Official Title: KPL-716-C201: A Phase 2a/b, Randomized, Double-Blind, Placebo-Controlled Study to Investigate the Efficacy, Safety, Tolerability and Pharmacokinetics of KPL-716 in Reducing Pruritus in Subjects with Prurigo Nodularis

NCT Number: NCT03816891

Document & Date: Protocol Version 6: 19-July-2021

PROTOCOL

KPL-716-C201: A Phase 2a/b, Randomized, Double-Blind, Placebo-Controlled Study to Investigate the Efficacy, Safety, Tolerability and Pharmacokinetics of KPL-716 in Reducing Pruritus in Subjects with Prurigo Nodularis

Protocol Status: Final
Protocol Version 6, 19 July 2021
Protocol Version 5, 21 December 2020
Replaces, Protocol Version 4, 4 September 2020
Replaces Protocol Version 3, 13 May 2019
Replaces Protocol Version 2, 01 February 2019
Replaces Version 1.1, 06 November 2018

Study Drug: KPL-716

Protocol Number: KPL-716-C201
IND Number: 132912

Sponsor:
Kiniksa Pharmaceuticals, Ltd.

Sponsor Medical Contact:
[redacted] MD, PhD
[redacted]

INVESTIGATOR AGREEMENT

I have read the following protocol and agree to conduct the study as described herein.

Investigator's Name (Print)

Investigator's Signature Date

SIGNATURE PAGE

Protocol Title:	A Phase 2a/b, Randomized, Double-Blind, Placebo-Controlled Study to Investigate the Efficacy, Safety, Tolerability and Pharmacokinetics of KPL-716 in Reducing Pruritus in Subjects with Prurigo Nodularis
Study Number:	KPL-716-C201
This study will be conducted in compliance with the clinical study protocol, International Council on Harmonisation (ICH) Good Clinical Practice and applicable regulatory requirements.	
Sponsor Signatory:	Sponsor's electronic signature is appended to this protocol.
[redacted] MD, MPH [redacted] Kiniksa Pharmaceuticals, Ltd. [redacted]	Signature [redacted] Date [redacted]

PROTOCOL CLARIFICATION FOR VERSIONS 4.0 AND LATER

For the purpose of maintaining protocol simplicity and to prevent misinterpretations or mistakes in the Phase 2b portion of the study, all Phase 2a study specifics have been removed, (starting from Version 4.0 of the protocol), as they are no longer applicable to investigational sites participating in the Phase 2b study.

Please refer to Version 3.0 of the protocol for specific Phase 2a study design details.

PROTOCOL SYNOPSIS

Title of Study: A Phase 2a/b, Randomized, Double-Blind, Placebo-Controlled Study to Investigate the Efficacy, Safety, Tolerability and Pharmacokinetics of KPL-716 in Reducing Pruritus in Subjects with Prurigo Nodularis
Phase of Clinical Development: Phase 2a/b
Study Population: Subjects with prurigo nodularis (PN) experiencing severe pruritus will be enrolled in this Phase 2b study.
Study Centers: Approximately 75 study centers are planned in North America, Europe, and Asia-Pacific
Number of Subjects (planned): Approximately 180 subjects
Primary Objective • To evaluate the efficacy of subcutaneous (SC) KPL-716 vs. placebo in reducing pruritus in PN subjects experiencing severe pruritus Secondary Objectives • To evaluate the effect of SC KPL-716 vs. placebo in improving sleep in PN subjects experiencing severe pruritus • To evaluate the effect of SC KPL-716 vs. placebo in improving quality of life in PN subjects experiencing severe pruritus • To evaluate the effect of SC KPL-716 vs. placebo in reducing disease severity in PN subjects experiencing severe pruritus • To evaluate the safety and tolerability of SC KPL-716 vs. placebo in PN subjects experiencing severe pruritus • To evaluate the pharmacokinetics (PK) of SC KPL-716 in PN subjects experiencing severe pruritus Exploratory Objectives • To evaluate the immunogenicity of SC KPL-716 in PN subjects experiencing severe pruritus • To evaluate the effect of KPL-716 vs. placebo on skin and blood biomarkers • To evaluate the correlation between KPL-716 responsiveness and co-morbidities in PN

Primary Efficacy Endpoint for Phase 2b

- Percent change from baseline in weekly average Worst Itch–Numeric Rating Scale (WI-NRS) at Week 16

Key Secondary Efficacy Endpoints for Phase 2b

- Proportion of subjects achieving at least a 6-point reduction from baseline in weekly average WI-NRS at Week 16
- Proportion of subjects achieving at least a 4-point reduction from baseline in weekly average WI-NRS at Week 16
- Proportion of subjects achieving 0 or 1 in PN-IGA at Week 16

Other Secondary Efficacy Endpoints for Phase 2b

Related to pruritus:

- Change and percent change from baseline in weekly average of WI-NRS over time
- Proportion of subjects achieving at least a 6-point reduction from baseline in weekly average WI-NRS over time.
- Proportion of subjects achieving at least a 4-point reduction from baseline in weekly average WI-NRS over time.

Related to disease severity:

- Proportion of subjects achieving 0 or 1 in PN-IGA over time
- Proportion of subjects with at least 2-point improvement from baseline in PN-IGA over time
- Proportion of subjects achieving 0 or 1 in Investigator's Global Assessment for Prurigo Nodularis-Stage (IGA-CNPG-S) over time
- Proportion of subjects with at least 2-point improvement from baseline in IGA-CNPG-S over time

Related to sleep:

- Change and percent change from baseline in weekly average of Sleep Loss Visual Analog Scale (VAS) over time

Related to quality of life:

- Change and percent change from baseline in ItchyQoL over time

Exploratory Efficacy Measures for Phase 2b:

- Proportion of subjects achieving 0 or 1 in IGA-CNPG-Activity (IGA-CNPG-A) over time
- Change from baseline in Prurigo Nodularis Nodule Assessment Tool (PN-NAT) over time
- Change from baseline in the total score of Patient Health Questionnaire (PHQ-9) over time
- Change from baseline in the total score of General Anxiety Disorder (GAD-7) over time
- Days and proportion of subjects using rescue medication over time

- Patient Global Impression of Prurigo Nodularis Severity (PGI-PN-S) over time
- Patient Global Impression of Change (PGIC) over time
- Change from baseline in skin and blood biomarkers over time

Safety Parameters for Phase 2b:

- Incidence rate and severity of treatment-emergent adverse events (TEAEs)
- Incidence rate and severity of study drug-related TEAEs
- Vital signs, electrocardiogram (ECG), and clinical laboratory test results

Other Parameters for Phase 2b:

- PK: Measurement of plasma concentrations of KPL-716
- Immunogenicity: Measurement of anti-drug (anti-KPL-716) antibodies (ADA)

Study Design for Phase 2b:

This is a randomized, double-blind, placebo-controlled study to investigate the efficacy, safety, tolerability, PK, and immunogenicity of KPL-716 administered SC in PN subjects experiencing severe pruritus.

The Phase 2b study (Figure 1) will consist of a 4-week Screening Period and a 16-week Double-Blind Period, followed by a 36-week Open-Label-Extension (OLE) Period. Approximately 180 PN subjects experiencing severe pruritus, will be randomized (at 1:1:1:1 ratio) into one of the following 4 arms: KPL-716 540 mg SC, once every 4 weeks (Q4W); KPL-716 360 mg SC, Q4W; KPL-716 120 mg SC, Q4W; or placebo SC, Q4W. A total of 4 doses of study drug will be administered during the Double-Blind Period to measure the efficacy, safety, and PK of KPL-716. The Phase 2b will utilize a washout monotherapy design in which concomitant therapies that could impact pruritus or disease severity will be prohibited from designated windows through the end of the OLE Period, thus removing the confounding effect of these therapies on the assessment of KPL-716 efficacy. Should subjects experience an exacerbation of symptoms that is significant enough to warrant intervention, oral antihistamines and/or topical corticosteroids may be provided 4 weeks post-randomization, as outlined in the Pharmacy Manual. The days of rescue medication use will be recorded by subjects in an e-Diary and types and duration of rescue medications used will be recorded as a concomitant medication.

After the Double-Blind Period, all subjects will have the option to receive KPL-716 360 mg SC, Q2W during the OLE Period to evaluate the long-term safety and PK. For subjects who complete the Double-Blind Period but choose not to participate in OLE, or who terminate earlier, an End of Study (EOS) Visit will be required 4 weeks following the date of last study drug dose.

An interim analysis may be performed after at least 50% of subjects have completed the Week 16 Visit. Additional details regarding the interim analysis, if performed, will be provided in the Statistical Analysis Plan (SAP) along with other analysis plan(s).

Subjects will follow the schedule below:

- Screening Period (minimum 7 days and maximum 28 days)
- Double-Blind Period (Day 1 [Baseline] to Week 16)
- Open-Label-Extension Period (End of Week 16 to Week 52)

The allowable visit window from Week 4 to Week 16 is ± 2 days and thereafter to Week 52 is ± 3 days.

At any point following randomization, home health nursing or telemedicine services may be applied to accommodate COVID-19 limitations to in-person visits and dosing.

Screening Period for Phase 2b:

After the informed consent form (ICF) is signed, subjects will enter the Screening Period for assessment of eligibility.

During the Screening Period, subjects' medical and surgical history will be reviewed including allergic history. Review of medical history will include PN disease history (year of first PN nodule and year of diagnosis) and history of co-morbidities. Prior and concomitant medications, therapies and procedures will be recorded for PN and any other medical condition. Vital signs will be measured, and subjects will undergo a full physical examination. Clinical laboratory tests and an ECG will be performed. Urine drug screen and pregnancy test (if applicable) will also be performed.

To be eligible, subjects must have a physician-documented diagnosis of PN with at least 20 nodules of approximately 0.5 to 2 cm. The nodules must be pruritic and present on at least 2 different anatomical locations (not be localized), involve the extremities, with extensor extremity involvement greater than the flexor extremity involvement. Nodules on the head (face and scalp) are not counted as an anatomical location for eligibility criteria. Each arm, each leg, and the trunk are considered different anatomical locations. The minimum required duration of disease is at least 6 months from the time of first PN nodule to Day 1, as affirmed by the subject.

At the Screening Visit, subjects will be asked to rate their pruritus severity (worst itch) over the last 24 hours on the WI-NRS. In addition, subjects will record their WI-NRS on a daily basis during the Screening Period. Subjects will be given training on Accurate Symptom Reporting and Placebo Response Reduction during the Screening Visit, Baseline Visit, and Visits of Weeks 4, 8 and 12, or as needed. The daily recordings can begin any time after the Screening Visit. Subjects will use internet connected devices for daily electronic recordings. To be eligible for study participation, subjects must have severe pruritus, defined as WI-NRS ≥7 at the Screening Visit and a mean weekly WI-NRS ≥7 for the week (7 consecutive days) immediately prior to randomization (at least 5 days recordings) on e-Diary.

During the Screening Period, whole-body medical photographs will be taken (upper front, lower front, upper back, and lower back) without the face and with the genitals covered. In addition, a representative area of disease will be determined by the PI at the Screening Visit, and medical photographs of this area will be taken and followed throughout the study. Medical photographs will be used for confirmation of diagnosis of PN as defined in the Study Manual and for assessment of disease severity over time. Subjects may be asked to return to the study site during the Screening Period for unscheduled visits for repeat screening procedures if needed.

Additional assessments during the Screening Period include those related to pruritus, sleep, quality of life, anxiety and depression and disease severity, etc. (see Schedule of Activities for details). Subjects will be instructed on the required washout for specific excluded medications. The subject reported daily recordings (WI-NRS and rescue medication use) will continue throughout the study for eligible subjects that proceed to dosing.

Collection of AEs and concomitant medications will begin after signing the ICF and will continue until the EOS Visit. For Schedule of Activities, please see Appendix 1.

In an effort to minimize subject burden and/or risk during the COVID-19 pandemic, sites may offer to split the Screening Visit into two parts; a virtual preliminary Screening Visit in which some assessments may be performed [e.g. ICF, medical history, concomitant medications, subject questionnaires (completed electronically) and some eligibility criteria], followed by an in-person visit in which all remaining eligibility assessments may be performed that require subjects to be

physically present (e.g. blood collection for clinical laboratories, ECG, medical photography, vital signs, and disease severity assessments).

Treatment Period for Phase 2b:

Pre-dose:

Prior to dosing on Day 1, subjects will undergo an additional review of eligibility, medical and surgical history, prior and concomitant medications, therapies, procedures, and AEs. Clinical laboratory results from the Screening Visit will be reviewed. Compliance with recording of daily WI-NRS for the 7 days immediately prior to dosing will also be reviewed. Urine drug screen and pregnancy test (if applicable) will be performed. Vital signs will be measured. ECG and a full physical examination will be performed.

Eligible subjects will undergo collection of safety blood and urine samples as well as blood samples for PK, ADA, and potential blood biomarkers. Medical photographs will be taken of the representative area of disease identified during the Screening Period. Whole-body photographs (upper front, lower front, upper back, and lower back) without the face and with genitals covered will also be captured prior to the first dose.

For subjects who provide additional consent for the collection of skin biopsies (optional), the biopsies (one lesional and one non-lesional) will be performed, along with medical photographs of the biopsy areas prior to biopsy collection.

Upon confirmation of subject eligibility and completion of required activities (Appendix 1), subjects will be randomized and proceed to dosing.

Randomization and Dosing:

Subjects will be randomized 1:1:1:1 to receive different dosing regimens of KPL-716 or placebo. At the end of the Double-Blind Period, all subjects will have the option to enter the OLE Period to receive KPL-716 360 mg SC Q2W. Stratification will be performed based on sex and years since the first nodule observed (i.e., ≥10 years vs. <10 years).

Subjects will be observed for 1-hour post-dosing with vital signs monitored. All doses of KPL-716 or matching placebo will be administered by the Investigator, a qualified investigational site designee, or home health nurse (in case of COVID-19 disruption) via SC injection during the Double-Blind Period.

Phase 2b:

- Arm A: KPL-716, 540 mg, SC, every 4 weeks
- Arm B: KPL-716, 360 mg, SC, every 4 weeks
- Arm C: KPL-716, 120 mg, SC, every 4 weeks
- Arm D: Placebo, SC, every 4 weeks

The dose levels and dosing intervals for Phase 2b have been chosen based on Phase 2a results so as not to exceed exposures observed in Phase 2a.

All procedures assigned to dosing days will be performed prior to study drug administration. The following activities will take place prior to each dose during the Double-Blind Period:

- Review of concomitant medications, therapies, and procedures
- Review of AEs
- Review of subject e-Diary compliance
- Vital signs (performed before and after dosing on each dosing day)

- Collection of blood for PK
- Completion of Sleep Loss VAS

The following activities will take place prior to dosing at designated study visits as outlined in Appendix 1:

- Physical examination and ECG
- Collection of safety blood and urine samples
- Pregnancy test (if applicable)
- Collection of PK and/or blood biomarker samples
- Medical photography
- Completion of patient questionnaires (ItchyQoL PHQ-9, GAD-7, PGI-PN-S, PGIC)
- Assessment of disease severity (PN-NAT, PN-IGA, IGA-CNPG-S, IGA-CNPG-A)
- Skin biopsies (optional)

AEs and concomitant medications will be collected throughout the study. Subjects will continue to complete their daily questionnaire on pruritus (WI-NRS) and rescue medication use until the EOS Visit.

In case of study drug discontinuation, subjects will continue to follow the schedule of activities for each visit minus study drug administration. Under these circumstances, the second set of biopsies (optional) will be performed at the earliest possible visit following early Double-Blind Period drug discontinuation, if applicable. In case of study drug interruption or missed dosing visits, subjects will resume the schedule of activities in accordance with their study day. In case of early withdrawal from the entire study, subjects will complete an EOS Visit 4 weeks after the last dose. In addition, if early termination occurs prior to the end of treatment period, biopsies should be collected at the EOS visit, if applicable.

Open-Label Extension Period for Phase 2b:

During the OLE Period, subjects will be administered KPL-716, 360 mg, SC, Q2W with the last dosing at Week 48 Visit. Subjects may be permitted to self-administer KPL-716 as an outpatient during the OLE provided the Safety Review Team (SRT) determines that the available safety and tolerability data support outpatient self-administration, the Investigator and the Medical Monitor approve the individual case, and the subject receives adequate training and successfully performs 3 KPL-716 self-administrations (e.g., Weeks 16, 18, and 20) under the supervision of study site personnel. If self-administration is not authorized by the SRT, the Investigator, or the Medical Monitor, or if an individual subject is unable/unwilling to perform self-administration, KPL-716 will continue to be administered by the Investigator, a qualified investigational site designee or home health nurse. During the OLE Period, subjects will also undergo vital signs measurement, review of concomitant medications, therapies and procedures, review of AEs, monitoring of compliance, and PK blood sample collection at visits according to the Schedule of Activities. Sleep Loss VAS, physical examination, clinical laboratory tests (including pregnancy testing if applicable), quality of life assessment, and evaluation of disease severity will be performed at designated visits. Subjects will continue to complete their daily questionnaires on pruritus and rescue medication use throughout the OLE Period. Should subjects self-administer drug, collection of AEs, concomitant medication use, and NRS compliance assessments at visits as outlined in Appendix 1 may be completed remotely by study staff.

The EOS Visit will include vital signs, full physical examination, ECG, clinical laboratory blood tests, urinalysis, and urine pregnancy test (if applicable) as well as PK, ADA, and biomarker blood sampling. Biopsies for biomarker assessment will be collected from subjects who provide

additional consent. All efficacy assessments for pruritus, sleep, quality of life and disease severity will also be completed at this visit. Medical photography of the whole body and the representative area (identified during the Screening Period and followed throughout the study) will be obtained. All subjects will complete an EOS Visit.

Duration of Phase 2b:

The planned study duration per subject for Phase 2b will be approximately 56 weeks including a maximum of 4 weeks for the Screening Period, 16 weeks for the Double-Blind Period, and 36 weeks for the OLE Period.

The minimum duration for the Screening Period will be 7 days.

Study Drug:

Study Drug: KPL-716 or matching placebo

Active Substance: KPL-716

Strength, Formulation, and Route of Administration: 180 mg/mL solution [redacted], subcutaneous administration.

Matching placebo: [redacted], subcutaneous administration.

Study Treatment:

For Phase 2b, subjects will be randomized to receive KPL-716 or matching placebo on Day 1 and will remain in the same treatment arm throughout the Double-Blind Period, then all subjects will have the option to participate in the OLE Period, starting dosing at the End of Week 16 Visit.

