alternative medical cause; or.
•Age < 55 years with no menses for 12 or more months without an alternative medical cause AND a follicle-stimulating hormone (FSH) level > 40 IU/L.

If the female subject is ≤ 55 years of age, postmenarchal, and has had no menses for ≥ 12 months AND has no history of permanent surgical sterilization (defined above), FSH should be tested at Screening.

•If FSH is not tested, it is assumed that the subject is of childbearing potential and protocol specified contraception is required.
•If the FSH is tested and the result is consistent with postmenopausal status, contraception is not required.
•If the FSH is tested and the result is consistent with premenopausal status, contraception is required, and pregnancy testing requirements for women of childbearing potential must be followed (see below).

A female who does not meet the definition of postmenopausal or permanently surgically sterile is considered of childbearing potential and is required to practice at least one of the following highly effective methods of birth control that is effective from Baseline Visit (or earlier) through at least 30 days after the last dose of study drug.

•Combined (estrogen and progestogen containing) hormonal contraception (oral, intravaginal, transdermal) associated with the inhibition of ovulation, initiated at least 30 days prior to Baseline Visit.
•Progestogen-only hormonal contraception (oral, injectable, implantable) associated with inhibition of ovulation, initiated at least 30 days prior to Baseline Visit.
•Bilateral tubal occlusion/ligation.
•Vasectomized partner(s) provided the vasectomized partner has received medical confirmation of the surgical success and is the sole sexual partner of the women of childbearing potential trial participant.

•Intrauterine device.
•Intrauterine hormone-releasing system.
•True abstinence (if acceptable per local requirements): Refraining from heterosexual intercourse when this is in line with the preferred and usual lifestyle of the subject. Periodic abstinence (e.g., using calendar, ovulation, symptothermal, postovulation methods) and withdrawal are not acceptable.
If required per local guidelines, male or female condom with or without spermicide OR cap, diaphragm or sponge with spermicide should be used in addition to one of the birth control methods listed above (excluding true abstinence).
If during the course of the study a female becomes surgically sterile or postmenopausal (defined above) and complete documentation is available, contraceptive measures as defined above are no longer required. It is important to note that contraception requirements described above are specifically intended to prevent pregnancy during exposure to the investigational therapy upadacitinib.

Contraception recommendations related to use of concomitant therapies prescribed per standard of care should be based on the local label.
Additional local requirements may apply.

At each visit, the study staff should review the pregnancy avoidance recommendations with each female of childbearing potential and document this discussion in the subject's source records.

5.6.4 Laboratory Testing

Serum chemistry, hematology, Hepatitis B Surface Antibody and Antigen (HBV), Hepatitis C Antibody (HCV) and Quantiferon Gold testing will be performed at screening to ensure subject safety prior to baseline. Serum chemistry and hematology will also be performed at weeks 12 and 24.

5.6.5 Physical Examination

A physical examination, including vital signs measurements (blood pressure, pulse and temperature), will be performed according to the schedule of events. The physical examination should include a thorough evaluation of the subject's skin. Any clinically significant abnormalities discovered during physical examinations after the Screening / Baseline visit should be documented and evaluated as potential adverse events.

5.6.6 Investigator's Global Assessment for Prurigo Nodularis (IGA-PN)

IGA-PN will be determined for all subjects at all visits during the study. Investigator's global assessment for prurigo nodularis (IGA PN) is a clinician-reported outcome that allows clinicians to assess the activity of PN (IGA PN-A) using a 5-point scale from 0 (clear) to 4 (severe); and the stage of the disease (IGA PN-S) using a 5-point scale from 0 (clear) to 4 (severe). *See Appendix A*

5.6.7 Patient Reported Outcomes

Subjects will complete the PRO's according to the schedule of assessments. Questionnaires should be prior to medical procedures and clinical evaluations.

5.6.7.1 Worst-Itch Numerical Rating Scale

(WI-NRS) is a PRO comprised of a single item rated on a scale from 0 ("No itch") to 10 ("Worst imaginable itch"). Participants are asked to rate the intensity of their worst pruritus (itch) over the past 24 hours using this scale.0.1 Worst Itch Numeric Rating Scale.[4] *See Appendix B*

5.6.7.2 Dermatology Life Quality Index

Dermatology Life Quality Index (DLQI)[5] to assess symptoms and impacts of dermatologic diseases on quality of life. *See Appendix C*

5.6.8 Early Discontinuation Procedures

Subjects will be prematurely discontinued from the study under the following conditions:

1. Subject requests to withdraw from the study.
2. Subject experiences an adverse event that makes it difficult or intolerable for the subject to continue treatment, or increases risk to the subject, or interferes with the investigator's ability to clinically evaluate the progress of the subject's treatment.
3. Subject begins an unapproved concomitant therapy for prurigo nodularis, atopic dermatitis or another medical condition that may increase risk to the subject if continuing study treatment.
4. Subject cannot be reached / lost to follow-up.
5. The study investigator suspends or terminates the study.
6. Other unanticipated reason.