Phase 2b:

- Arm A: KPL-716 at 540 mg SC on Day 1 and at Weeks 4, 8, and 12 during the Double-Blind Period
- Arm B: KPL-716 at 360 mg SC on Day 1 and at Weeks 4, 8 and 12 during the Double-Blind Period
- Arm C: KPL-716 at 120 mg (see Pharmacy Manual for formulation instructions) SC on Day 1 and at Weeks 4, 8 and 12 during the Double-Blind Period
- Arm D: Placebo SC on Day 1 and at Weeks 4, 8, and 12 during the Double-Blind Period

Study Assessments:

Efficacy Assessment:

Efficacy in reduction of pruritus will be assessed via daily recording of WI-NRS. Efficacy in improvement of sleep will be assessed via Sleep Loss VAS. Impact on quality of life will be assessed via ItchyQoL, PHQ-9, and GAD-7. Impact on disease severity will be followed by PN-IGA, PN-NAT, IGA-CNPG-S, IGA-CNPG-A, PGI-PN-S, and PGIC. See Schedule of Activities Appendix 1.

An area representative of the subject's disease will be chosen at the Screening Visit and followed over time through medical photography at designated time points. Whole-body photographs and/or images of biopsy locations (prior to collection of biopsies), if applicable, will be taken at indicated study visits.

Skin biopsies will be collected pre- and post-treatment during this study. Skin biopsies are encouraged but optional. Two individual punch biopsies (one from lesional skin and one from adjacent non-lesional skin) will be collected prior to dosing at Day 1, and post-treatment biopsies

will be collected at Week 16 or EOS. Biopsy collection procedures and processing will be outlined in a separate manual.

Safety Assessments:

Safety will be assessed by monitoring of AEs, measurements of vital signs, physical examination, ECG evaluation, and clinical laboratory tests.

PK Assessment:

PK blood samples will be collected from all subjects as specified in the Schedule of Activities. PK samples will be collected pre-dose on dosing days.

Biomarker Assessment:

Blood samples will be collected from all subjects for biomarkers analysis. Biomarker samples will be collected pre-dose on dosing days as specified in the Schedule of Activities.

Immunogenicity Assessment:

Blood samples for ADA assessment will be collected from all subjects pre-dose on dosing days as specified in the Schedule of Activities.

Selection of Phase 2b Study Population:

Inclusion Criteria:

1. Male or female aged 18 to 80 years, inclusive, at the time of consent.
2. Have a physician-documented diagnosis of PN that is confirmed by review of medical photography (as outlined in the Study Manual) during the Screening Period. Duration of PN (since the time of first PN nodule) must be at least 6 months from the time of first PN nodule to Day 1, as affirmed by the subject.
3. Have at least 20 nodules of approximately 0.5 to 2 cm at the Screening Visit and Day 1. The nodules must be pruritic and present on at least 2 different anatomical locations (not be localized), involve the extremities, with extensor extremity involvement greater than the flexor extremity involvement. Nodules on the head (face and scalp) are not counted as an anatomical location for eligibility criteria. Each arm, each leg, and trunk are considered different anatomical locations.
4. Subject has severe pruritus, defined as WI-NRS ≥7 at the Screening Visit and a mean weekly WI-NRS ≥7 for the week (7 consecutive days) immediately prior to randomization (at least 5 days of recordings) on eDiary.
5. PN-IGA score of ≥3 (on a scale of 0-4, in which 3 is moderate and 4 is severe) at Screening and Baseline Visits
6. Sexually active female subjects must be:
   - postmenopausal, defined as at least 12 consecutive months post cessation of menses (without an alternative medical cause) and confirmed by a follicular stimulating hormone (FSH) test, or
   - surgically sterile following documented hysterectomy, bilateral salpingectomy, bilateral oophorectomy or
   - nonpregnant, nonlactating, and having agreed to use a highly effective method of contraception from the Screening Visit until 16 weeks after final study drug administration.
     - Note: highly effective methods of contraception include:

- hormonal contraceptives associated with inhibition of ovulation (stable dose for at least 4 weeks prior to first dose)
- intrauterine device
- intrauterine system
- double barrier methods of contraception (barrier methods include male condom, female condom, cervical cap, diaphragm, contraceptive sponge) in conjunction with spermicide.
- tubal ligation
- vasectomized male partner

7. Sexually active male subjects must have documented vasectomy or must agree to use a highly effective method of contraception as defined above with their partners of childbearing potential from first dose until 16 weeks after final study drug administration.
8. Male subjects must agree to refrain from donating sperm from first dose until 16 weeks after the last study drug administration. Female subjects must agree to refrain from donating eggs from first dose until 16 weeks after the last study drug administration.
9. Female of childbearing potential must have a negative serum β-hCG test at the Screening Visit and negative urine pregnancy test on Day 1.
10. Able to comprehend and willing to sign an Informed Consent Form and able to abide by the study restrictions and comply with all study procedures for the duration of the study.
11. Subjects must be on optimized and stable treatment for co-morbidities for at least 28 days prior to Day 1.

Exclusion Criteria:

1. Use of the following medications within the indicated timeframe prior to Day 1 and does not agree to refrain from the use of the medications throughout the study (except those specified in the Pharmacy Manual):
    a. Systemic corticosteroids (IV/IM/oral): 4 weeks; Note: Intranasal corticosteroids, eye drops containing corticosteroids, and inhaled corticosteroids for stable medical conditions are allowed.
    b. Intralesional corticosteroids and intra-articular corticosteroids: 6 weeks
    c. Topical treatments for PN including but not limited to corticosteroids, calcineurin inhibitors, phosphodiesterase inhibitors, retinoids, calcipotriol, capsaicin, camphor, polidocanol, cannabinoids, gabapentin, or tars: 2 weeks
    d. Antihistamines: 2 weeks
    e. Immunomodulators (for example, cyclosporin, methotrexate, retinoids, azathioprine, mycophenolate, and thalidomide): 4 weeks
    f. Neuroactive drugs such as gabapentin and pregabalin: 4 weeks
    g. Cannabinoids: 2 weeks
    h. Opioid antagonists or agonists: 5 half-lives if known or 4 weeks
    i. Janus kinase inhibitors: 5 half-lives if known or 4 weeks
    j. Dupilumab: 8 weeks
    k. Any other marketed biologic: 5 half-lives or within 4 months of using rituximab

l. Any investigational drug: 5 half-lives

m. Phototherapy involving UVA, UVB, or excimer: 4 weeks

n. Tanning salon use: 4 weeks

o. Live attenuated vaccine: 12 weeks

2. Has received any investigational biologic or non-biologic drug that targets Oncostatin M, IL-31, IL-31 receptor α, or Oncostatin M receptor β in the past 3 months.
3. Required rescue therapy for PN during the Screening Period or expected to require rescue therapy within 4 weeks following the Baseline Visit.
4. Has a significant exacerbation and/or skin eruption during the Screening Period (prior to the study drug administration) that requires medical intervention.
5. Presence of scabies, insect bite, lichen simplex chronicus, psoriasis, acne, folliculitis, habitual picking, lymphomatoid papulosis, chronic actinic dermatitis, dermatitis herpetiformis, sporotrichosis, bullous disease, and/or skin condition other than PN or atopic dermatitis unless approved by the Sponsor.
6. Plan to change emollients or moisturizers, or to have bath oil treatment for relief of pruritus during the course of the trial.
7. Presence of psychogenic pruritus or neuropathic pruritus at the Screening Visit.
8. Presence of severe depression as indicated by PHQ-9 total score of ≥20 or item 9 score >0 at the Screening Visit or Day 1.
9. Presence of severe anxiety as indicated by GAD-7 score of ≥15 at the Screening Visit or Day 1.
10. Presence of severe chronic pain (e.g., back pain, migraine, osteoarthritis, etc., defined as ≥7.0 on 0 to 10 NRS scale with 0 being no pain and 10 being the worst pain possible) at the Screening Visit.
11. Presence of uncontrolled hyperthyroidism or hypothyroidism or uncontrolled diabetes defined as hemoglobin A1c >7.5%.
12. Presence or history of cancer or lymphoproliferative disease within 5 years prior to the Screening Visit, with the exception of basal and squamous cell carcinoma of the skin or in situ carcinoma of the cervix successfully treated and considered controlled.
13. Presence or history of immune deficiency, or opportunistic infections.
14. Positive results for hepatitis B surface antigen (HbsAg) and/or hepatitis B anti-core antibody (anti-HBc) but negative results for anti-surface antibody (anti-HBs) at the Screening Visit.
15. Positive results for hepatitis C antibody unless patient received curative therapy and a negative viral load is documented.
16. Human immunodeficiency virus (HIV) infection or positive HIV serology at the Screening Visit.
17. Positive COVID-19 viral test at the Screening Visit or suspected COVID-19 infection at the Baseline Visit.
18. Subject is on hemodialysis or peritoneal dialysis.
19. Latent or active TB, as determined by a positive Quantiferon-based TB test result at the Screening visit.

20. Laboratory abnormalities that fall outside the windows below at the Screening Visit:
    a. Alanine aminotransferase >3 x upper limit of normal (ULN)
    b. Aspartate aminotransferase >3 x ULN
    c. Gamma-glutamyl transferase >3 x ULN
    d. Blood bilirubin >2 x ULN
    e. Hemoglobin more than 1g/dL below the lower limit of normal for sex per the laboratory in which screening lab is performed.
    f. Platelet count <150,000/ µL
    g. Neutrophil count < 1,500/µL
21. Major surgery within 12 weeks prior to Day 1 or has a major surgery planned during the study.
22. Has an active infection, including skin infection, requiring systemic treatment within 4 weeks and/or topical treatment within 2 weeks of Day 1. Subject has an active or chronic parasitic infection.
23. Any medical or psychiatric condition which, in the opinion of the Investigator or the Sponsor, may place the subject at increased risk as a result of study participation, interfere with study participation or study assessments, affect compliance with study requirements, or complicate interpretation of study results.
24. Has a known hypersensitivity to KPL-716 or its excipients.
25. Has a known history of drug or alcohol abuse in the last 2 years prior to Day 1. Has more than eight drinks (5 ounces of wine, 12 ounces of beer or 1.5 ounces of liquor) weekly for females and 15 drinks weekly for males.
26. Has a positive urine drug screen for opiates, opioids, methadone, cocaine, phencyclidine, or amphetamines at the Screening Visit or Day 1. Exceptions may be made if a subject is on a medication for a stable concomitant condition that explains the positive drug screen result.
27. Has had a severe allergic reaction to any foods or medications including anaphylactic reactions, unless approved by the Sponsor.
28. For subject providing consent for the optional skin biopsy, presence or history of coagulation disorders, hypertrophic scar, or keloid, or currently under treatments with chronic anti-coagulants (aspirin ≤ 325mg/day is acceptable).

Statistical Methods for Phase 2b:

All clinical study data will be presented in subject data listings. Descriptive statistics will be presented for all endpoints and will include number of subjects (n), mean, standard deviation, first quartile, median, third quartile, minimum and maximum for continuous variables, and frequency and percentage for categorical and ordinal variables.

Statistical analyses for the Phase 2a and Phase 2b portions of the study will be conducted separately. An integrated analysis of the pooled data may be performed at the end of the study depending on the results of these individual analyses. The primary efficacy endpoint in Phase 2b will be analyzed with ANCOVA including treatment as fixed effect, baseline WI-NRS, and randomization stratification factor as covariates.

For key secondary efficacy endpoints, the difference of proportions and the corresponding 95% CI for the difference of proportions will be displayed. Treatment groups will be compared using a

Cochran-Mantel-Haenszel test controlling for the randomization stratification variables. Details for the analyses including handling subjects randomized to different treatment durations and dose levels will be specified in the SAP.

Multiple comparison/Multiplicity:

As this is a dose finding study, there is no multiplicity adjustment planned for the comparisons of multiple doses of KPL-716 versus placebo.

Determination of Sample Size:

The Phase 2b sample size calculation is based on the primary efficacy endpoint (percentage change from baseline of WI-NRS at Week 16) using a two-sample t-test.

Approximately 180 subjects in total will be equally randomized to the 4 arms of Phase 2b. At Week 16, 53% and 30% reduction in weekly average of WI-NRS are assumed for KPL-716 and placebo arms, respectively. For each comparison, assuming treatment effect of 23% difference in weekly average WI-NRS reduction from baseline at Week 16 and standard deviation of 35%, and two-sided alpha of 0.05, 38 subjects in each arm will guarantee 80% power to the treatment effect. Approximately 45 patients in each arm are required after adjusting for 15% lost follow up.

Randomization Strata:

- Sex: Male vs Female
- Years since first nodule observation: ≥10 years vs <10 years

Analysis Sets:

Modified Intent-to-Treat Analysis Sets:

All randomized subjects who receive at least 1 dose of KPL-716 or placebo and have at least 1 post-baseline efficacy assessment in the double-blind Treatment Period will be included in the modified intent-to-treat (mITT) analysis set.

Safety Analysis Sets:

All randomized subjects who take at least 1 dose of KPL-716 or placebo will be included in the Safety Analysis Set.

Per Protocol (PP) Analysis Sets:

All mITT subjects who have no important protocol deviations that may potentially bias efficacy analyses of the study will be included in the PP set.

Pharmacokinetic (PK) Analysis Sets:

Subjects who received KPL-716 and who had at least one PK sample will be included in the PK population.

Analysis of Efficacy:

The primary efficacy endpoint in Phase 2b will be analyzed with ANCOVA including treatment as fixed effect, baseline WI-NRS, and randomization as covariates. Details will be specified in the Phase 2b SAP.

Analysis of Safety:

All safety analyses will be conducted based on the Safety Analysis Set. Summary tables will be done for safety endpoints (treatment emergent AEs, labs, vital signs, etc.). All safety data will be listed by subject. Details for the analysis of safety data will be provided in the SAP.

PK Analyses:

For all subjects, serum samples will be collected before each dose at time points shown in Appendix 1 in order to quantify concentrations of KPL-716. Descriptive statistics will be calculated for the serum concentrations of KPL-716 by visit. Individual listings of plasma concentrations will be provided.

Biomarker Analyses:

Skin and blood biomarker levels will be analyzed.

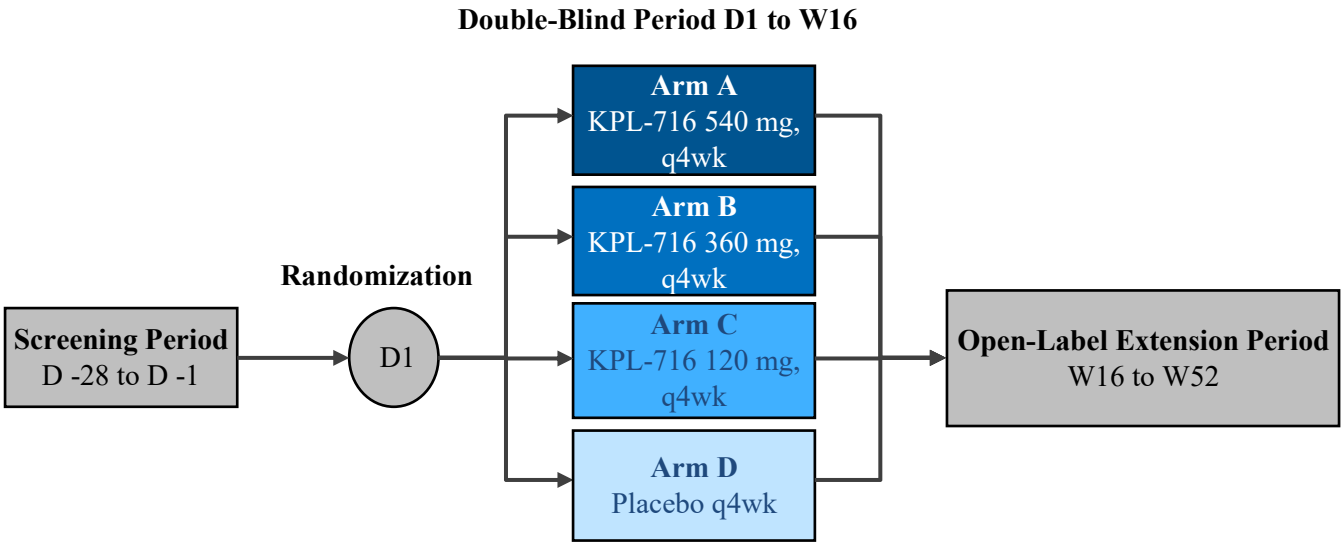
Immunogenicity Analyses:

Serum ADA will be listed and summarized by treatment group and overall using descriptive statistics.

Interim Analysis:

An interim analysis for Phase 2b portion may be conducted after at least 50% subjects complete Week 16 Visit. If the interim analysis is conducted in the Phase 2b part, a two-sided alpha of 0.0001 will be spent. The two-sided alpha level for the final Phase 2b efficacy analysis will be 0.05. Additional details regarding the interim analysis, if performed, will be provided in the SAP along with other analysis plans.

Figure 1 Phase 2b Study Design Diagram



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LIST OF ABBREVIATIONS

Abbreviation or Specialist Term	Explanation
ADA	anti-drug antibodies (anti-KPL-716 antibodies)
AE	adverse event
AESI	AE of special interest
Anti-HBc	hepatitis B core antibody
Anti-HBs	hepatitis B surface antibody
ASR	Accurate Symptom Reporting
ATC	Anatomical Therapeutic Chemical
$AUC_{0-\infty}$	Area under the concentration-time curve from time zero to infinity
β-hCG	β-human chorionic gonadotropin
BMI	body mass index
C_{max}	maximum concentration
CRO	Clinical Research Organization
EDC	electronic data capture
ECG	electrocardiogram
eCRF	electronic Case Report Form
EOS	end of study
FSH	Follicle-stimulating hormone
GAD-7	General Anxiety Disorder
HBV	hepatitis B virus
HbsAg	hepatitis B surface antigen
HCV	hepatitis C virus
HIV	human immunodeficiency virus
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Council for/Conference on Harmonization
IEC	International Ethics Committee
IGA-CNPG-A	Investigator's Global Assessment for Prurigo Nodularis-Activity
IGA-CNPG-S	Investigator's Global Assessment for Prurigo Nodularis-Stage
IMP	investigational medicinal product
IRB	Institutional Review Board
ISR	injection site reaction
IWRS	interactive web response system
LIFR	leukemia inhibitory factor receptor
MedDRA	Medical Dictionary for Regulatory Activities
NOAEL	no observed adverse effect level
NRS	Numerical Rating Scale
OSM	oncostatin M
OSMRβ	oncostatin M Receptor beta
PD	pharmacodynamic(s)
PGI-PN-S	Patient Global Impression of Prurigo Nodularis Severity
PGIC	Patient Global Impression of Change
PHQ-9	Patient Health Questionnaire

Abbreviation or Specialist Term	Explanation
PK	pharmacokinetic(s)
PN	prurigo nodularis
PN-IGA	Prurigo Nodularis Investigator Global Assessment
PP	per-protocol
PRR	Placebo Response Reduction
PT	preferred term
Q	quartile
QTcF	QT interval corrected for heart rate using Fridericia's method
SAE	serious adverse event
SAP	Statistical Analysis Plan
SC	subcutaneous(ly)
SOC	System Organ Class
SRT	Safety Review Team
TEAE	treatment-emergent adverse event
ULN	upper limit of normal
VAS	Visual Analog Scale
WI-NRS	Worst Itch Numeric Rating Scale

1 INTRODUCTION

1.1 Background

Prurigo nodularis (PN) is a chronic skin disease characterized by symmetrically distributed, intensely pruritic hyperkeratotic nodules most frequently affecting extensor extremities and the trunk (1, 2). PN is recognized as the nodular subtype of a recently described umbrella condition called Chronic Prurigo, which encompasses a larger variety of lesions ranging from papule to umblicated ulcers to plaques (1).

There are no 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, antiepileptics and antidepressants, phototherapy and photochemotherapy are often tried with limited success and in some cases with unfavorable risk benefit ratio (3). As a result, PN carries a significant unmet medical need as the intractable itching, the intense scratching and the ensuing skin lesions lead to sleep loss, embarrassment, anxiety, and depression and overall diminish quality of life (4).

Histologically, PN is characterized by thick compact orthohyperkeratosis, irregular epidermal hyperplasia, increased capillaries, an inflammatory infiltrate consisting of mainly lymphocytes and macrophages and to a lesser degree eosinophils and neutrophils, increased fibroblasts, and vertical fibrosis of the papillary dermis (5). Although the exact etiology of PN is unknown, the symptomatology of the disease implicates pruritic pathways and its histologic features point to epidermal activation, inflammation, and fibrosis.

PN is associated with a number of co-morbidities including infections (HIV and hepatitis C), chronic kidney disease, malignancies, endocrine, hematologic, gastrointestinal, cardiovascular, pulmonary, dermatologic and psychiatric conditions (6, 7). Chronic pruritus is a feature of many of these co-morbidities. In a subset of patients with chronic pruritus, whether idiopathic in origin or in association with a co-morbidity, chronic pruritus and chronic scratching lead to neuronal sensitization and the onset of a vicious itch-scratch cycle that ultimately results in the development of nodules. Although chronic pruritus in the context of an underlying condition can trigger PN, once PN develops its clinical course and severity appear to be independent of the original underlying condition such that treatment of the underlying condition is not sufficient to treat PN (1).

In addition to published studies describing cohorts of PN patients (6, 7, 8, 9) , Kiniksa undertook an observational study, which enrolled 54 PN patients in the United States and Europe, to understand better the clinical manifestations, standard of care management, natural history and pathogenesis of the disease (Data on file at Kiniksa). In approximately 13% to 50% of patients, no underlying condition was identified as the trigger for the chronic pruritus that led to PN suggesting that some patients may have an idiopathic form of the disease (7 and Data on file at Kiniksa). The two largest published studies, with 108 patients in Germany and 909 patients in the US, found atopic dermatitis in association with PN in only 7 and 10.7% of PN patients, respectively (6, 7). Although atopic dermatitis is not a common underlying condition in PN, atopic disposition is believed to be prevalent with 46% and 65% of patients described to have atopic diathesis in 2 separate studies (7 and 9). Whether presence of atopy impacts the pathogenesis of PN and/or its clinical course and whether it defines a specific subset of patients remains to be seen. In a broader sense, it also remains to

be seen whether the presence or absence of an underlying condition or the type of underlying condition impacts the mechanism of disease in PN or whether all circumstances lead to a common pathway of chronic pruritis that drives disease pathogenesis in PN.

The primary objective of this study is to investigate the efficacy of KPL-716 in reducing pruritus in PN. The secondary objectives are to investigate the impact of KPL-716 on sleep loss, quality of life and disease severity. Clinical response and/or biomarker studies will be used to understand whether KPL-716 responsiveness is limited to a specific subset of patients with PN. For the rationale of the study, please see Section 1.3.

1.2 Summary of Nonclinical Pharmacology

A series of in vitro studies have been conducted with KPL-716 to characterize its binding properties and biologic activity. For details on the in vitro profiles, refer to the Investigator's Brochure (IB).

KPL-716 was well tolerated in multi-dose 7-week and 26-week primate toxicity studies. In the 7-week toxicity study, cynomolgus monkeys were dosed once every other week with either an intravenous (IV) bolus injection of up to 500 mg/kg KPL-716 or a subcutaneous (SC) injection of 300 mg/kg KPL-716, for a total of 3 doses. The multi-dose, 7-week, preclinical toxicology study in cynomolgus monkeys revealed no specific toxicities, and the no observed adverse effect levels (NOAELs) for systemic toxicity were 500 mg/kg for IV administration and 300 mg/kg for SC administration. For further details, refer to the IB.

In the chronic toxicology study, weekly administration of KPL-716 by IV bolus injection or SC at doses up to 200 mg/kg IV/SC for 26 weeks (27 total doses) was well tolerated in cynomolgus monkeys. Based on these results under the conditions and duration of the study provided in the preliminary report, the NOAEL was considered to be 200 mg/kg IV/SC, the highest dose tested. A low level of anti-drug antibody (ADA) response was noted in the toxicity study, which was not unexpected because KPL-716 is a fully human antibody. The magnitude of the ADA response was judged to be insufficient to impact toxicokinetic evaluations

1.3 Study Rationale

KPL-716 is a first-in-class, fully human monoclonal antibody against oncostatin receptor beta (OSMRβ). OSMRβ is a cell surface receptor that heterodimerizes with IL-31 receptor alpha (IL-31Rα) to mediate signaling of IL-31. It also heterodimerizes with gp130 to mediate signaling of oncostatin (OSM). By targeting a single epitope (OSMRβ), KPL-716 is designed to simultaneously inhibit signaling of IL-31 and OSM, 2 cytokine pathways, which are important in pruritus, inflammation, hyperkeratosis, and fibrosis. In contrast, KPL-716 does not inhibit signaling of OSM down the leukemia inhibitory factor receptor (LIFR) pathway, a pathway implicated in hematopoiesis and platelet synthesis (10).

PN is a disease characterized by intractable pruritus and hyperkeratotic nodules. In addition to hyperkeratosis and epidermal hyperplasia, typical histologic abnormalities include lymphocytic, monocytic and to a lesser degree granulocytic inflammation and dermal papillary fibrosis (5). KPL-716 via its dual pathway mechanism is predicted to reduce pruritus and potentially modulate these other aspects of disease pathology in PN. A clinical relief on pruritus intensity was observed at therapeutic doses based on the Phase 1b study

results in atopic dermatitis patients (Protocol KPL-716-C001 and data on file). It is also anticipated that inhibition of signaling of two pathways critical in pruritus, inflammation, hyperkeratosis, and fibrosis ultimately may improve severity of disease from the baseline and may offer additional advantages beyond current therapies. The targeted nature of the KPL-716 mechanism of action is also expected to offer safety advantages compared to immunosuppressive therapies as well as systemic and topical corticosteroids.

The role of IL-31 in pruritus is well established, as IL-31 receptor inhibition has been shown to decrease pruritus in subjects with atopic dermatitis (11, 12). The published literature suggests that IL-31 plays a role in PN. Two studies have shown increased IL-31 mRNA expression levels in the lesional skin of PN patients compared to healthy volunteers and patients with psoriasis (13, 14). Another study showed IL-31 and IL-31Rα protein expression in a subset of inflammatory cells in PN skin though to a lesser extent than that seen in atopic dermatitis (15). In a Phase 1b study, KPL-716-C001, KPL-716 demonstrated OSMRβ target engagement and an early signal of efficacy by reducing pruritus in subjects with atopic dermatitis. Please see IB. KPL-716 is therefore being investigated in this Phase 2 study for its efficacy in reducing pruritus in patients with PN (primary endpoint). The reduction in pruritus is anticipated to improve sleep and quality of life. Therefore, this study will investigate the impact of KPL-716 on sleep and quality of life (secondary endpoints).

OSM, the other cytokine pathway inhibited by KPL-716, has been shown to play a role in inflammation, epidermal integrity, and fibrosis, 3 pathways important in PN pathogenesis. OSM increases the production of IL-4Rα and IL-13Rα (16-21). OSM also increases IL-4 production and synergizes with IL-4 and IL-13 to upregulate downstream signaling events such as eotaxin production (16, 18, 19, 20, 21, and 22). Similarly, OSM synergizes with IL-17A and increases CCL2 and IL-6 production (21). OSM impacts epidermal barrier function by modulating genes important in keratinocyte activation and differentiation (16 17). Finally, OSM levels are increased in fibrotic diseases and OSM over expression in animal models has been shown to result in fibrotic changes (19, 23). The interplay between OSM and multiple pathologic processes in PN, from hyperkeratosis to inflammation to fibrosis, suggests that KPL-716 may modulate disease severity. Therefore, the impact of KPL-716 in disease severity will be investigated in this study (secondary endpoints). Clinical effect on pruritus, sleep, quality of life and disease severity will be measured using existing and novel patient reported outcomes and disease scoring tools.

This Phase 2 study will utilize a wash out monotherapy design and enroll subjects with a physician-documented diagnosis of PN of at least 6 months duration from the time of first PN nodule as affirmed by the subject. There are currently no established diagnostic criteria for PN. In order to differentiate PN from other pruritic inflammatory skin conditions and to ensure uniformity of diagnosis across the study, certain disease characteristic features are included under eligibility criteria. As an exploratory objective, clinical response may be correlated with biomarker changes if collected to understand whether KPL-716 responsiveness is broad or limited to a specific subset of PN patients.

Ultimately, the data from this Phase 2 study will help establish the therapeutic dose and regimen of KPL-716 for treatment of pruritus and potentially for disease modification in PN and inform the study population for Phase 3.

1.4 Justification for Using a Placebo Control Arm

Currently there are no approved therapeutics for PN. Some conventional therapeutics (such as, topical corticosteroids, immunosuppressants, phototherapy) have been used off-label in clinical practice with mild to moderate efficacy at best. These treatments are often associated with severe adverse effects. Given the average duration of the disease (over 9 years in the KPL-716-C201 Phase 2a trial), many patients have exhausted these conventional off-label therapeutics without satisfactory results. Thus, it is not reasonable or ethical to compare with or add-on to any of those off-label therapeutics.

The efficacy measures on pruritus, sleep and quality of life are subjective assessments; therefore, they are not suitable for use in an open-label trial because subjects are likely to be biased due to expectations of improvement. Thus, a placebo-controlled, double-blind, and randomized study is the best setting to assess the therapeutic effects and safety of KPL-716. It has been a common practice to use placebo-control for pruritus trials in the scientific community. The placebo in this trial consists of commonly approved excipients, with well-established safety profiles.

1.5 Benefit-risk Assessment

KPL-716 is anticipated to offer a therapeutic benefit to patients with chronic pruritic inflammatory skin diseases through its dual inhibition of IL-31 and OSM, 2 cytokine pathways important in pruritus, inflammation, hyperkeratosis, and fibrosis. In the first-in-human study of KPL-716, Part 1 and 4 of KPL-716-C001, KPL-716 demonstrated OSMRß target engagement and an early signal of efficacy by reducing pruritus in subjects with atopic dermatitis. For a summary of clinical pharmacodynamic (PD) data from KPL-716-C001, please see the IB. KPL-716-C201 phase 2a primary efficacy endpoint analysis showed clinical benefits in both pruritus reduction and skin lesion improvement.

PN is a debilitating disease in which patients suffer from intractable pruritus and disfiguring skin nodules for which there are no approved therapies. KPL-716 is being tested in this Phase 2 study for its potential efficacy in reducing pruritus in patients with PN (primary endpoint) through inhibition of IL-31 signaling. A reduction in pruritus is anticipated to improve sleep and quality of life in subjects with PN (secondary endpoint), as was seen in the Phase 1b study in subjects with atopic dermatitis and in Phase 2a PN patients. Given the potential impact of OSM on pathologic processes important in PN, hyperkeratosis, inflammation and fibrosis, the inhibition of OSM signaling by KPL-716 may also provide benefit in reducing disease severity. At a minimum, it is anticipated that subjects in this study would benefit from the assessment of their medical status and routine interactions with investigative dermatologists. For Phase 2b, all subjects (including the placebo arm) will have the option of being dosed with KPL-716 360 mg, SC, Q2W during the OLE Period to maximize potential benefits but not exceed the doses tested previously (i.e., 720 mg SC or 7.5 mg/kg IV, or 360 mg SC weekly).

As described previously, in the first-in-human study (KPL-716-C001), 50 healthy volunteers (Part 3) and 75 subjects with atopic dermatitis (Part 1 and 4) were exposed to single or repeat doses of KPL-716 up to 7.5 mg/kg IV or 12 weekly 360 mg SC or placebo. In the KPL-716-C201 Phase 2a, 49 PN patients (n = 23 in KPL-716, n = 26 in placebo) were given 720 mg SC loading dose and followed by up to 15 weekly dosing of 360 mg SC or placebo. In the KPL-716-C202 Phase 2 trial on a basket of chronic pruritus conditions (chronic

idiopathic pruritis, plaque psoriasis, chronic idiopathic urticaria, lichen simplex chronicus, and lichen planus, n = 58), subjects were treated with 720 mg loading dose and 7 weekly dosing of 360 mg SC or placebo. Among all the studies, one serious adverse event (SAE) of angioedema was reported (KPL-716-C202, blinded), rated as possibly related. After treatment with oral antihistamine and corticosteroids, the subject recovered without the need for hospitalization. There were no deaths, or dose-limitation events. Drug-related or possibly related treatment-emergent AEs were infrequent. For additional information, please see the IB.

The available toxicology and prior human data support the dose level and duration of treatment in this study. No specific safety concerns are anticipated with inhibition of signaling through OSMRβ in PN subjects experiencing severe pruritus as KPL-716 does not inhibit constitutive signaling of OSM down the LIFR pathway, a pathway implicated in hematopoiesis and platelet synthesis (10). New and unknown adverse events (AEs) may emerge in a new study as the drug is investigated under chronic use with prolonged exposure in a new disease population.

There may be some discomfort from collection of blood samples, subcutaneous study drug injections and other procedures. Subcutaneous injections and skin biopsies can infrequently lead to skin irritation, local inflammation, secondary skin infection, as well as vasovagal reactions. There is no theoretic base or evidence that KPL-716 treatment may interfere with immune system. For mitigating risks during COVID-19 pandemic, we will exclude any subjects with active SARS-CoV-2 virus infection. The subjects will undergo supervised study procedures and will be closely monitored for adverse experiences during their participation in the study.

Overall, the benefit-risk assessment favors the continuation of the Phase 2b portion of the study.

2 OBJECTIVES

2.1 Primary Objective

- To evaluate the efficacy of SC KPL-716 vs. placebo in reducing pruritus in PN subjects experiencing severe pruritus

2.2 Secondary Objectives

- To evaluate the effect of SC KPL-716 vs. placebo in improving sleep in PN subjects experiencing severe pruritus
- To evaluate the efficacy of SC KPL-716 vs. placebo in improving quality of life in PN subjects experiencing severe pruritus
- To evaluate the effect of SC KPL-716 vs. placebo in reducing disease severity in PN subjects experiencing severe pruritus
- To evaluate the safety and tolerability of SC KPL-716 vs. placebo in PN subjects experiencing severe pruritus
- To evaluate the pharmacokinetics (PK) of SC KPL-716 in PN subjects experiencing severe pruritus

2.3 Exploratory Objectives

- To evaluate the immunogenicity of SC KPL-716 in PN subjects experiencing severe pruritus
- To evaluate the effect of KPL-716 vs. placebo on skin and blood biomarkers
- To evaluate the correlation between KPL-716 responsiveness and co-morbidities in PN

3 ENDPOINTS

3.1 Primary Efficacy Endpoint for 2b

- Percent change from baseline in weekly average Worst Itch–Numeric Rating Scale (WI-NRS) at Week 16

3.2 Key Secondary Efficacy Endpoints for 2b

- Proportion of subjects achieving at least a 6-point reduction from baseline in weekly average WI-NRS at Week 16
- Proportion of subjects achieving at least a 4-point reduction from baseline in weekly average WI-NRS at Week 16
- Proportion of subjects achieving 0 or 1 in PN-IGA at Week 16

3.3 Other Secondary Efficacy Endpoints for Phase 2b

Related to pruritus:

- Change and percent change from baseline in weekly average of WI-NRS over time
- Proportion of subjects achieving at least a 6-point reduction from baseline in weekly average WI-NRS over time.
- Proportion of subjects achieving at least a 4-point reduction from baseline in weekly average WI-NRS over time.

Related to disease severity:

- Proportion of subjects achieving 0 or 1 in PN-IGA over time
- Proportion of subjects with at least 2-point improvement from baseline in PN-IGA over time
- Proportion of subjects achieving 0 or 1 in Investigator's Global Assessment for Prurigo Nodularis-Stage (IGA-CNPG-S) over time
- Proportion of subjects with at least 2-point improvement from baseline in IGA-CNPG-S over time

Related to sleep:

- Change and percent change from baseline in weekly average of Sleep Loss Visual Analog Scale (VAS) over time

Related to quality of life:

- Change and percent change from baseline in ItchyQoL over time

Exploratory Efficacy Measures:

- Proportion of subjects achieving 0 or 1 in IGA-CNPG-Activity (IGA-CNPG-A) over time
- Change from baseline in Prurigo Nodularis Nodule Assessment Tool (PN-NAT) over time

- Change from baseline in the total score of Patient Health Questionnaire (PHQ-9) over time
- Change from baseline in the total score of General Anxiety Disorder (GAD-7) over time
- Days and proportion of subjects using rescue medication over time
- Patient Global Impression of Prurigo Nodularis Severity (PGI-PN-S) over time
- Patient Global Impression of Change (PGIC) over time
- Change from baseline in skin and blood biomarkers over time

3.4 Safety Parameters for Phase 2b

- Incidence rate and severity of treatment-emergent AEs (TEAEs)
- Incidence rate and severity of study drug-related TEAEs
- Vital signs, electrocardiogram (ECG), and clinical laboratory test results

3.5 Other Parameters for 2b

- PK: Measurement of plasma concentrations of KPL-716
- Immunogenicity: Measurement of anti-KPL-716 ADA

4 INVESTIGATIONAL PLAN

4.1 Study Design

This is a randomized, double-blind, placebo-controlled study to investigate the efficacy, safety, tolerability, PK, and immunogenicity of KPL-716 administered SC in PN subjects experiencing severe pruritus.

The Phase 2b (Figure 1) portion of the study will consist of a 4-week Screening Period and a 16-week Double-Blind Period followed by a 36-week Open-Label-Extension (OLE) Period. Approximately 180 PN subjects experiencing severe pruritus will be randomized (at 1:1:1:1 ratio) into one of the following 4 arms: KPL-716 540 mg SC, once every 4 weeks (Q4W); KPL-716 360 mg SC, Q4W; KPL-716 120 mg SC, Q4W; or placebo SC, Q4W. A total of 4 doses of study drug will be administered during the Double-Blind Period to measure the efficacy, safety, and PK of KPL-716. The Phase 2b portion of the study will utilize a washout monotherapy design in which concomitant therapies that could impact pruritus or disease severity will be prohibited from designated windows through the end of the OLE Period, thus removing the confounding effect of these therapies on the assessment of KPL-716 efficacy. Should subjects experience an exacerbation of symptoms that is significant enough to warrant intervention, oral antihistamines and/or topical corticosteroids may be provided 4 weeks post-randomization, as outlined in the Pharmacy Manual. The days of rescue medication use will be recorded in an e-Diary and types and duration of rescue medications used will be recorded as a concomitant medication.