Any subject who prematurely discontinues the study should complete the week 24 (End of Study) assessments.

6 COMPLAINTS/ADVERSE EVENTS/SERIOUS ADVERSE EVENTS

Adverse events will be collected from the time of the first dose of product during the study until 30 days following the intake of the last dose taken during the study period. An AE is defined as any untoward medical occurrence in a subject or clinical investigation subject administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not the event is considered causally related to the use of the product.

Such an event can result from use of the drug as stipulated in the protocol or labeling, as well as from accidental or intentional overdose, drug abuse, or drug withdrawal. Any worsening of a pre-existing condition or illness is considered an AE. Worsening in severity of a reported AE should be reported as a new AE. Laboratory abnormalities and changes in vital signs are considered to be AEs only if they result in discontinuation from the study, necessitate therapeutic medical intervention, meets protocol specific criteria and/or if the investigator considers them to be AEs.

The investigator will monitor each subject for clinical and laboratory evidence of AEs on a routine basis throughout the study. All AEs will be followed to a satisfactory conclusion. An elective surgery/procedure scheduled to occur during a study will not be considered an AE if the surgery/procedure is being performed for a pre-existing condition and the surgery/procedure has been preplanned prior to study entry. Elective surgery will not be allowed during the study until the primary endpoint has been assessed (Week 16). However, if the pre-existing condition deteriorates unexpectedly during the study (e.g., surgery performed earlier than planned), then the deterioration of the condition for which the elective surgery/procedure is being done will be considered an AE. If any of the following events are reported, then the following supplemental form must be completed.

If an AE meets any of the following criteria, it is to be reported to AbbVie as an SAE within 24 hours of the site being made aware of the SAE:

Death of Subject- An event that results in the death of a subject.

Life-Threatening- An event that, in the opinion of the investigator, would have resulted in immediate fatality if medical intervention had not been taken. This does not include an event that would have been fatal if it had occurred in a more severe form.

Hospitalization or Prolongation of Hospitalization- An event that results in an admission to the hospital for any length of time or prolongs the subject's hospital stay. This does not include an emergency room visit or admission to an outpatient facility.

Congenital Anomaly- An anomaly detected at or after birth, or any anomaly that results in fetal loss.

Persistent or Significant Disability/Incapacity- An event that results in a condition that substantially interferes with the activities of daily living of a study subject. Disability is not intended to include experiences of relatively minor medical significance such as headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (e.g., sprained ankle).

Important Medical Event Requiring Medical or Surgical Intervention to Prevent Serious Outcome- An important medical event that may not be immediately life threatening or result in death or hospitalization, but based on medical judgment may jeopardize the subject and may require medical or surgical intervention to prevent any of the outcomes listed above (i.e., death of subject, life threatening, hospitalization, prolongation of hospitalization, congenital anomaly, or persistent or significant disability/incapacity). Additionally, any elective or spontaneous abortion or stillbirth is considered an important medical event. Examples of such events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

Special Situations - accidental or intentional overdose, medication error, occupational or accidental exposure, off-label use, drug abuse, drug misuse, lack of efficacy, or drug withdrawal must be reported to AbbVie within 30 calendar days.

All AEs reported from the time of study drug administration until 30 days after discontinuation of study drug administration will be collected, whether solicited or spontaneously reported by the subject. In addition, SAEs and protocol-specified

nonserious AEs will be collected from the time the subject signs the study-specific informed consentAdverse events will be monitored throughout the study to identify any of special interest that may indicate a trend or risk to subjects.