After the Double-Blind Period, all subjects will have the option to receive KPL-716 360 mg SC, Q2W during the OLE Period to evaluate long-term safety and PK. For subjects who complete the Double-Blind Period but choose not to participate in OLE, or who terminate earlier, an End of Study (EOS) Visit will be required 4 weeks following the date of last study drug dose.

An interim analysis may be performed after at least 50% of subjects have completed the Week 16 Visit. Additional details regarding the interim analysis, if performed, will be provided in the Statistical Analysis Plan (SAP) along with other analysis plan(s).

Subjects will follow the schedule below:

- Screening Period (minimum 7 days and maximum 28 days)
- Double-Blind Period (Day 1 [Baseline] to Week 16)
- Open-Label-Extension Period (End of Week 16 to Week 52)

The allowable visit window from Week 4 to Week 16 is ± 2 days and thereafter to Week 52 is ± 3 days.

At any point following randomization, home health nursing or telemedicine services may be applied to accommodate COVID-19 limitations to in-person visits and dosing.

4.1.1 Screening Period for Phase 2b

After the informed consent form (ICF) is signed, subjects will enter the Screening Period for assessment of eligibility.

During the Screening Period, subject's medical and surgical history will be reviewed including allergic history. Review of medical history will include PN disease history (year of first PN nodule and year of diagnosis) and history of co-morbidities. Prior and concomitant medications, therapies and procedures will be recorded for PN and any other medical condition. Vital signs will be measured, and subjects will undergo a full physical examination. Clinical laboratory tests and an ECG will be performed. Urine drug screen and pregnancy test (if applicable) will also be performed.

To be eligible, subjects must have a physician-documented diagnosis of PN with at least 20 nodules of approximately 0.5 to 2 cm. The nodules must be pruritic and present on at least 2 different anatomical locations (not be localized), involve the extremities, with extensor extremity involvement greater than the flexor extremity involvement. Nodules on the head (face and scalp) are not counted as an anatomical location for eligibility criteria. Each arm, each leg, and the trunk are considered different anatomical locations. The minimum required duration of disease is at least 6 months from the time of first PN nodule to Day 1, as affirmed by the subject.

At the Screening Visit, subjects will be asked to rate their pruritus severity (worst itch) over the past 24 hours on the WI-NRS. In addition, subjects will record their WI-NRS on a daily basis during the Screening Period. Subjects will be given training on Accurate Symptom Reporting (ASR) and Placebo Response Reduction (PRR) during the Screening Visit, Baseline Visit, and Weeks 4, 8 and 12, or as needed. The daily recordings can begin any time after the Screening Visit. Subjects will use internet-connected devices for daily electronic recordings. To be eligible for study participation, subjects must have severe pruritus, defined as WI-NRS ≥7 at the Screening Visit and a mean weekly WI-NRS ≥7 for the week (7 consecutive days) immediately prior to randomization (at least 5 days of recordings) on e-Diary.

During the Screening Period, whole-body medical photographs will be taken (upper front, lower front, upper back, and lower back) without the face and with the genitals covered. In addition, a representative area of the disease will be determined by the PI at the Screening Visit, and medical photographs of this area will be taken and followed throughout the study. Medical photographs will be used for confirmation of diagnosis of PN as defined in the Study Manual and for assessment of disease severity over time. Subjects may be asked to return to the study site during the Screening Period for unscheduled visits for repeat screening procedures if needed.

Additional assessments at the Screening Visit may include those related to pruritus, sleep, quality of life, anxiety and depression, disease severity, etc. Subjects will be instructed on the required washout for specific excluded medications. The daily recordings (WI-NRS and rescue medication) will continue throughout the study for eligible subjects that proceed to dosing.

Collection of AEs and concomitant medications will begin after signing the ICF and will continue until the EOS Visit. For Schedule of Activities, please see Appendix 1.

In an effort to minimize subject burden and/or risk during the COVID-19 pandemic, sites may offer to split the Screening Visit into two parts; a virtual preliminary Screening Visit in which some assessments may be performed [e.g. ICF, medical history, concomitant medications, subject questionnaires (completed electronically) and some eligibility criteria],

followed by an in-person visit in which all remaining eligibility assessments may be performed that require subjects to be physically present (e.g. blood collection for clinical laboratories, ECG, medical photography, vital signs, and disease severity assessments).

4.1.2 Treatment Period

4.1.2.1 Pre-dose

Prior to dosing on Day 1, subjects will undergo review of eligibility, medical and surgical history, prior and concomitant medications, therapies and procedures and AEs. Clinical laboratory results from the Screening Visit will be reviewed. Compliance with recording of daily WI-NRS for the 7 days immediately prior to dosing will also be reviewed. Urine drug screen and pregnancy test (if applicable) will be performed. Vital signs will be measured. ECG and a full physical examination will be performed.

Eligible subjects will undergo collection of safety blood and urine samples as well as blood samples for PK, ADA, and potential blood biomarkers. Medical photographs will be taken of the representative area of disease identified during the Screening Period. Whole-body photographs (upper front, lower front, upper back, and lower back) without the face and with genitals covered will also be captured prior to the first dose. For subjects who provide additional consent for the collection of skin biopsies (optional), the biopsies (one lesional and one non-lesional) will be performed along with medical photographs of the biopsy areas prior to biopsy collection. Skin biopsies are optional. Upon confirmation of subject eligibility and completion of required activities (Appendix 1), subjects will be randomized and proceed to dosing.

4.1.2.2 Randomization and Dosing

Subjects will be randomized 1:1:1:1 to receive different dosing regimens of KPL-716 or placebo. At the end of the Double-Blind Period, all subjects will have the option to enter the OLE Period to receive KPL-716 360 mg SC Q2W. Stratification will be performed based on sex and years since the first nodule observed (i.e., ≥10 years vs. <10 years).

Phase 2b: Figure 1

- Arm A: KPL-716, 540 mg, SC, every 4 weeks
- Arm B: KPL-716, 360 mg, SC, every 4 weeks
- Arm C: KPL-716, 120 mg, SC, every 4 weeks
- Arm D: Placebo, SC, every 4 weeks

The dose levels and dosing intervals for Phase 2b have been chosen based on Phase 2a results so as not to exceed exposures observed in Phase 2a.

All procedures assigned to dosing days will be performed prior to study drug administration. The following activities will take place prior to each dose during the Double-Blind Period:

- Review of concomitant medications, therapies, and procedures

- Review of AEs
- Review of subject compliance
- Vital signs (performed before and after dosing on each dosing day)
- Collection of blood for PK
- Completion of Sleep Loss VAS

The following activities will take place prior to dosing at designated study visits if applicable as outlined in Appendix 1:

- Physical examination and ECG
- Collection of safety blood and urine samples
- Pregnancy test (if applicable)
- Collection of PK and/or blood biomarker samples
- Medical photography
- Completion of patient questionnaires (ItchyQoL, PHQ-9, GAD-7, PGI-PN-S, PGIC)
- Assessment of disease severity (PN-NAT, PN-IGA, IGA-CNPG-S, IGA-CNPG-A)
- Skin biopsies (Skin biopsies are optional)

AEs and concomitant medications will be collected throughout the study. Subjects will continue to complete their daily questionnaire on pruritus (WI-NRS) and sleep until the EOS Visit.

In case of study drug discontinuation, subjects will continue to follow the schedule of activities for each visit minus study drug administration. Under these circumstances, the second set of biopsies (optional) will be performed at the earliest possible visit following early Double-Blind Period drug discontinuation, if applicable. In case of study drug interruption or missed dosing visits, subjects will resume the schedule of activities in accordance with their study day. In case of early withdrawal from the entire study, subjects will complete an EOS Visit 4 weeks after the last dose. In addition, if the early termination occurs prior to the end of the treatment period, biopsies should be collected at the EOS visit, if applicable.

4.1.3 OLE for Phase 2b

During the OLE Period, subjects will be administered KPL-716, 360 mg, SC, Q2W with the last dosing at the Week 48 Visit. In the OLE portion of the study subjects may be permitted to self-administer KPL-716 as outpatients provided all of the following conditions are met:

- Safety Review Team (SRT) determines that the available safety and tolerability data support outpatient self-administration.

- Study subjects receive adequate training and successfully performs 3 KPL-716 self-administrations (e.g., Weeks 16, 18, and 20) under the supervision of study site personnel.
- Study Investigator and Study Medical Monitor approve individual subject to self-administer drug.

If self-administration is not authorized by the SRT, the Investigator, Medical Monitor, or an individual subject is unable/unwilling to perform self-administration, KPL-716 will continue to be administered by the Investigator, a qualified investigational site designee or home health nurse. During the OLE Period, subjects will also undergo vital signs measurement, review of concomitant medications, therapies and procedure, review of AEs, monitoring of compliance, and PK blood sample collection at visits according to the Schedule of Activities. Sleep Loss VAS, physical examination, clinical laboratory tests (including pregnancy testing if applicable), quality of life assessment, and evaluation of disease severity will be performed at designated visits. Subjects will continue to complete their daily questionnaires on pruritus and rescue medication use throughout the OLE Period. Should subjects self-administer drug, collection of AEs, concomitant medication use, and NRS compliance assessments ,as outlined in Appendix 1, may be completed remotely by study staff.

The EOS Visit will include vital signs, full physical examination, ECG, clinical laboratory blood tests, urinalysis, and urine pregnancy test (if applicable) as well as PK, ADA, and biomarker blood sampling. Biopsies for biomarker assessment will be collected from subjects who provide additional consent. All efficacy assessments for pruritus, sleep, quality of life and disease severity will also be completed at this visit. Medical photography of the whole body and the representative area (identified during the Screening Period and followed throughout the study) will be obtained. All subjects will complete an EOS Visit.

4.2 Duration of Phase 2b

The planned study duration per subject for Phase 2b will be approximately 56 weeks including a maximum of 4 weeks for the Screening Period, 16 weeks for the Double-Blind Period, and 36 weeks for the OLE Period.

The minimum duration for the Screening Period will be 7 days.

4.3 Study Drug

Study Drug: KPL-716 or matching placebo

Active Substance: KPL-716

Strength, Formulation and Route of Administration: 180 mg/mL solution [redacted], subcutaneous administration.

Matching placebo: [redacted], subcutaneous administration.

4.4 Study Treatment

For Phase 2b, subjects will be randomized to receive KPL-716 or matching placebo on Day 1 and will remain in the same treatment arm throughout the Double-Blind Period, then all subjects will have the option to participate in the OLE Period, starting dosing at the End of Week 16 Visit.

Phase 2b: Figure 1

- Arm A: KPL-716 at 540 mg SC on Day 1 and at Weeks 4, 8, and 12 during the Double-Blind Period
- Arm B: KPL-716 at 360 mg SC on Day 1 and at Weeks 4, 8, and 12 during the Double-Blind Period
- Arm C: KPL-716 at 120 mg (see Pharmacy Manual for formulation instructions) SC on Day 1 and at Weeks 4, 8, and 12 during the Double-Blind Period
- Arm D: Placebo SC on Day 1 and at Weeks 4, 8, and 12 during the Double-Blind Period

4.5 Selection of Doses in the Study

In the first-in-human study of KPL-716, Part 1 of KPL-716-C001, KPL-716 demonstrated OSMRß target engagement and an early signal of efficacy by reducing pruritus in subjects with atopic dermatitis. In that study, a single IV dose of KPL-716 was given to subjects with atopic dermatitis at escalating doses of 0.3 mg/kg, 1.5 mg/kg, and 7.5 mg/kg. The decrease from baseline in pruritus intensity was compared between KPL-716 recipients at the top IV dose of 7.5 mg/kg (n = 10) and pooled IV placebo recipients (n = 10). Target engagement was established, as a single dose of KPL-716 7.5 mg/kg IV reduced pruritus rapidly, within the first week of study drug exposure, compared to placebo. For a summary of clinical PD data from Part 1 of KPL-716-C001, please see IB.

Conclusive PK/PD correlation to determine C_{eff} following single dose administration of KPL-716 in subjects with atopic dermatitis was not feasible due to the small sample size in lower dose groups in the Phase 1b study. Nonetheless, an anti-pruritic effect was evident after KPL-716 administration at 7.5 mg/kg as a single IV dose, which resulted in a maximum concentration (C_{max}) of 217 µg/mL and area under the concentration-time curve $(AUC)_{0-\infty}$ of 59,700 µg•hr/mL. The anti-pruritic effect of KPL-716 was still evident 28 days after the single IV dose of 7.5 mg/kg, which corresponded to blood concentration levels of approximately 30 µg/mL at Day 28. Although it was not possible to ascertain the precise magnitude of the antipruritic effect after 4 weeks because of topical corticosteroid coadministration, data suggested that efficacy persisted to approximately 6 weeks. There is also uncertainty around the C_{eff} for the anti-inflammatory effect via OSM axis inhibition. To establish proof of concept in patients with PN, a new study population, the SC dosing regimen for this Phase 2a study was chosen to mimic and extend into chronic dosing the PK parameters achieved with the 7.5 mg/kg IV administered as a single dose, given that it had previously demonstrated a prolonged anti-pruritic effect. Chronic dosing via the SC route was selected for this study rather than IV administration as a more practical and patient-friendly route of administration.

PK analysis of a single SC dose of KPL-716 at 360 mg administered to healthy volunteers demonstrated that peak blood concentrations of 31 μg/mL were achieved slowly in 125 hours and declined with a half-life of 168 hours (7 days). Comparison of PK parameters across dose levels and routes of administration in healthy volunteers and subjects with atopic dermatitis showed that exposures were similar in the 2 study populations. In both populations, as dose increased, half-life also increased consistent with a TMDD profile. Furthermore, bioavailability between healthy volunteers and AD subjects at the evaluated dose levels was generally comparable (42% vs. 65%); the number of subjects in these analyses were small. Based on the similarities in PK parameters between healthy volunteers and atopic dermatitis subjects despite anticipated differences in target expression levels, it is likely that PK parameters in PN patients will also follow the same patterns.

The Phase 2a in PN patients, under the regimen of 720 mg loading dose with up to 15 weekly 360 mg SC doses, demonstrated clinical efficacy and an acceptable safety profile. The C_{max} and C_{trough} were 235 and 220 μg/mL at week 16, respectively, in the 16-week dosing cohort. Clinical efficacy persisted when drug concentration dropped to approximately 30 μg/mL among responders 9 weeks after last dosing. However, it is not certain if C_{eff} is 30 μg/mL or lower as the follow-up period may be insufficient. Additionally, the observed exposure metrics from interim PK samples were largely comparable with predicted concentration-time profiles using the updated PK model (including all subjects from KPL-716-C001). This model was thus used to conduct regimen simulation for Phase 2b. Four repeated doses of 540 mg Q4W could reach a steady status with $C_{trough} \geq 10$, 20, or 30 μg/mL in 95%, 77%, or 51% of subjects, respectively; therefore, this regimen could be efficacious if C_{eff} is 30 μg/mL or lower. Four repeated doses of 360 mg Q4W SC could reach a steady status with $C_{trough} \geq 5$ μg/mL in 88% of subjects and $C_{trough} \geq 10$ μg/mL in 68% of subjects. This regimen could provide a reasonable coverage for an estimated C_{eff} of 5-8 μg/mL concluded from the cynomolgus monkey itch model study. Four repeated doses of 120 mg Q4W SC could reach a steady status with C_{trough} above 5 or 10 μg/mL in 1.6% or 0.1% of subjects, respectively. Thus, 120 mg Q4W SC is chosen as a subtherapeutic dose. A 16-week treatment/observation is used to allow for at least 4 repeated doses of each regimen to reach steady status. No loading dose is planned to avoid masking onset of efficacy and efficacy differentiation among the different dose regimens. Per the PK simulation, continuous treatment in OLE with 360 mg, SC, Q2W results in at least 96% or 82% of subjects with $C_{trough} \geq 10$ or 20 μg/mL and C_{max} and C_{trough} (i.e., < 100 μg/mL) is below the level achieved in the Phase 2a QW dose but higher than the Q4W doses in the blinded portion of the study. If follows that the proposed Q2W OLE dose provides a more robust drug coverage than the Q4W doses while assumed at least as safe as higher Phase 2a QW exposures, thus complementing the exploration for an efficacious and safe dose overall.

The available pre-clinical toxicology data support the selection of the above doses. The multi-dose, 7-week, preclinical toxicology study in cynomolgus monkeys revealed no specific toxicities, and the highest administered dose (500 mg/kg IV) was identified as the NOAEL. In a chronic toxicology study, weekly administration of KPL-716 by IV bolus injection or SC at doses up to 200 mg/kg for 26 weeks (27 total doses) was well tolerated in cynomolgus monkeys. Based on these results under the conditions and duration of the study provided in the study report, the NOAEL was considered to be 200 mg/kg IV/SC, the highest dose tested. The number of doses and the dose levels in this Phase 2b study are well

supported by the number of doses (total of 27) and the NOAEL (200 mg/kg) in the chronic toxicology study.

The available safety data support the selection of above dose levels. In the first-in-human study (KPL-716-C001), 50 healthy volunteers (Part 3) and 75 subjects with atopic dermatitis (Part 1 and 4) were exposed to single or repeat doses of KPL-716 or placebo. In the KPL-716-C201 Phase 2a, 49 PN patients (n = 23 in KPL-716, n = 26 in placebo) were weekly dosed at 360 mg SC (with 720 mg loading dose) or placebo for 8 or 16 weeks. In the KPL-716-C202 Phase 2 trial on a basket of chronic pruritus conditions (chronic idiopathic pruritis, plaque psoriasis, chronic idiopathic urticaria, lichen simplex chronicus, and lichen planus, n = 58), subjects were treated with active drug (720 mg loading dose followed by 360 mg weekly SC dosing) or placebo for 8 weeks. Among all the studies, one SAE of angioedema was reported (KPL-716-C202, blinded), rated as possibly related to study drug. After treatment with oral antihistamine and corticosteroids, the subject recovered without the need for hospitalization. There were no deaths or dose-limitation events. Drug-related or possibly related treatment-emergent AEs were infrequent. For additional information, please see the IB.

The objective of the Phase 2b study is to define the minimally efficacious dose by exploring the clinical response to varying C_{trough} levels. Another objective is to identify a likely practical dosing regimen to carry forward into subsequent confirmatory studies. In the Phase 2b study, subjects will be randomized 1:1:1:1 to receive 4 different dosing regimens of KPL-716 or placebo SC: KPL-716 540 mg SC, Q4W; KPL-716 360 mg SC, Q4W; KPL-716 120 mg SC, Q4W; or placebo SC, Q4W, during the Double-Blind Period. After the Double-Blind Period, all subjects will have the option to receive KPL-716 360 mg SC, Q2W during the OLE Period to evaluate the long-term safety and PK, and to maximize potential benefits but not exceed the doses tested previously (i.e., 720 mg SC or 7.5 mg/kg IV or 360 mg SC weekly).