Adverse Events of Special Interest

The following AESIs will be monitored during the study:

•Serious infections
•Opportunistic infections
•Herpes zoster
•Tuberculosis
•Malignancy (all types)
•GI perforations
•Adjudicated cardiovascular events (e.g., major adverse cardiovascular event [MACE])
•Anemia
•Neutropenia
•Lymphopenia
•Increased serum creatinine and renal dysfunction
•Hepatic events and increased hepatic transaminases
•Elevated creatine phosphokinase
• embolic and thrombotic events (non-cardiac, non-central nervous system)

Adverse Event Severity and Relationship to Study Drug

The investigators will rate the severity of each AE according to the National Cancer Institute Common
Terminology Criteria for Adverse Events version 4.03.
If no grading criteria are provided for the reported event, then the event should be graded follows:

Mild (Grade 1) Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated

Moderate (Grade 2) Minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental activities of daily living (ADL)

Severe (Grade 3 to 5) Grade 3 Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL (selfcare ADL refer to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden)

Grade 4 Life-threatening consequences; urgent intervention indicated

Grade 5 Death related to AE

The investigator will use the following definitions to assess the relationship of the AE to the use of study drug:
Reasonable Possibility – After consideration of factors including timing of the event, biologic plausibility, clinical judgment, and potential alternative causes, there is sufficient evidence (information) to suggest a causal relationship.

No Reasonable Possibility – After consideration of factors including timing of the event, biologic plausibility, clinical judgment, and potential alternative causes, there is insufficient evidence (information) to suggest a causal relationship. For causality assessments, events assessed as having a reasonable possibility of being related to the study drug will be considered "associated." Events assessed as having no reasonable possibility of being related to study drug will be considered "not associated." In addition, when the investigator has not reported a causality or deemed it not assessable, AbbVie will consider the event associated.

If an investigator's opinion of no reasonable possibility of being related to study drug is given, an Other cause of event must be provided by the investigator for the SAE.

Pregnancy
While not an AE, pregnancy in a study subject must be reported to AbbVie within 1 working day after the site becomes aware of the pregnancy. If a pregnancy occurs in a study subject or in the partner of a study subject, information regarding the pregnancy and the outcome will be collected. In the event of pregnancy occurring in a subject's partner during the study, written informed consent from the partner must be obtained prior to collection of any such information. AbbVie will provide a separate consent form for this purpose. Pregnancy in a subject's partners will be collected from the date of the first dose through 30 days following the last dose of study drug. Subjects should avoid pregnancy throughout the course of the study, starting with the Screening Visit through 30 days after the last study drug administration for female subjects. Results of a positive pregnancy test or confirmation of a pregnancy will be assessed starting with the Screening Visit through the final study visit. Subjects who become pregnant during the study must be

discontinued. The pregnancy outcome of an elective or spontaneous abortion, stillbirth or congenital anomaly is considered a SAE and must be reported to AbbVie within 24 hours after the site becomes aware of the event.

7 INVESTIGATIONAL PRODUCT HANDLING

7.1 Investigational Product Receipt

At study initiation and as needed thereafter, upadacitinib 15mg will be shipped to a responsible person at the investigator's institution, who will check the amount and condition of the drug, and maintain a record of this information. The master accountability log will be maintained by un-blinded pharmacy staff.

7.2 Investigational Product Storage

Investigational product will be stored per the storage conditions identified on drug label. At the study site, all IP will be stored in a locked, safe area to prevent unauthorized access. Records of the actual storage conditions during the period of the study will be maintained.

8 RECORD RETENTION

The investigator must retain these documents according to local laws or requirements. Essential documents include, but are not limited to, the following:

- Signed informed consent documents for all subjects;
- Subject identification code list, screening log (if applicable), and enrollment log;
- Record of all communications between the Investigator and the IRB/EC; Composition of the IRB/EC; g
- Record of all communications between the Investigator and Abbvie.
- List of Sub-investigators and other appropriately qualified persons to whom the Investigator has delegated significant study-related duties, together with their roles in the study, curriculum vitae, and their signatures;
- Copies of CRFs (if paper) and of documentation of corrections for all subjects;
- IP accountability records;
- All other source documents (subject records, hospital records, laboratory records, etc);

- All other documents as listed in Section 8 of the ICH consolidated guideline on GCP (Essential Documents for the Conduct of a Clinical Trial).

The Investigator must notify Abbvie if he/she wishes to assign the essential documents to someone else, remove them to another location or is unable to retain them for a specified period. If the Investigator is unable to meet this obligation, the Investigator must ask Abbvie for permission to make alternative arrangements. Details of these arrangements should be documented. All study documents should be made available if required by relevant health authorities. Investigator/Institution should take measures to prevent accidental or premature destruction of these documents.

To protect subjects' confidentiality, all subjects and their associated samples will be assigned numerical study identifiers or "codes." No identifiable information will be provided to Abbvie.

8.1 Study Monitoring

The investigator will self-monitor all study records for accuracy, completeness, and compliance with the protocol and GCPs and federal regulations. All study records will be made available to Abbvie representatives upon request. Study site facilities and study records will be made available to regulatory authorities' inspectors if an inspection takes place. The investigator will notify Abbvie if this occurs.

8.2 Statistics

It is desired to enroll 25 patients.
Primary Endpoint: Proportion of participants with improvement (reduction) in worst-itch numeric rating scale (WI-NRS) by ≥4 from baseline to Week 16 [Time Frame: Baseline to Week 12] WI-NRS is a patient-reported outcome (PRO) comprised of a single item rated on a scale from 0 ("No itch") to 10 ("Worst imaginable itch.
Secondary Endpoints: Percent improvement (reduction) in worst-itch numeric rating scale (WI-NRS) by ≥4 from baseline to Week 24
IGA PN-S 0 or 1 at weeks 12 & 24
IGA PN-A 0 or 1 at week 12 & 24
Percent improvement of PN-S & PN-A at week 12 & 24
DLQI improvement at weeks 12 & 24
Adverse Events

8.2.1 Additional Statistical Considerations

The objective of the statistical analyses is to assess the efficacy and safety of upadacitinib for the treatment of subjects with moderate to severe PN who are candidates for systemic therapy. The Primary Analysis for all efficacy endpoints will be conducted after all continuing subjects have completed the study activities up to Week 16. The Intent-to-Treat (ITT) Population consists of all randomized subjects and will be used for the efficacy analyses. A Per-Protocol Population may be defined if deemed necessary to exclude subjects with major protocol violations. The criteria to define the Per-protocol Population will be detailed in the SAP. Subjects to be excluded from the Per-Protocol Population will be finalized before week 16. The Per-Protocol Population, if defined, will be used to analyze the primary efficacy endpoint.

The Safety Population consists of all randomized subjects who received at least 1 dose of study drug. An All Upadacitinib Treated Population consists of all subjects who received at least one dose of upadacitinib in the study. This population will be used to provide a comprehensive summary of safety.

Statistical Analyses for Efficacy

All efficacy endpoints will be analyzed on the ITT population. In addition, the primary efficacy endpoints will be analyzed in the Per-Protocol Population, if defined.

No missing data imputation will be applied, and all assessments prior to premature discontinuation from study drug will be used.

Statistical Analyses for Safety – how will data be summarized? % of patients with AEs?

The safety analyses will be carried out using the Safety Population. % of patients with AE’s will be assessed inclusive of physical examination, laboratory assessments, and vital signabnormalities.

Note that missing safety data will not be imputed.

8.3 Schedule of Events

	V1	V2	V3	V4	V5	V6	V7	V8
Procedures/Non-Procedure Description	SCR	BL	WK4	WK8	WK12	WK16	WK20	WK24
Informed Consent	X							
Medical History and Demographics	X	X						
Inclusion/Exclusion Criteria	X	X						
Prior/Concurrent Medications/Procedures	X	X	X	X	X	X	X	X
Physical Examination	X	X	X	X	X	X	X	X
Serum Pregnancy	X							
Hepatitis B & C profile. Quantiferon Gold	X							
Safety Labs	X					X		X
Urine Pregnancy Test		X	X	X	X	X	X	X
Safety / AE Assessment	X	X	X	X	X	X	X	X
Patient Reported Outcomes / Questionnaires		X	X	X	X	X	X	X
Clinical Severity / Efficacy Assessments	X	X	X	X	X	X	X	X
Pharmacy Dispense/Drug Accountability		X	X	X	X	X	X	X