4.6 Study Assessments

4.6.1 Efficacy Assessment

Efficacy in reduction of pruritus will be assessed via daily recording of WI-NRS. Efficacy in improvement in sleep will be assessed via Sleep Loss VAS. Impact on quality of life will be assessed via ItchyQoL, PHQ-9, and GAD-7. Impact on disease severity will be followed by PN-IGA, PN-NAT, IGA-CNPG-S, IGA-CNPG-A, PGI-PN-S, and PGIC. See Schedule of Activities Appendix 1.

An area representative of the subject's disease will be chosen at the Screening Visit and followed over time through medical photography at designated time points. Whole-body photographs and images of biopsy locations (prior to collection of biopsies), if applicable, will be taken at indicated study visits.

Skin biopsies will be collected pre- and post-treatment during this study. Skin biopsies are encouraged but optional. Two individual punch biopsies (one from lesional skin and one from adjacent non-lesional skin) will be collected prior to dosing at Day 1 and post-treatment biopsies will be collected at Week 16 or EOS. Biopsy collection procedures and processing will be outlined in a separate manual.

4.6.2 Safety Assessments

Safety will be assessed by monitoring of AEs, measurements of vital signs, physical examination, ECG evaluation, and clinical laboratory tests.

4.6.3 PK Assessments

PK blood samples will be collected from all subjects as specified in the Schedule of Activities. PK samples will be collected pre-dose on dosing days.

4.6.4 Biomarker Assessment

Blood samples will be collected from all subjects for biomarker analysis. Blood samples will be collected pre-dose on dosing days as specified in the Schedule of Activities.

4.6.5 Immunogenicity Assessments

Blood samples for ADA assessment will be collected from all subjects pre-dose on dosing days as specified in the Schedule of Activities.

4.7 Selection of Study Population

4.7.1 Inclusion Criteria

1. Male or female aged 18 to 80 years, inclusive, at the time of consent.

2. Have a physician-documented diagnosis of PN that is confirmed by review of medical photography (as outlined in the Study Manual) during the Screening Period. Duration of PN (since the time of first PN nodule) must be at least 6 months from the time of first PN nodule to Day 1, as affirmed by the subject.

3. Have at least 20 nodules of approximately 0.5 to 2 cm at the Screening Visit and Day 1. The nodules must be pruritic and present on at least 2 different anatomical locations (not be localized), involve the extremities, with extensor extremity involvement greater than the flexor extremity involvement. Nodules on the head (face and scalp) are not counted as an anatomical location for eligibility criteria. Each arm, each leg, and trunk are considered different anatomical locations.

4. Subject has severe pruritus, defined as WI-NRS ≥7 at the Screening Visit and a mean weekly WI-NRS ≥7 for the week (7 consecutive days) immediately prior to randomization (at least 5 days of recordings) on eDiary.

5. PN-IGA score of ≥3 (on a scale of 0-4, in which 3 is moderate and 4 is severe) at Screening and Baseline Visits.
6. Sexually active female subjects must be:

    - postmenopausal, defined as at least 12 consecutive months post cessation of menses (without an alternative medical cause) and confirmed by a follicular stimulating hormone (FSH) test, or

- surgically sterile following documented hysterectomy, bilateral salpingectomy, bilateral oophorectomy or

- nonpregnant, nonlactating, and having agreed to use a highly effective method of contraception from the Screening Visit until 16 weeks after final study drug administration.

    - Note: highly effective methods of contraception include:

        - hormonal contraceptives associated with inhibition of ovulation (stable dose for at least 4 weeks prior to first dose)

        - intrauterine device

        - intrauterine system

        - double barrier methods of contraception (barrier methods include male condom, female condom, cervical cap, diaphragm, contraceptive sponge) in conjunction with spermicide.

        - tubal ligation

        - vasectomized male partner

7. Sexually active male subjects must have documented vasectomy or must agree to use a highly effective method of contraception as defined above with their partners of childbearing potential from first dose until 16 weeks after final study drug administration.

8. Male subjects must agree to refrain from donating sperm from first dose until 16 weeks after the last study drug administration. Female subjects must agree to refrain from donating eggs from first dose until 16 weeks after the last study drug administration.

9. Female of childbearing potential must have a negative serum β-human chorionic gonadotropin (β-hCG) test at the Screening Visit and negative urine pregnancy test on Day 1.

10. Able to comprehend and willing to sign an Informed Consent Form and able to abide by the study restrictions and comply with all study procedures for the duration of the study.

11. Subjects must be on optimized and stable treatment for co-morbidities for at least 28 days prior to Day 1.

4.7.2 Exclusion Criteria

1. Use of the following medications within the indicated timeframe prior to Day 1 and does not agree to refrain from the use of the medications throughout the study (except these specified in the Pharmacy Manual):

a. Systemic corticosteroids (IV/IM/oral): 4 weeks; Note: Intranasal corticosteroids, eye drops containing corticosteroids, and inhaled corticosteroids for stable medical conditions are allowed.

b. Intralesional corticosteroids and intra-articular corticosteroids: 6 weeks

c. Topical treatments for PN including but not limited to corticosteroids, calcineurin inhibitors, phosphodiesterase inhibitors, retinoids, calcipotriol, capsaicin, camphor, polidocanol, cannabinoids, gabapentin, or tars: 2 weeks

d. Antihistamines: 2 weeks

e. Immunomodulators (for example, cyclosporin, methotrexate, retinoids, azathioprine, mycophenolate, and thalidomide): 4 weeks

f. Neuroactive drugs such as gabapentin and pregabalin: 4 weeks

g. Cannabinoids: 2 weeks

h. Opioid antagonists or agonists: 5 half-lives if known or 4 weeks

i. Janus inase inhibitors: 5 half-lives if known or 4 weeks

j. Dupilumab: 8 weeks

k. Any other marketed biologic: 5 half-lives or within 4 months of using rituximab

l. Any investigational drug: 5 half-lives

m. Phototherapy involving UVA, UVB, or excimer: 4 weeks

n. Tanning salon use: 4 weeks

o. Live attenuated vaccine: 12 weeks

2. Has received any investigational biologic or non-biologic drug that targets Oncostatin M, IL-31, IL-31 receptor α, or Oncostatin M receptor β in the past 3 months.

3. Required rescue therapy for PN during the Screening Period or expected to require rescue therapy within 4 weeks following the Baseline Visit.

4. Has a significant exacerbation and/or skin eruption during the Screening Period (prior to the study drug administration) that requires a medical intervention.

5. Presence of scabies, insect bite, lichen simplex chronicus, psoriasis, acne, folliculitis, habitual picking, lymphomatoid papulosis, chronic actinic dermatitis, dermatitis herpetiformis, sporotrichosis, bullous disease and/or skin condition other than PN or atopic dermatitis unless approved by the Sponsor.

6. Plan to change emollients or moisturizers, or to have bath oil treatment for relief of pruritus during the course of the trial.

7. Presence of psychogenic pruritus or neuropathic pruritus at the Screening Visit.
8. Presence of severe depression as indicated by PHQ-9 total score of ≥20 or item 9 score > 0 at the Screening Visit or Day 1.
9. Presence of severe anxiety as indicated by GAD-7 score of ≥15 at the Screening Visit or Day 1.
10. Presence of severe chronic pain (e.g., back pain, migraine, osteoarthritis, etc., defined as ≥7.0 on 0 to 10 NRS scale with 0 being no pain and 10 being the worst pain possible) at the Screening Visit.
11. Presence of uncontrolled hyperthyroidism or hypothyroidism or uncontrolled diabetes defined as hemoglobin A1c >7.5%.
12. Presence or history of cancer or lymphoproliferative disease within 5 years prior to Screening Visit, with the exception of basal and squamous cell carcinoma of the skin or in situ carcinoma of the cervix successfully treated and considered controlled.
13. Presence or history of immune deficiency, or opportunistic infections.
14. Positive results for hepatitis B surface antigen (HbsAg) and/or hepatitis B anti-core antibody (anti-HBc) but negative results for anti-surface antibody (anti-HBs) at the Screening Visit.
15. Positive results for hepatitis C antibody unless patient received curative therapy and a negative viral load is documented.
16. Human immunodeficiency virus (HIV) infection or positive HIV serology at the Screening Visit.
17. Positive COVID-19 viral test at Screening Visit or suspected COVID-19 infection at Baseline Visit.
18. Subject is on hemodialysis or peritoneal dialysis.
19. Latent or active TB, as determined by a positive Quantiferon-based TB test result at Screening Visit.
20. Laboratory abnormalities that fall outside the windows below at the Screening Visit:
    a. Alanine aminotransferase >3 x upper limit of normal (ULN)
    b. Aspartate aminotransferase >3 x ULN
    c. Gamma-glutamyl transferase >3 x ULN
    d. Blood bilirubin >2 x ULN
    e. Hemoglobin more than 1g/dL below the lower limit of normal for sex per the laboratory in which screening lab is performed
    f. Platelet count <150,000/ µL

g. Neutrophil count <1,500/µL

21. Major surgery within 12 weeks prior to Day 1 or has a major surgery planned during the study.

22. Has an active infection, including skin infection, requiring systemic treatment within 4 weeks and/or topical treatment within 2 weeks of Day 1. Subject has an active or chronic parasitic infection.

23. Any medical or psychiatric condition which, in the opinion of the Investigator or the Sponsor, may place the subject at increased risk as a result of study participation, interfere with study participation or study assessments, affect compliance with study requirements, or complicate interpretation of study results.

24. Has a known hypersensitivity to KPL-716 or its excipients.

25. Has a known history of drug or alcohol abuse in the last 2 years prior to Day 1. Has more than eight drinks (5 ounces of wine, 12 ounces of beer or 1.5 ounces of liquor) weekly for females and 15 drinks weekly for males.

26. Has a positive urine drug screen for opiates, opioids, methadone, cocaine, phencyclidine, or amphetamines at the Screening Visit or Day 1. Exceptions may be made if a subject is on a medication for a stable concomitant condition that explains the positive drug screen result.

27. Has had a severe allergic reaction to any foods or medications including anaphylactic reactions, unless approved by the Sponsor.

28. For subject providing consent for the optional skin biopsy, presence or history of coagulation disorders, hypertrophic scar, or keloid, or currently under treatments with chronic anti-coagulants (aspirin ≤ 325mg/day is acceptable).

4.8 Subject Number and Identification

Each subject that signs the ICF and enters the Screening Visit will be assigned a unique screening number. The study site will record these numbers on a screening log, document reasons for screening failure or eligibility, whichever is applicable.

Once a subject qualifies for randomization, a unique treatment code will be obtained from a designated center via the interactive web response system (IWRS), which will assign the treatment for the subject. The randomization number will be kept on-file at study site and included in the electronic case report form (eCRF).

4.9 Subject Withdrawal and Replacement

Subjects may withdraw from the study drug treatment or from the entire study at any time for any reason, without prejudice to their medical care. The Investigator also has the right to discontinue treatment with and withdraw subjects from the study for any of the following reasons:

- Adverse event

- Life threatening or other unacceptable toxicity
- Subject requires use of a prohibited concomitant medication or therapy
- General or specific changes in the subject's condition unacceptable for further treatment within the study parameters, in the Investigator's opinion
- Severe noncompliance
- Lost to follow-up (Subjects will be defined as lost to follow up if they have not responded to 3 phone calls and one certified letter)
- Subject withdrawal of consent
- A decision to modify or discontinue development of the drug

In case of study drug interruption or missed dosing visits, subjects will resume the schedule of activities in accordance with their study day.

In case of study drug discontinuation, subjects will continue to follow the schedule of activities for each visit minus dosing. Under these circumstances, the second set of biopsies will be performed at the earliest possible visit. Skin biopsies are optional.

If a subject withdraws from the entire study, the subject must complete the EOS Visit. In addition, if the early termination occurs prior to the last week of treatment, biopsies should be collected at the EOS visit.

If the subject withdraws from study treatment and also withdraws consent for disclosure of future information, no further evaluations should be performed, and no additional data should be collected. The Sponsor may retain and continue to use any data collected before such withdrawal or consent.

Subjects will not be replaced.

4.10 Study Termination or Temporary Suspension

The Sponsor reserves the right to temporarily suspend or terminate this study in part or whole at any time. The reasons for temporarily suspending or terminating the study may include but are not limited to:

- The incidence or severity of AEs in this or other studies indicates a potential health hazard to subjects
- Subject enrollment is unsatisfactory
- Non-compliance that might significantly jeopardize the validity or integrity of the study
- Recommendation to suspend or terminate the study by independent body such as a Health Authority

- Sponsor decision to terminate development

Where required by applicable regulations, the investigator or head of the medical institution must inform the Institutional Review Board (IRB)/International Ethics Committee (IEC) promptly and provide the reason(s) for the suspension/termination. If the study is suspended for safety reasons and it is deemed appropriate by the sponsor to resume the study, approval from the relevant regulatory authorities (and IECs when applicable) will be obtained prior to resuming the study.

5 STUDY TREATMENTS

5.1 Description, Storage, Packaging, and Labeling

The study drug will be supplied by the Sponsor, along with the batch/lot numbers and Certificates of Analysis (CoA). Study drug refers to KPL-716 and the matching placebo.

- Active Ingredient: KPL-716
- Strength, Formulation Form and Route of Administration: 180 mg/mL solution [redacted] for subcutaneous administration.

KPL-716 drug product is a sterile solution formulation, supplied as a single-use vial for SC injection. The 3 mL Schott vials are filled with 2.3 mL to allow for a delivered volume up to 2 mL, and an extractable dose up to 360 mg/vial.

Refer to Pharmacy Manual on reconstitution of 120 mg dose with the above KPL-716 drug product.

The placebo is also a sterile solution formulation, supplied as a single-use vial for SC injection. The same 3 mL Schott vials are used for the placebo with each vial filled with 2.3 mL to allow for a delivered volume up to 2 mL.

Study drug labeling will be in compliance with applicable, local, and national regulations.

Study drug may be dispensed only under the supervision of the Investigator or an authorized designee and only for administration to the study subjects.

Study drug must be stored in a secure area with limited access and allows for required storage conditions. The Investigator, or an authorized designee, will ensure that all study drug is stored in a secured area, under recommended storage conditions, and in accordance with applicable regulatory requirements. To ensure adequate records, all study drugs will be accounted for using drug accountability forms as instructed by the Sponsor.

The study drug and placebo will be prepared in such a way as to preserve the study blind across dose levels. Storage conditions and study drug handling procedures will be detailed in the Pharmacy Manual.

5.2 Study Treatment Administration

Investigators participating in this study will assume responsibility for complying with all procedures and guidelines for the use of KPL-716 as outlined in the study protocol, the Investigator's Brochure, and other study-related materials provided by the Sponsor and/or designee.

In Phase 2b, subjects will be randomized 1:1:1:1 to receive 4 different dosing regimens of KPL-716 or placebo during the Double-Blind study period.

Phase 2b: Figure 1

- Arm A: KPL-716, 540 mg, SC, every 4 weeks
- Arm B: KPL-716, 360 mg, SC, every 4 weeks
- Arm C: KPL-716, 120 mg, SC, every 4 weeks
- Arm D: Placebo, SC, every 4 weeks.

In the OLE, subjects will be administered KPL-716, 360 mg, SC, Q2W with the last dosing at the Week 48 Visit. Subjects may be permitted to self-administer KPL-716 as outpatients during the OLE, provided the SRT determines that the available safety and tolerability data support outpatient self-administration, the Investigator and Medical Monitor approve the individual case, and the subject receives adequate training and successfully performs 3 KPL-716 self-administrations (e.g., Weeks 16, 18, and 20) under the supervision of study site personnel. If self-administration is not authorized by the SRT the Investigator, or Medical Monitor, or if an individual subject is unable/unwilling to perform self-administration, KPL-716 will continue to be administered by the Investigator, a qualified investigational site designee or home health nurse.

5.3 Randomization

All subjects who are eligible for study participation will be randomized prior to study drug administration. Eligible subjects will be randomized to receive KPL-716 or placebo. The randomization will be based on a computer-generated treatment randomization schedule prepared before the study by the Sponsor or designee. Randomization will be stratified on the basis of sex and years since first nodule observation (≥ 10 years vs <10 years).

An IWRS will issue a unique treatment code to each subject, which will assign the treatment for the subject. Prior to each dosing, the medical ID number of the vial to be administered will be obtained from the IWRS based on the computer-generated treatment randomization schedule. The study drug will be prepared and administered according to instructions in the Pharmacy Manual. An unblinded pharmacist, or unblinded authorized designee, will be required to prepare drug for administration, in accordance with the Pharmacy Manual, to uphold study blinding.

5.4 Blinding

This will be a double-blind, placebo-controlled study. As such, the Investigator, the subjects, the Sponsor, and remaining clinical site staff will be blinded to treatment. Only unblinded pharmacists and/or unblinded clinical site staff, for the purpose of preparing of study drug doses, will be aware of subject treatment arm assignments.

The unblinded treatment assignment for each individual subject may be made available to the Investigator through the IWRS only in the event of a medical emergency or an adverse reaction that necessitates identification of the study drug for the medical management or welfare of that subject. Except in a medical emergency, the Investigator and blinded clinical site staff will remain blinded during the conduct of the study. The process and requirements for unblinding will be detailed in an Unblinding Plan. The date/initials and reason for the Investigator and/or clinical staff removing the study blind will be documented.

5.5 Study Treatment Compliance

The following measures will be employed to ensure study treatment and procedures compliance:

- All doses will be administered under the supervision of the Investigator or an authorized designee. Subjects may be permitted to self-administer KPL-716 as an outpatient during the OLE provided the SRT determines that the available safety and tolerability data support outpatient self-administration, the Investigator and Medical Monitor approve the individual case, and the subject receives adequate training and successfully performs 3 KPL-716 self-administrations (e.g., Weeks 16, 18, and 20) under the supervision of study site personnel. If self-administration is not authorized by the SRT, the Investigator, or the Medical Monitor, or if a subject is unable/unwilling to perform self-administration, KPL-716 will continue to be administered by the Investigator, a qualified investigational site designee or home health nurse.

- At each dosing occasion, accountability of study drug will be performed.

5.6 Study Drug Accountability

The accurate record of the medical ID number of the study drug administered will be maintained including the exact volume and the date and time of dispensing. This study drug accountability record will be available for inspection at any time by the unblinded study monitor. At the completion of the study, the original drug accountability record will be available for review by the Sponsor upon request. Used vials and containers will be destroyed upon satisfactory completion of the treatment compliance and study drug accountability procedures. Any unused unit doses will be retained until completion of the study.

At the completion of the study, unused study drug remaining at the sites (if applicable) will be returned to the Sponsor or designee or disposed of by the study sites that have appropriate drug destruction standard operating procedures and per the Sponsor's written instructions.

For further details refer to the Pharmacy Manual.