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7. APPENDICES

Appendix A
INVESTIGATOR'S GLOBAL ASSESSMENT OF PRURIGO NODULARIS: ACTIVITY AND STAGE

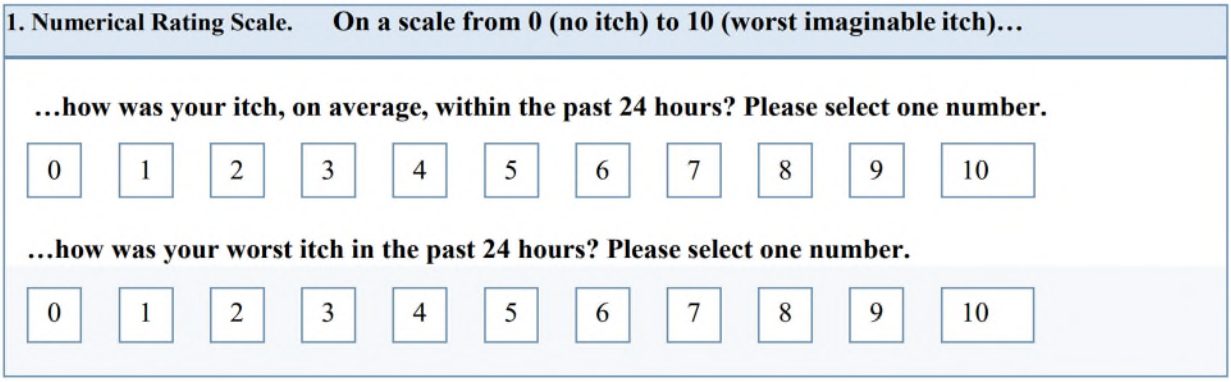
Score	Category	Description: Activity (IGA PN-A)
0	Clear	No nodules have excoriations or crusts

1	**Almost Clear**	Very small proportion of nodules have excoriations or crusts (up to approximately 10% of all nodules)
2	**Mild**	Minority of nodules have excoriations or crusts (approximately 11-25% of all nodules)
3	**Moderate**	Many nodules have excoriations or crusts (approximately 26-75% of all nodules)
4	**Severe**	Majority of nodules have excoriations or crusts (approximately 26-75% of all nodules)

Score	**Category**	**Description: Stage (IGA PN-S)**
0	**Clear**	No nodules (0 nodules)
1	**Almost Clear**	Rare, flattened lesions, with no more than 5 dome-shaped palpable nodules (approximately 1-5 nodules)
2	**Mild**	Few, mostly flattened lesions, with small number of dome-shaped palpable nodules (approximately 6-19 nodules)
3	**Moderate**	Many lesions, partially flattened, and dome-shaped palpable nodules (approximately 20-100 nodules)
4	**Severe**	Abundant lesions, majority are dome-shaped palpable nodules (over 100 nodules)

Appendix B

WI-NRS



Appendix C

Dermatology Life Quality Index

DERMATOLOGY LIFE QUALITY INDEX

DLQI

Hospital No: Date:
Name: Score:
Address: Diagnosis:

The aim of this questionnaire is to measure how much your skin problem has affected your life OVER THE LAST WEEK. Please tick ☑ one box for each question.

1.	Over the last week, how **itchy**, **sore**, **painful** or **stinging** has your skin been?	Very much A lot A little Not at all	❒ ❒ ❒ ❒	
2.	Over the last week, how **embarrassed** or **self conscious** have you been because of your skin?	Very much A lot A little Not at all	❒ ❒ ❒ ❒	
3.	Over the last week, how much has your skin interfered with you going **shopping** or looking after your **home** or **garden**?	Very much A lot A little Not at all	❒ ❒ ❒ ❒	Not relevant ❒
4.	Over the last week, how much has your skin influenced the **clothes** you wear?	Very much A lot A little Not at all	❒ ❒ ❒ ❒	Not relevant ❒
5.	Over the last week, how much has your skin affected any **social** or **leisure** activities?	Very much A lot A little Not at all	❒ ❒ ❒ ❒	Not relevant ❒
6.	Over the last week, how much has your skin made it difficult for you to do any **sport**?	Very much A lot A little Not at all	❒ ❒ ❒ ❒	Not relevant ❒
7.	Over the last week, has your skin prevented you from **working** or **studying**?	Yes No	❒ ❒	Not relevant ❒

	If "No", over the last week how much has your skin been a problem at **work** or **studying**?	A lot A little Not at all	❒ ❒ ❒	
8.	Over the last week, how much has your skin created problems with your **partner** or any of your **close friends** or **relatives**?	Very much A lot A little Not at all	❒ ❒ ❒ ❒	Not relevant ❒
9.	Over the last week, how much has your skin caused any **sexual difficulties**?	Very much A lot A little Not at all	❒ ❒ ❒ ❒	Not relevant ❒
10.	Over the last week, how much of a problem has the **treatment** for your skin been, for example by making your home messy, or by taking up time?	Very much A lot A little Not at all	❒ ❒ ❒ ❒	Not relevant ❒

Please check you have answered EVERY question. Thank you.