6 CONCOMITANT THERAPIES AND OTHER RESTRICTIONS

6.1 Concomitant Medications

All subjects enrolled in this study must agree to follow the study protocol with respect to concomitant medications from the Screening Visit through the EOS Visit. The following medications are prohibited from designated timepoints before Day 1 (as noted in the exclusion criteria) and throughout the study.

a. Systemic corticosteroids (IV/IM/oral). Note: Intranasal corticosteroids, eye drops containing corticosteroids, and inhaled corticosteroids for stable medical conditions are allowed.

b. Intralesional corticosteroids and intra-articular corticosteroids

c. Topical treatments for PN including but not limited to corticosteroids, calcineurin inhibitors, phosphodiesterase inhibitors, retinoids, calcipotriol, capsaicin, camphor, polidocanol, cannabinoids, gabapentin, or tars

d. Antihistamines

e. Immunomodulators (for example, cyclosporin, methotrexate, retinoids, azathioprine, mycophenolate, and thalidomide)

f. Neuroactive drugs such as gabapentin and pregabalin

g. Cannabinoids (other routes)

h. Opioid antagonists or agonists

i. Janus kinase inhibitors

j. Dupilumab

k. Any other marketed biologic

l. Any investigational drug

m. Phototherapy involving UVA, UVB, or excimer

n. Tanning salon use

o. Live attenuated vaccine

Topical corticosteroids and antihistamines may be provided 4 weeks after randomization as rescue medications for an exacerbation of symptoms that is significant enough to warrant intervention.

For further details refer to the Pharmacy Manual.

6.2 Diet

History of drug or alcohol abuse in the last 2 years prior to Day 1 is an exclusion criterion. Screening for drugs of abuse may be performed at the discretion of the Investigator and in consultation with the Sponsor at any time during the study.

6.3 Smoking

Current users of nicotine >3 packs per day or nicotine equivalent/day is exclusionary for this study. Should subjects become non-compliant with these restrictions during the study, premature discontinuation may be considered by the Investigator, in consultation with the Sponsor, according to the terms stipulated in Section 4.10.

6.4 Blood Donation

Subjects are restricted from receiving blood or donating blood from Day 1 to the EOS Visit.

6.5 Contraception

Nonpregnant, nonlactating sexually active women of childbearing potential must agree to use a highly effective method of contraception from the Screening Visit until 16 weeks after final study drug administration.

- Note: highly effective methods of contraception include:
    - hormonal contraceptives associated with inhibition of ovulation (stable dose for at least 4 weeks prior to first dose)
    - intrauterine device
    - intrauterine system
    - double barrier methods of contraception (barrier methods include male condom, female condom, cervical cap, diaphragm, contraceptive sponge) in conjunction with spermicide.
    - tubal ligation
    - vasectomized male partner

Sexually active male subjects must have documented vasectomy or must agree to use a highly effective method of contraception as defined above with their partners of childbearing potential from first dose until 16 weeks after final study drug administration.

7 STUDY ASSESSMENTS AND PROCEDURES

Every effort should be made to schedule and perform study visits on the nominal day as outlined in Appendix 1.

7.1 Pharmacokinetic Assessments

PK blood samples will be collected by venipuncture at the times shown in Appendix 1. Procedures for collection, processing, and shipping of PK blood samples will be detailed in the Laboratory Manual.

7.2 Immunogenicity Assessment

ADA blood samples for immunogenicity will be collected by venipuncture at the times indicated in Appendix 1. Procedures for collection, processing, and shipping of immunogenicity blood samples will be detailed in the Laboratory Manual.

7.3 Clinical Response Assessments

Clinical response assessments will be conducted at times specified in Appendix 1. Pruritus will be assessed using daily recording of WI-NRS. Sleep will be assessed using Sleep Loss VAS at each study visit. Quality of life will be followed via ItchyQoL, PHQ-9, and GAD-7. Disease severity will be evaluated using PN-NAT, PN-IGA, IGA-CNPG-S, IGA-CNPG-A, PGI-PN-S, PGIC, as well as medical photography. Biomarkers will be assessed in the blood and the skin to understand the mechanism of clinical response to KPL-716.

7.3.1 Daily NRS Tool

The Daily NRS Tool (provided in Appendix 2: Daily NRS Tool for Phase 2b) contains one numerical rating scale to assess subjects' pruritus (WI-NRS) and one Yes/No question regarding the use of rescue medication for itch relief. The Daily NRS Tool will be used daily during the Screening Period through the EOS Visit.

7.3.2 Worst Itch Numerical Rating Scale

Subjects will be asked to assign a numerical score to the intensity of their most severe (worst) pruritus using a scale from 0 to 10, with 0 indicating no pruritus and 10 indicating the worst imaginable pruritus. This pruritus NRS will be used to assess subjects' daily level of worst pruritus during the Screening Period through the EOS Visit. The WI- NRS is provided in the Daily NRS Tool Appendix 2: Daily NRS Tool for Phase 2b.

7.3.3 Sleep loss Visual Analog Scale (Sleep Loss VAS)

Subjects will be asked to place a line perpendicular to the VAS line at the point that represents the intensity of their average sleeplessness experienced over the previous 3 nights using a scale from 0 to 10, with 0 indicating no sleeplessness and 10 indicating the worst imaginable sleeplessness at every visit (24). The Sleep Loss VAS (Appendix 5: Sleep Loss Assessment (average during the past 3 nights) is administered per the Schedule of Activities.

7.3.4 Prurigo Nodularis Nodule Assessment Tool (PN-NAT)

PN-NAT is a novel exploratory tool for the evaluation of disease severity based on estimate of the number of nodules over the whole body, estimate of hardness of nodules in representative area, estimate of extent of excoriation over the whole body, distribution of nodules, exact number of nodules in the representative area. There are 5 components to PN-NAT. Patients may present with smaller papular lesions, scarring, or post-inflammatory hyper- or hypo-pigmentation of the skin, which are not considered as part of this assessment. A score is assigned to each component based on the appearance of the disease at the time of the evaluation without referring to the baseline state. PN-NAT is provided in Appendix 3: Prurigo Nodularis Nodule Assessment Tool (PN-NAT). The PN-NAT tool is administered at designated visits.

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

PN-IGA is a novel exploratory tool for the overall assessment of PN disease severity based on the elevation of the nodules and number of elevated nodules. The IGA will be performed by the Investigator. The IGA utilizes a 5-point scale that ranges from 0 (clear) to 4 (severe disease). Patients may present with smaller papular lesions, scarring, or post-inflammatory hyper- or hypo-pigmentation of the skin, which are not considered as part of this assessment. An IGA score is assigned based on the appearance of the disease at the time of the evaluation without referring to the baseline state. Every effort will be made for the same Investigator to assess PN-IGA over time. PN-IGA is provided in Appendix 4: Prurigo Nodularis Investigator's Global Assessment (PN-IGA). The PN-IGA tool is administered at designated visits.

7.3.6 Investigator's Global Assessment of Prurigo Nodularis-Stage (IGA-CNPG-S)

IGA-CNPG-S is a novel tool for the assessment of PN disease severity based on the number of palpable nodules. The IGA will be performed by the Investigator. The IGA utilizes a 5-point scale that ranges from 0 (clear) to 4 (severe). A score is assigned based on the appearance of the disease at the time of the evaluation without referring to the baseline state. Every effort will be made for the same Investigator to assess IGA-CNPG-S over time. The IGA-CNPG-S is provided in Appendix 7: Investigator's Global Assessment for Prurigo Nodularis-Stage (IGA-CNPG-S). The IGA-CNPG-S tool is administered at designated visits.

7.3.7 Investigator's Global Assessment of Prurigo Nodularis-Activity (IGA-CNPG-A)

IGA-CNPG-A is a novel tool for the assessment of PN disease activity based on the proportion of nodules with excoriations and crusts. The IGA will be performed by the Investigator. The IGA utilizes a 5-point scale that ranges from 0 (clear) to 4 (severe). A score is assigned based on the appearance of the disease at the time of the evaluation without referring to the baseline state. Every effort will be made for the same Investigator to assess IGA-CNPG-A over time. The IGA-CNPG-A is provided in Appendix 8: Investigator's Global Assessment for Prurigo Nodularis-Activity (IGA-CNPG-A). The IGA-CNPG-A tool is administered at designated visits.

7.3.8 Medical Photographs

Standardized medical photographs will include photographs of the whole body, of the representative area (as the same area identified in the PN-NAT assessment) and biopsy areas.

Photographs will be collected pre-dose on dosing days. Whole body photographs will be taken of the upper front, lower front, upper back and lower back at 4 timepoints: Screening Visit, prior to dosing at Day 1, End of Double-Blind Period (Week 16), and the EOS Visits. The representative areas of the subject's disease will be photographed as detailed in Schedule of Activities. Sites of lesional and non-lesional biopsies will be photographed before dosing at Day 1 and at End of Double-Blind Period, prior to performing biopsies. Medical photographs will be used for confirmation of diagnosis of PN as outlined in the Study Manual and to follow response to therapy over time. Medical photographs will also be used to link skin biomarker data with the gross morphology of the skin.

Photographs will not include the face or genitals. Subject-identifiable information will be removed. In case of early termination or early withdrawal, medical photographs will be performed during subject's EOS Visit.

Instructions on taking the medical photographs are provided in study manuals.

7.3.9 ItchyQoL questionnaire

The ItchyQoL tool (Appendix 11: ItchyQoL Questionnaire

) focuses on impact of pruritus on daily activities and on the level of psychological stress. It contains 22 items. The frequency items are scored using a 5-point Likert scale ranging from "never" to "all the time". The bother items are scored from 1 (not bothered) to 5 (severely bothered). The recall period in ItchyQoL is the past week. There is a total score and 3 subscale scores: Symptom subscale, Functional subscale, and Emotional subscale (25). The ItchyQoL will be administered at designated visits.

7.3.10 Patient Health Questionnaire (PHQ-9)

The PHQ-9 (Appendix 9: Patient Health Questionnaire (PHQ-9) is a patient-reported measure that assesses the subject's general mental health. The PHQ-9 contains 9 items scored on a Likert scale ranging from 0: "not at all" to 3: "every day." The recall period is the past 2 weeks. Question 10 asks the subject to rate the impact of these problems on work, daily activities, and relationships. The PHQ-9 will be administered at designated visits.

7.3.11 General Anxiety Disorder (GAD-7)

The GAD-7 (Appendix 10: Generalized Anxiety Disorder (GAD-7) is a patient-reported survey that assesses the subject's level of anxiety. The GAD-7 contains 7 items scored on a Likert scale ranging from 0: "not at all" to 3: "nearly every day." The recall period is the past 2 weeks. The GAD-7 will be administered at designated visits.

7.3.12 Patient Global Impression of Prurigo Nodularis Severity (PGI-PN-S)

The PGI-PN-S (Appendix 12: Patient Global Impression of Prurigo Nodularis Severity (PGI-PN-S) is a patient-reported questionnaire that assesses the subject's impression of PN disease severity at the time of evaluation. It is scored from 0: "absent" to 4: "severe."

7.3.13 Patient Global Impression of Change (PGIC)

The PGIC (Appendix 6: Patient Global Impression of Change (PGIC) is a patient-reported survey that assesses the subject's impression of change on prurigo nodularis since the beginning of the study. Scoring ranges from -1: "very much improved" to 7: "very much worse."

7.4 Biomarker Assessments

7.4.1 Blood Sample Collection and Processing

Blood samples will be collected by venipuncture at the times indicated in Appendix 1. Blood biomarker profiles will be analyzed. Skin biomarker analyses will be performed and may include markers related to pruritus, inflammation, and/or fibrosis.

7.4.2 Skin Biopsy Collection and Processing

Subjects will undergo skin biopsy sampling for biomarker analysis at the times indicated in Appendix 1. Skin biopsies are optional. Skin biopsies will be collected pre- and post-treatment during the study.

Specific instructions will be provided in a separate manual.

7.5 Safety and Tolerability Assessments

7.5.1 Adverse Events

7.5.1.1 Adverse Event Definition and Categorization

The investigator is responsible for collecting all AEs that are observed or reported during the study from the time the subject signs the ICF through the EOS Visit, regardless of their relationship to study drug or their clinical significance.

An AE is any untoward medical occurrence in a subject or clinical investigation subject administered a pharmaceutical product, which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and/or unintended sign (including an abnormal laboratory finding), symptom or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product.

AEs also include: any worsening compared to baseline (i.e., any clinically significant change in frequency and/or intensity) of a pre-existing condition that is temporally associated with the use of the study drug; abnormal laboratory findings considered by the reporting investigator to be clinically significant.

A treatment-emergent AE (TEAE) is defined as any event not present before exposure to study drug or any event already present that worsens in either intensity or frequency after exposure to study drug.

The condition of subjects will be monitored from time of signing the ICF through the EOS Visit. In addition, subjects will be observed for any signs or symptoms and asked about their condition by open questioning, such as "How have you been feeling since you were last asked?", at every study visit from the Screening Visit through the EOS Visit.

All non-serious AEs, whether volunteered, elicited, or noted on the physical examination, and SAEs will be recorded from the Screening Visit (signing the ICF) through the EOS Visit. The AE information collected during the period from the Screening Visit until study drug administration on Day 1 is intended only for establishing a baseline status for subjects and for recording any screening procedure-related AEs. The nature, time of onset, duration, and severity of all AEs, both serious and non-serious, will be documented, together with an Investigator's opinion of the relationship to study drug administration.

Identification and reporting of injection site reactions (ISRs) will be performed in the context of safety surveillance for Adverse Events as outlined above. KPL-716 will be administered subcutaneously into an area of normal skin unaffected by PN, recording and reporting of ISRs will be provided to study sites.

Any changes or additions to the subject's concomitant medications will be entered into the eCRF with appropriate start and stop dates.

AEs or laboratory anomalies that are critical to safety evaluations and must be reported by the investigator to the sponsor and/or Clinical Research Organization (CRO) medical monitor.

All AEs and SAEs will be followed until resolution, until the Investigator and Sponsor agree that follow-up is no longer necessary, or the subject withdraws consent from the study or is lost to follow up. Any SAEs that are ongoing after completion of the last study visit or early termination should be followed up until the outcome has been determined.

The causal relationship between an AE and the study drug will be defined as below:

- Not Related: when the AE is definitely caused by the subject's underlying clinical state, or the study procedure/conditions
- Unlikely Related: when the temporal association between the AE and the drug is such that the drug is not likely to have any reasonable association with the AE
- Possibly Related: when the AE follows a reasonable temporal sequence from the time of drug administration but could have been produced by the subject's clinical state or the study procedures/conditions
- Related: when the AE follows a reasonable temporal sequence from administration of the drug, abates upon discontinuation of the drug, follows a known or hypothesized cause-effect relationship, and (if appropriate) reappears when the drug is reintroduced.

The severity of an AE will be recorded as one of the following:

- Mild: easily tolerated, does not interfere with normal daily activities, does not require intervention
- Moderate: causes some interference with daily activities; minimal, local, or noninvasive intervention indicated
- Severe: medically significant event; daily activities limited or completely halted; hospitalization or prolongation of hospitalization may be indicated.

Every reasonable effort will be made to follow subjects who have AEs. Any subject who has an ongoing AE at the EOS Visit will be followed, where possible, until resolution.

7.5.1.2 Adverse Drug Reactions

All noxious and unintended responses to an investigational medicinal product (IMP; i.e., where a causal relationship between an IMP and an AE is at least a reasonable possibility) related to any dose should be considered adverse drug reactions.

7.5.1.3 Adverse Event of Special Interest

An adverse event of special interest (AESI) is an adverse event (serious or nonserious) of scientific and medical concern, specific to the IMP or program, for which ongoing monitoring and rapid communication by the Investigator to the Sponsor may be appropriate. Such events may require further investigation on site in a timely manner by the investigator or designee in order to characterize and understand them. AESIs may be added or removed during a study by protocol amendment. Angioedema is considered as an AESI for detailed reporting and timely processing.

7.5.1.4 Serious Adverse Events

An SAE is defined as any untoward medical occurrence that at any dose:

- results in death, includes all deaths, even those that appear to be completely unrelated to study drug (e.g., car accident where subject is a passenger)
- is life-threatening. An AE is life-threatening if the subject was at immediate risk of death from the event as it occurred (i.e., does not include a reaction that might have caused death if it had occurred in a more serious form). For instance, drug-induced hepatitis that resolved without evidence of hepatic failure would not be considered life-threatening even though drug-induced hepatitis can be fatal.
- requires inpatient hospitalization or prolongation of existing hospitalization. Hospitalization signifies that the subject has been admitted to the hospital or short-stay-type unit, or an emergency room stay for longer than 24 hours for observation and/or treatment at a level of care which would not have been appropriate at the study site. Hospitalization for elective treatment of a pre-existing non-worsening condition or, which is not the result of an AE, are not considered an AE. The details of such hospitalizations must be recorded on the medical history or physical examination page of the eCRF. Complications occurring during hospitalization are AEs and are SAEs if they cause prolongation of the current hospitalization or meet other criteria that define SAEs.
- results in persistent or significant disability/incapacity. Disability is defined as a substantial disruption of a person's ability to conduct normal life functions. An AE is incapacitating or disabling if it results in a substantial and/or permanent disruption of the subject's ability to carry out normal life functions.
- is a congenital anomaly/birth defect
- is an important medical event

- Any suspected transmission via a medicinal product of an infectious agent reaction.

Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered SAEs when, based upon appropriate medical judgment, they may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

All SAEs will be followed until resolution, until the Investigator and the Sponsor agree that follow-up is no longer necessary, or the subject withdraws consent or is lost to follow-up.

Serious Adverse Event and AESI Reporting

Investigator Reporting Responsibilities to the Sponsor

SAEs and/or AESI due to any cause, whether or not related to the study drug, must be reported to the Sponsor or designee within 24 hours of occurrence or when the Investigator becomes aware of the event. A completed SAE report form must be submitted including a full description of the event and sequelae in the format detailed in the SAE reporting form. The following contact information is to be used for SAE reporting:

[redacted]

The event must also be recorded on the standard AE eCRF. Preliminary reports of SAEs must be followed by detailed descriptions as soon as possible including clear and redacted photocopies of hospital case reports, consultant reports, autopsy reports, and other documents when requested and applicable and if available.

Investigator Reporting Responsibilities to IRB

Unanticipated problems posing risks to study subjects will be reported to the IRB/IEC per their institutional policy. Copies of each report and documentation of IRB/IEC notification and acknowledgement of receipt will be kept in the Investigator's study file.

Sponsor Reporting Responsibilities to Participating Investigators

It is the responsibility of the Sponsor or designee to immediately notify all participating Investigators of any AE associated with the use of the study drug that is both serious and unexpected, as well as any finding from tests in laboratory animals that suggest a significant risk for human subjects.

7.5.2 Pregnancy

Formal reproduction toxicology testing of KPL-716 has not yet been performed.

Female subjects of childbearing potential must therefore agree to use a highly effective and protocol approved contraceptive method (Section 6.5) for the duration of the study and until

16 weeks after last study drug administration under this protocol. Regular pregnancy tests will be performed for female subjects of childbearing potential, as defined in Appendix 1.

Male subjects who have a female partner of childbearing potential must agree to use a highly effective and protocol approved contraceptive method (Section 6.5) for the duration of the study and until 16 weeks after last study drug administration under this protocol.

If a subject becomes pregnant while participating in the study, study drug dosing must be discontinued immediately.

A female subject must immediately inform the Investigator if she becomes pregnant during the study. A male subject must inform the Investigator if his female partner becomes pregnant during the study. Pregnancies occurring up to 16 weeks after last study drug administration must be reported to the Investigator. The Investigator must report all pregnancies to the Sponsor or designee immediately and no later than 24 hours of their first knowledge of the pregnancy. The Investigator should counsel the subject that it is unknown what effects study drug might have on a fetus. Monitoring of the subject should continue until conclusion of the pregnancy.

Instances of fetal death or congenital abnormality, if brought to the attention of the Investigator at any time after cessation of the study treatment and considered by the Investigator to be possibly related to the study treatment, must be reported to the Sponsor as an SAE.

7.5.3 Clinical Laboratory Evaluations

Blood and urine samples will be collected for clinical laboratory evaluations (including clinical chemistry, hematology, urinalysis, and serology) at the time points specified in Appendix 1.

Subjects will be asked to provide urine samples for a drugs of abuse screen at the Screening Visit and Day 1 prior to dosing and at any time during the study at the discretion of the Investigator and in consultation with the Sponsor, if needed.

For all female subjects of childbearing potential, the serum pregnancy test will be performed at the Screening Visit and the urine pregnancy test will be performed at the designated timepoints in Appendix 1. Dosing should not proceed if urine pregnancy test is positive, until a negative serum pregnancy test is confirmed. Postmenopausal status will be confirmed via FSH testing at Screening.

An Investigator will perform a clinical assessment of all clinical laboratory test results.

After Screening, any clinically significant abnormal findings should be reported as AEs.

7.5.4 Vital Signs

Supine blood pressure (systolic and diastolic), pulse rate, respiratory rate, and body temperature will be assessed at every visit from the Screening Visit through the EOS Visit as outlined in Appendix 1. Subjects must be supine for at least 5 minutes before blood pressure and pulse rate measurements.

Vital signs may also be performed at other times if judged to be clinically appropriate by the Investigator or if the ongoing review of the safety data suggests a more detailed assessment of vital signs is required. All measurements will be performed singly and may be repeated if outside the relevant clinical reference range. Additional vital sign assessments may be performed if clinically indicated, in the opinion of the Investigator.

7.5.5 12-Lead Electrocardiogram

The 12-lead ECG recording will be performed at the designated time points as outlined Appendix 1.

Resting 12-lead ECGs will be recorded after the subject has been supine and at rest for at least 5 minutes.

Single 12-lead ECGs will be repeated twice if either of the following criteria apply:

- QT interval corrected for heart rate using Fridericia's method - QTcF interval >500 ms in men and women
- QTcF change from the baseline (pre-dose) is >60 msec.

Additional 12-lead ECGs may be performed at other times if judged to be clinically appropriate or if the ongoing review of the data suggests a more detailed assessment of ECGs is required. The Investigator or designee will perform a clinical assessment of each 12-lead ECG.

Any new clinically significant ECG abnormalities occurring during the study will be recorded as AEs.

7.5.6 Physical Examination

A full physical examination or an abbreviated physical examination will be performed at the timepoints specified in Appendix 1.

A full physical examination includes head/neck/thyroid; eyes/ears/nose/throat (EENT); respiratory; cardiovascular; lymph nodes; abdomen; skin; musculoskeletal; and neurological. Breast, anorectal, and genital examinations will be performed only if medically indicated.

An abbreviated physical examination includes cardiovascular, respiratory, abdominal exams and as indicated based on subject's symptoms.

7.5.7 Safety Data Review

A SRT including 2 physicians from the Sponsor, 1 CRO medical monitor (if needed) and critical cross-functional team members from the Sponsor will meet periodically to review AEs/SAEs, reasons for study discontinuations, and key clinical and laboratory assessments. SRT members will be blinded to subject treatment assignment. The SRT will operate under the SOPs of the sponsor SRT.

The study may be terminated if unexpected, significant, or unacceptable safety risks to enrolled subjects arise, or if recommended by applicable board(s) after review of safety and efficacy data.

8 SAMPLE SIZE AND DATA ANALYSES

8.1 General Considerations

All statistical analyses will be performed using Statistical Analysis Software (SAS®) Version 9.4 or later. All clinical study data will be presented in subject data listings. Descriptive statistics will be presented for all endpoints and will include number of subjects (n), mean, standard deviation, first quartile (Q1), median, third quartile (Q3), minimum and maximum for continuous variables, and frequency and percentage for categorical and ordinal variables.

Unless otherwise specified, all tests will be two-tailed using pre-specified levels of significance.

Statistical analyses for the Phase 2b portion of the study will be conducted separately. An integrated analysis of the pooled data may be performed at the end of the study depending on the results of these individual analyses. Details for the analyses will be specified in the SAP.

8.2 Handling of Dropouts and Missing Data

Criteria for removal of subjects from therapy or assessments are explained in Section 4.10. To the extent possible, attempts will be made to minimize the amount of missing data through measures planned in the study conduct. Details for handling missing values will be specified in the SAP.

8.3 Multiple Comparisons/Multiplicity

As this is a dose finding study, there is no multiplicity adjustment planned for the comparisons of multiple doses of KPL-716 versus placebo.

8.4 Determination of Sample Size

The Phase 2b sample size calculation is based on the primary efficacy endpoint percentage change from baseline of WI-NRS at Week 16 using a two-sample t-test.

Approximately 180 subjects in total will be equally randomized to the 4 arms of Phase 2b. At Week 16, 53% and 30% reduction in weekly average of WI-NRS are assumed for KPL-716 and placebo arms, respectively. For each comparison, assuming treatment effect of 23% difference in weekly average WI-NRS reduction from baseline at Week 16 and standard deviation of 35%, and two-sided alpha of 0.05, 38 subjects in each arm will guarantee 80% power to the treatment effect. Approximately 45 patients in each arm are required after adjusting for 15% lost follow up.

8.5 Analysis Populations

The following analysis sets will be defined for the Phase 2b portion of the study.

8.5.1 Modified Intent-to-Treat Analysis Sets

All randomized subjects who receive at least 1 dose of KPL-716 or placebo and have at least 1 daily WI-NRS score in the double-blind Treatment Period will be included in the modified

intent-to-treat (mITT) analysis set. Efficacy analyses will be based on the mITT analysis sets. All mITT analyses will be based on each subject's randomized treatment assignment.

8.5.2 Safety Analysis Sets

All randomized subjects who take at least 1 dose of KPL-716 or placebo will be included in the Safety Analysis Set. Safety analyses will be based on the treatment (KPL-716 or Placebo) that was administered to each subject.

8.5.3 Per Protocol (PP) Analysis Sets

All mITT subjects who have no important protocol deviations that may potentially bias efficacy analyses of the study will be included in the PP set.

8.5.4 Pharmacokinetic Analysis Sets

Subjects who received KPL-716 and who had at least one PK sample will be included in the PK population.

8.6 Analysis of Efficacy

All efficacy analyses will be performed on the mITT analysis set. The primary efficacy endpoint in Phase 2b will be analyzed with ANCOVA including treatment as fixed effect, baseline WI-NRS, and randomization stratification factors as covariates.

For key secondary efficacy endpoints, the difference of proportions and the corresponding 95% CI for the difference of proportions will be displayed. Treatment groups will be compared using a Cochran-Mantel-Haenszel test controlling for the randomization stratification variables.

The analyses of primary and key secondary efficacy endpoints will be repeated using the PP set to assess the sensitivity of the results to important protocol deviations that could potentially bias the analysis. All efficacy data will be listed by subject.

Details will be specified in the Phase 2b SAP.

8.7 Analysis of Safety

All safety analyses will be conducted based on the Safety Analysis Set. Summary tables will be done for safety endpoints (treatment emergent AEs, labs, vital signs, etc.). All safety data will be listed by subject. Details for the analysis of safety data will be provided in the SAP.

8.7.1 Adverse Events

Adverse events will be mapped to preferred term (PT) and system organ class (SOC) using the most up to date Medical Dictionary for Regulatory Activities (MedDRA). AEs that begin after the first administration of study drug or existing AEs that worsen after the first dose of study medication are considered TEAEs. The number and percentage of subjects reporting TEAEs will be summarized for each treatment group by MedDRA SOC and PT, by severity, and by relationship to study treatment. The number and percentage of subjects with serious AEs, and the number and percentage of subjects with AEs leading to treatment

discontinuation will also be summarized for each treatment group by MedDRA system organ class and preferred term.

8.7.2 Clinical and Laboratory Events and Analyses

Continuous laboratory data will be examined for trends using descriptive statistics of actual values and changes from baseline over time in each treatment group. These data will also be categorized as low, normal, or high based on the reference ranges of the central laboratory. Shift tables from baseline to each post baseline time point will be presented.

8.7.3 Vital Signs

Vital signs will be summarized using descriptive statistics of actual values and changes from baseline over time. The incidence of clinically notable vital signs will be summarized by treatment group.

8.7.4 Physical Examination

Clinically significant new or worsened physical examination abnormalities following treatment will be recorded as AEs and will be reflected in the summary of AEs.

8.7.5 Concomitant Medications

Concomitant medications will be coded using WHO Drug Dictionary and will be classified by Anatomical Therapeutic Chemical (ATC) classification level 4 and PT for the Safety Analysis Set. Frequencies and percentages of subjects using each concomitant medication will be presented for the Safety Analysis Set overall, and by treatment group. All medication use will be listed regardless of the timing of the start of the medication.

8.8 Pharmacokinetic Analyses

For all subjects, serum samples will be collected before each dose at time points shown in Appendix 1 to quantify concentrations of KPL-716. Descriptive statistics will be calculated for the serum concentrations of KPL-716 by visit. Individual listings of plasma concentrations will be provided.

Pharmacokinetic data may be used in a subsequent population pharmacokinetic evaluation that will be conducted outside of this study and described in a separate report.

8.9 Biomarker Analyses

Skin and blood biomarkers levels will be analyzed and summarized in a separate report

8.10 Immunogenicity Analyses

Serum ADA will be listed and summarized by treatment group and overall using descriptive statistics.

8.11 Gene Expression Analyses

Biomarker profiles (eg, potentially cytokines, chemokines, and other inflammatory markers) will be analyzed from blood samples. Gene expression will also be analyzed from skin biopsy specimens. Other gene expression analyses may be performed for target genes related to pruritus, inflammation, and/or fibrosis as determined by the Sponsor and summarized in a separate report.

Descriptive statistics and changes from baseline, as applicable, will be calculated for gene expression. No inferential statistical analyses are planned.

8.12 Interim Analyses

An interim analysis for Phase 2b portion may be conducted after at least 50% subjects complete Week 16 Visit. If the interim analysis is conducted in the Phase 2b part, a two-sided alpha of 0.0001 will be spent. The two-sided alpha level for the final Phase 2b efficacy analysis will be 0.05. Additional details regarding the interim analysis, if performed, will be provided in the SAP along with other analysis plans.

9 QUALITY CONTROL AND QUALITY ASSURANCE

9.1 Auditing

The study may be audited or reviewed by Kiniksa Quality Assurance department, IRB/IEC, and/or regulatory authority at any time. The study site is required to allow for study-related monitoring, audits, IRB review, and regulatory inspections by providing direct access to the study source data and documents.

Measures will be undertaken to protect the confidentiality of records that could identify subjects, ensuring the privacy and confidentiality rules are followed in accordance with applicable regulatory requirements.

9.2 Monitoring

The Sponsor will designate a Study Monitor who will be responsible for monitoring this clinical trial. The Study Monitor will monitor the study conduct, eCRF and source documentation completion and retention, and accurate study drug accountability. To this end, the Study Monitor will visit the study site at scheduled intervals per the Sponsor requirements and will be expected to be in frequent contact with the study site through verbal and written communication. It is essential that the Study Monitor has access to all documents, related to the study and the individual subjects, at any time these are requested. In turn, the Study Monitor will adhere to all requirements for subject confidentiality as outlined in the ICF. The Investigator and Investigator's staff will be expected to cooperate with the Study Monitor, to be available during a portion of the monitoring visit to answer questions, and to provide any missing information.

Monitoring to review study drug receipt, inventory, storage, documentation, and handling will be conducted by the study monitor. In Part 2b this activity may be performed by separate unblinded study monitor.

Specific details will be outlined in the Clinical Monitoring Plan.

10 DATA HANDLING AND RECORD KEEPING

10.1 Data Handling

The Sponsor's CRO will be responsible for data management of this study, including quality of the data. The study site will be responsible for data entry into the electronic data capture system (EDC) system. A comprehensive validation check program will verify the data. Discrepancies will be generated automatically in the system at the point of entry or added manually for resolution by the study site staff.

The Data Management Plan will outline the quality checks to be performed on the data. Study data transfers will be outlined in Data Transfer Agreements.

10.2 Case Report Form

Data will be captured in source documentation at study sites and then entered into the eCRFs or EDC by staff at the study site. Following data entry, the eCRF pages and the data entry will undergo quality control checks in accordance with written procedures. Any discrepancies will be resolved in the database.

Following all data validation steps, the Investigator will sign the completed electronic data prior to any planned interim data analysis snapshots and/or a final database lock.

10.3 Records

Records and documents, including signed ICF, pertaining to the conduct of this study must be retained by the study site in accordance with 21 Code of Federal Regulations 312.62(c). No records may be destroyed during the retention period without the written approval of the Sponsor. No records should be transferred to another location or a third-party vendor without a written notification to the Sponsor.

Study records will be maintained by the Sponsor or Designee. Record and document keeping will be detailed in a separate plan.

11 ETHICAL AND REGULATORY CONSIDERATIONS

11.1 Ethics Committee or Institutional Review Board

Prior to the start of the study, the following documents will be reviewed and approved by the participating IRB/IEC according to local procedures:

- protocol
- ICF
- subject recruitment procedures (e.g., advertisements)
- any other written information to be provided to subjects.

The IRB will be informed by the Investigator of any changes to the approved protocol.

Any amendments to the protocol will require IRB/IEC approval. Any administrative amendments to the protocol will be provided to IRBs/IECs according to IRB/IEC procedures.

The IRB/IEC will be informed by the Investigator of serious and unexpected SAEs in accordance with the IRB/IEC reporting requirements. The Investigator will provide the IRB/IEC with progress reports per IEB/IEC procedures.

11.2 Regulatory Considerations

The study will be conducted in accordance with the protocol and with:

- consensus ethical principles derived from international ethics guidelines, including the Declaration of Helsinki and Council for International Organizations of Medical Sciences Ethical Guidelines
- International Conference on Harmonization (ICH) E6 Guideline for Good Clinical Practice
- applicable local laws and regulations.

The Investigator will be responsible for the overall conduct at the study site and adherence to the requirements of the ICH guidelines and all other applicable local regulations.

11.3 Informed Consent

Prior to starting participation in the study, each subject will be provided with a study-specific ICF that includes all required elements of informed consent per ICH and local regulations. The ICF will give details of the study drug, procedures, and potential risks of the study. Subjects will be instructed that they are free to obtain further information from the Investigator and that their participation is voluntary, and they have the right to voluntarily withdraw from the study at any time.

Following discussion of the study with the study site personnel, subjects will sign and date the ICF in the presence of a qualified staff member to indicate that they are voluntarily giving their informed consent. One copy will be given to the subject, and the original signed ICF will be maintained in the subject's records at the study site.

Skin biopsies are optional in this study.

11.4 Subject Confidentiality

All personal data collected and processed for the purposes of this study should be managed by the Investigator and his/her staff with adequate precautions to ensure confidentiality and security according to national and/or local laws and regulations on personal data protection.

Sponsor and study vendor databases will similarly be managed and maintained according to national and/or local laws and regulations to prevent unauthorized access, disclosure, dissemination, alteration or loss of information and personal data. In the event of any such data security breach, immediate action will be taken by sponsor and/or study vendor to remedy the breach, assess the extent of data exposure, and implement appropriate measures to limit possible adverse effects.

Monitors, auditors, and other authorized agents of the Sponsor and/or its designee, the ethics committees approving this research, as well as that of any other applicable agency(ies), will be granted secured direct access to the study subjects' original medical records for verification of clinical study procedures and/or data, without violating the confidentiality of the subjects to the extent permitted by the law and regulations. In any presentations of the results of this study or in publications, the subjects' identity will remain confidential.

11.5 Protocol Amendments

Protocol amendments will be submitted to the IRB/IEC and to regulatory authorities in accordance with local regulatory requirements. Approval must be obtained from the IRB/IEC and regulatory authorities (as locally required) before implementation of any changes, except for changes necessary to eliminate an immediate hazard to subjects, as defined by regulatory requirements.

12 ADMINISTRATIVE ASPECTS

12.1 Disclosure

All information provided regarding the study, as well as all information collected and/or documented during the study, shall be regarded as confidential of the Sponsor. The Investigator (and/or designee) agrees to use such information solely for carrying out the study and to not disclose such information in any way without a prior written permission from the Sponsor. Study information from this protocol will be posted on publicly available clinical trial registers according to local regulations.

12.2 Reports and Publications

The Sponsor shall have the sole and exclusive right to publish information obtained from the study, including any data, results, and conclusions. Investigators participating in the study execution may be invited to participate in the authorship of a potential publication in a manner commensurate with their participation in the study execution and in accordance with International Committee of Medicinal Journal Editors standards.

12.3 Finances and Insurance

Financing and insurance will be addressed in a separate agreement.

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14 APPENDICES

14.1 Appendix 1: Schedule of Activities

Table 1 Schedule of Activities for Phase 2b

Study Visits	Screen-ing	Double-Blind Period						Open-Label Extension Period[14]																
Week (W)	W-4 to W0	Base-line	W2	W4	W8	W12	W16/EOT	W18	W20	W22[15]	W24[15]	W26[15]	W28[15]	W30[15]	W32	W34[15]	W36[15]	W38[15]	W40[15]	W42[15]	W44[15]	W46[15]	W48	W52/EOS
Day (D)	D -28 to -1	D1	D15	D29	D57	D85	D113	D127	D141	D155	D169	D183	D197	D211	D225	D239	D253	D267	D281	D295	D309	D323	D337	D365
Study Procedures	Windows (Days)	0	±2	±2	±2	±2	±2	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3
Informed consent	X																							
Demographics	X																							
Medical and surgical history	X	X																						
Prior medications, therapies, procedures	X	X																						
Eligibility Assessment	X	X																						
ASR and PRR training[8]	X	X		X	X	X																		
Safety Assessments																								
Physical examination[1]	X	X	X	X	X	X	X	X	X						X								X	X
Vital signs[3]	X	X	X	X	X	X	X	X	X						X								X	X
Body weight, height, BMI[2]	X	X	X	X	X	X	X	X	X						X								X	X
ECG (12-lead)[3]	X	X			X		X																	X
Quantiferon-based TB test	X																							
Adverse event monitoring	From the Screening Visit through the EOS Visit (Week 52)																							
Concomitant meds/therapies/ procedures	From the Screening Visit through the EOS Visit (Week 52)																							
Compliance assessment	From the Screening Visit through the EOS Visit (Week 52)																							

Study Visits	Screen-ing	Double-Blind Period						Open-Label Extension Period[14]															
Week (W)	W-4 to W0	Base-line	W2	W4	W8	W12	W16/EOT	W18	W20	W22[15]	W24[15]	W26[15]	W28[15]	W30[15]	W32	W34[15]	W36[15]	W38[15]	W40[15]	W42[15]	W44[15]	W46[15]	W48	W52/ EOS
Day (D)	D -28 to -1	D1	D15	D29	D57	D85	D113	D127	D141	D155	D169	D183	D197	D211	D225	D239	D253	D267	D281	D295	D309	D323	D337	D365
Study Procedures	Windows (Days)	0	±2	±2	±2	±2	±2	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3
Laboratory Tests																								
Clinical laboratory blood tests	X	X	X	X	X	X	X	X	X						X								X	X
Urinalysis	X	X					X								X								X	X
Pregnancy test[4]	X	X			X		X								X								X	X
Serology (HIV, HBV, HCV)	X																							
COVID-19 test	X	X[5]																						
Urine Drug of Abuse screen[6]	X	X																						
Dosing																								
Randomization		X																						
Study drug administration [7,14]		X		X	X	X	X[13]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Drug accountability		X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Efficacy and PD Measures																								
Daily NRS Tool for assessment of pruritus and rescue medication use[8]	From the Screening Visit through the EOS Visit (Week 52)																							
Sleep Loss VAS	X	X	X	X	X	X	X	X	X						X								X	X
IGA-CNPG-S	X	X	X	X	X	X	X	X	X						X								X	X
IGA-CNPG-A	X	X	X	X	X	X	X	X	X						X								X	X
PN-NAT	X	X	X	X	X	X	X	X	X						X								X	X
PN-IGA	X	X	X	X	X	X	X	X	X						X								X	X

Study Visits	Screen-ing	Double-Blind Period						Open-Label Extension Period[14]															
Week (W)	W-4 to W0	Base-line	W2	W4	W8	W12	W16/EOT	W18	W20	W22[15]	W24[15]	W26[15]	W28[15]	W30[15]	W32	W34[15]	W36[15]	W38[15]	W40[15]	W42[15]	W44[15]	W46[15]	W48	W52/ EOS
Day (D)	D -28 to -1	D1	D15	D29	D57	D85	D113	D127	D141	D155	D169	D183	D197	D211	D225	D239	D253	D267	D281	D295	D309	D323	D337	D365
Study Procedures	Windows (Days)	0	±2	±2	±2	±2	±2	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3
PGI-PN-S	X	X	X	X	X	X	X	X	X						X								X	X
ItchyQoL	X	X		X	X	X	X	X	X						X								X	X
PHQ-9	X	X			X		X		X						X								X	X
GAD-7	X	X			X		X		X						X								X	X
PGIC				X	X	X	X		X						X								X	X
Medical photographs – representative areas[9]	X	X		X	X	X	X	X	X						X								X	X
Medical photographs – whole body[9]	X	X					X																	X
Medical photographs – prior to biopsies[10]		X					X																	
Skin biopsies[10]		X					X																	
Blood biomarker samples[11]		X			X		X																	
PK and Immunogenicity Evaluation																								
PK samples[12]		X	X	X	X	X	X	X	X						X								X	X
ADA samples		X	X	X	X	X	X	X	X						X								X	X

ADA = anti-drug antibodies; ASR = accurate symptom reporting; β hCG = β-human chorionic gonadotropin; BMI = body mass index; ECG = electrocardiogram; EOS = end of study; EOT = end of treatment; GAD-7 = General Anxiety Disorder-7; HBV = hepatitis B virus; HCV = hepatitis C virus; HIV = human immunodeficiency virus; WI-NRS = Worst itch numeric rating scale; PD = pharmacodynamic; PHQ-9= Patient Health Questionnaire-9; PK = pharmacokinetics; PN-NAT = Prurigo Nodularis Nodule Assessment Tool; PN-IGA = Prurigo Nodularis Investigator Global Assessment; PRR = placebo response reduction; ItchyQoL = Itchy Quality of Life; VAS=Visual Analog Scale; IGA-CNPG-S = Investigator's Global Assessment for Prurigo Nodularis-Stage; IGA-CNPG-A = Investigator's Global Assessment for

Prurigo Nodularis-Activity; PGIC = Patient Global Impression of Change; PGI-PN-S = Patient Global Impression of Prurigo Nodularis Severity. Subjects may be asked to return to the study site if needed to complete eligibility assessment. At prescreening, potentially eligible subjects may be matched with the closest study site.

[1] At the Screening Visit, prior to dosing on Day 1, Week 16 and at the EOS Visit (Week 52), a full physical examination will be performed to assess the following systems: head/neck/thyroid; eyes/ears/nose/throat (EENT); respiratory; cardiovascular; lymph nodes; abdomen; skin; musculoskeletal; and neurological. Breast, anorectal, and genital examinations will be performed only if medically indicated. At all other designated visits, a focused examination on skin condition and an abbreviated physical examination will be performed consisting of cardiovascular, respiratory, and abdominal systems and as indicated based on subjects' symptoms. Additional physical examinations may be performed at any time if medically indicated per the Investigator's medical judgement.

[2] Height will be measured, and BMI will be calculated only at the Screening Visit. Weight will be measured at all designated study visits.

[3] Blood draws and ECG (12-lead ECG) will be recorded within 2 hours of dosing. ECG and vital signs will be performed prior to blood draws, skin biopsies and medical photography.

[4] Females of childbearing potential only. A serum βhCG pregnancy test is performed at the Screening Visit. A urine βhCG test is performed at all later time points and a serum βhCG test is performed if urine βhCG test is positive at these timepoints. Dosing should not proceed if urine pregnancy test is positive, until a negative serum pregnancy test is confirmed.

[5] Baseline COVID results not required to proceed with randomization dosing.

[6] Additional screening for drugs of abuse may be performed at the discretion of the Investigator and in consultation with the Sponsor at any time during the study.

[7] On dosing days, all blood samples (safety, PK, ADA, biomarkers, serum pregnancy if indicated, etc.), all urine samples (urinalysis, pregnancy, urine drug screen if indicated), all efficacy assessments (Sleep Loss VAS, PN-NAT, PN-IGA, etc.), all patient reported outcomes (ItchyQoL, PHQ-9, GAD-7), all medical photography, ECG and/or skin biopsies will be performed prior to dosing. Subjects will be randomized to receive KPL-716 or placebo on Day 1. Subjects will be observed for 1 hour after each dosing. Vital signs will be measured at the end of the 1-hour observation period and adverse events will be recorded if any. In case study drug treatment is interrupted or discontinued, subjects should continue with study visits as outlined in the Schedule of Activities, minus dosing. In case of early withdrawal, subjects will follow the schedule of activities for the EOS Visit (Week 52).

[8] At the Screening Visit, subjects will be instructed through ASR and PRR training to evaluate the intensity of their WI-NRSon a daily basis. The ASR and PRR training should be repeated monthly until Week 12 or as needed. The daily recordings can begin any time after the Screening Visit. Eligible subjects will continue daily recording of WI-NRS and rescue medication use from Day 1 through the EOS Visit.

[9] At the Screening Visit, medical photographs will be taken of the representative area of subject's disease as determined by the PI. The same representative area will be followed over time. In addition, whole body medical photographs will be captured (upper front and lower front, upper back, and lower back) without the face and with the genitals covered. Confirmation of diagnosis of PN will be performed by review of medical photographs (Refer to Study Manual) prior to each subject's randomization.

[10] Skin biopsies will be collected pre- and post-treatment during the study, Skin biopsies are optional. A medical photograph of the location of the biopsies (prior to biopsies) will be taken.

[11] Blood samples for biomarkers include serum sample(s) and whole blood sample(s) for each individual patient.

[12] PK blood samples will be collected prior to study drug administration on dosing days.

[13] This study drug administration (which is part of the OLE) will only occur if subjects elect to be in the OLE.

[14] All subjects will have the option to receive KPL-716 360 mg SC, Q2W during the OLE Period to evaluate long-term safety and PK.

[15] Should subjects self-administer drug, collection of AEs, concomitant medication use, and NRS compliance assessments may be completed remotely by study staff.

14.2 Appendix 2: Daily NRS Tool for Phase 2b

<table>
<tr><td colspan="2">Daily Assessment of Itch and Rescue Medications in Prurigo Nodularis
Instructions: Please select the box that best describes your experience with prurigo nodularis <u>over the past 24 hours.</u></td></tr>
<tr><td>1. Over the <u>past 24 hours</u>, how would you rate your <u>most severe itch</u>?</td><td>0 ☐ No itch
1 ☐
2 ☐
3 ☐
4 ☐
5 ☐
6 ☐
7 ☐
8 ☐
9 ☐
10 ☐ Worst imaginable itch</td></tr>
<tr><td colspan="2">Instructions: The next question is about your rescue medication use for itch over the past 24 hours.</td></tr>
<tr><td>2. Please mark below if you used any medication to reduce itch other than the study drug.</td><td>Yes ☐ No ☐</td></tr>
</table>

14.3 Appendix 3: Prurigo Nodularis Nodule Assessment Tool (PN-NAT)

Instructions: The purpose of this tool is to assess the *severity* of nodule burden and guide the physician's assessment of a patient's prurigo nodularis. Patients may present with smaller papular lesions, scarring, or post-inflammatory hyper- or hypo-pigmentation of the skin, which are not considered as part of this assessment. Using your clinical judgment and the guidelines provided below, please select a score for each item that best describes the patient's prurigo nodularis right now.

Please refer to the following definitions to guide the assessment:

- "Nodule" is defined as a raised hard lesion of approximately 0.5 cm to 2 cm in diameter
- "Smaller papular lesion" is defined as a raised lesion of less than 0.5 cm in diameter
- "Scarring" is defined as fibrous tissue that has replaced normal skin after damage by injury or disease
- "Post-inflammatory hyperpigmentation" is defined as increased pigmentation in the location where there used to be inflammation
- "Post-inflammatory hypopigmentation" is defined as decreased pigmentation in an area where there used to be inflammation
- "Excoriation" is defined as a scratch mark or a linear break in the skin that that could be open or covered with blood or crust

Estimate of the Number of Nodules Over the Whole Body	
Score	
0	0 nodules
1	1-9 nodules
2	10-19 nodules
3	20-49 nodules
4	≥50 nodules
Estimate of Extent of Excoriations Over the Whole Body	
Score	
0	0 nodules are excoriated
1	<25% of nodules are excoriated
2	25%-75% of nodules are excoriated
3	>75% of nodules are excoriated
Distribution of Nodules	
Select all body parts with nodules	Upper arm (from the elbow to the shoulder) • right • left Lower arm (from the elbow to the hand) • right • left Trunk including chest, abdomen, groin, or buttocks • front trunk • back trunk • groin

	• buttocks Upper leg (from the knee to the upper thigh) • right • left Lower leg (from the knee to the foot) • right • left
Number of body parts with nodules	
Exact nodule count in representative area	
Select the Representative Area Please refer to the user manual for instructions to select a representative area.	Upper arm (from the elbow to the shoulder) • right • left Lower arm (from the elbow to the hand) • right • left Trunk including chest, abdomen, groin, or buttocks • front trunk • back trunk • groin • buttocks Upper leg (from the knee to the upper thigh) • right • left Lower leg (from the knee to the foot) • right • left
Exact number of nodules in representative area	

Estimate of Hardness of Nodules in Representative Area	
Score	
0	0 nodules are hard
1	<25% of nodules are hard
2	25%-75% of nodules are hard
3	>75% of nodules are hard

14.4 Appendix 4: Prurigo Nodularis Investigator's Global Assessment (PN-IGA)

Instructions: The purpose of this tool is to assess the severity of nodule burden and guide the physician's global assessment of a patient's prurigo nodularis based on (a) the presence /absence of nodules and (b) the size of nodules as defined by their elevation. Patients may present with smaller papular lesions, scarring, or post-inflammatory hyper- or hypo-pigmentation of the skin, which are not considered as part of this assessment. Using your clinical judgment and the guidelines provided below, please select a score for each item that best describes the patient's prurigo nodularis right now.

Please refer to the following definitions to guide the assessment:

1. "Nodule" is defined as a raised hard lesion of approximately 0.5 cm to 2 cm in diameter
2. "Smaller papular lesion" is defined as a raised lesion of less than 0.5 cm in diameter
3. "Scarring" is defined as fibrous tissue that has replaced normal skin after damage by injury or disease
4. "Post-inflammatory hyperpigmentation" is defined as increased pigmentation in the location where there used to be inflammation
5. "Post-inflammatory hypopigmentation" is defined as decreased pigmentation in an area where there used to be inflammation

Estimate of the Number of Nodules Over the Whole Body	
Grade (select one)	Morphological Descriptor
○ Clear	No nodules
○ Almost Clear	Nodules are present, none (0%) are severely elevated (> 0.5 cm in elevation)
○ Mild	Nodules are present, few (less than 25%) are severely elevated (> 0.5 cm in elevation)
○ Moderate	Nodules are present, some (25%-75%) are severely elevated (> 0.5 cm in elevation)
○ Severe	Nodules are present, most (greater than 75%) are severely elevated (> 0.5 cm in elevation)

14.5 Appendix 5: Sleep Loss Assessment (average during the past 3 nights)

Please place a perpendicular line at the point that represents the intensity of your average sleeplessness over the past 3 nights using the scale below, where 0 indicates no sleeplessness and 10 indicates the worst imaginable sleeplessness.

0 1 2 3 4 5 6 7 8 9 10

Measure: _____cm Subject Initials : _____

14.6 Appendix 6: Patient Global Impression of Change (PGIC)

Since the start of the study, my prurigo nodularis is:

✓ one box only:

(1) ☐ Very Much Improved
(2) ☐ Much Improved
(3) ☐ Minimally Improved
(4) ☐ No Change
(5) ☐ Minimally Worse
(6) ☐ Much Worse
(7) ☐ Very Much Worse

14.7 Appendix 7: Investigator's Global Assessment for Prurigo Nodularis-Stage (IGA-CNPG-S)

IGA for Chronic nodular Prurigo (Prurigo nodularis) Stage, Version 2.0 _06.Dec.2018_English

Center for Chronic Pruritus, University Hospital Münster, Germany

IGA Chronic Nodular Prurigo Stage© (IGA-CNPG S)

Version 2.0 (December 06 2018)

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

14.8 Appendix 8: Investigator's Global Assessment for Prurigo Nodularis-Activity (IGA-CNPG-A)

IGA for Chronic nodular Prurigo (Prurigo nodularis) Activity, Version 2.0_06.Dec.2018_English

Center for Chronic Pruritus, University Hospital Münster, Germany

IGA Chronic Nodular Prurigo Activity© (IGA-CNPG A)

Version 2.0 (December 06 2018)

Score	Category	Description: Activity (IGA-CNPG 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 76-100% of all nodules)

14.9 Appendix 9: Patient Health Questionnaire (PHQ-9)

PATIENT HEALTH QUESTIONNAIRE-9 (PHQ-9)

Over the last 2 weeks, how often have you been bothered by any of the following problems? *(Use "✓" to indicate your answer)*	Not at all	Several days	More than half the days	Nearly every day
1. Little interest or pleasure in doing things	0	1	2	3
2. Feeling down, depressed, or hopeless	0	1	2	3
3. Trouble falling or staying asleep, or sleeping too much	0	1	2	3
4. Feeling tired or having little energy	0	1	2	3
5. Poor appetite or overeating	0	1	2	3
6. Feeling bad about yourself — or that you are a failure or have let yourself or your family down	0	1	2	3
7. Trouble concentrating on things, such as reading the newspaper or watching television	0	1	2	3
8. Moving or speaking so slowly that other people could have noticed? Or the opposite — being so fidgety or restless that you have been moving around a lot more than usual	0	1	2	3
9. Thoughts that you would be better off dead or of hurting yourself in some way	0	1	2	3

FOR OFFICE CODING 0 + _____ + _____ + _____
=Total Score: _____

If you checked off any problems, how difficult have these problems made it for you to do your work, take care of things at home, or get along with other people?

Not difficult at all	Somewhat difficult	Very difficult	Extremely difficult
☐	☐	☐	☐

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14.10 Appendix 10: Generalized Anxiety Disorder (GAD-7)

GAD-7

Over the last 2 weeks, how often have you been bothered by the following problems? *(Use "✔" to indicate your answer)*	Not at all	Several days	More than half the days	Nearly every day
1. Feeling nervous, anxious or on edge	0	1	2	3
2. Not being able to stop or control worrying	0	1	2	3
3. Worrying too much about different things	0	1	2	3
4. Trouble relaxing	0	1	2	3
5. Being so restless that it is hard to sit still	0	1	2	3
6. Becoming easily annoyed or irritable	0	1	2	3
7. Feeling afraid as if something awful might happen	0	1	2	3

(For office coding: Total Score T____ = ____ + ____ + ____)

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14.11 Appendix 11: ItchyQoL Questionnaire

Site number: _____ Subject initials: _____ Subject number: _____ Visit date (dd/mmm/yyyy): _____
Time of completion: _____:_____

The following questions concern your feelings about your itchy skin condition. Please check the answer that best describes your experience.	**How often during the past week do these statements apply to you?**				
	NEVER	**RARELY**	**SOMETIMES**	**OFTEN**	**ALL THE TIME**
1. My itchy skin condition bleeds.	☐1	☐2	☐3	☐4	☐5
2. My skin hurts because of my itchy skin condition.	☐1	☐2	☐3	☐4	☐5
3. My itchy skin condition burns or stings.	☐1	☐2	☐3	☐4	☐5
4. I get scars from my itchy skin condition.	☐1	☐2	☐3	☐4	☐5
5. I need to scratch my itchy skin condition.	☐1	☐2	☐3	☐4	☐5
6. Temperature or seasonal changes aggravate my itchy skin condition.	☐1	☐2	☐3	☐4	☐5
7. I spend a lot of money treating my itchy skin condition.	☐1	☐2	☐3	☐4	☐5
8. My itchy skin condition makes it hard to work or do what I enjoy.	☐1	☐2	☐3	☐4	☐5
9. My itchy skin condition affects my interaction with others. (For example: family, friends, close relationships, etc.)	☐1	☐2	☐3	☐4	☐5

The following questions concern your feelings about your itchy skin condition. Please check the answer that best describes your experience.	**How often during the past week do these statements apply to you?**				
	NEVER	**RARELY**	**SOMETIMES**	**OFTEN**	**ALL THE TIME**
10. My itchy skin condition affects how well I sleep.	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
11. My itchy skin condition often makes it difficult to concentrate.	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
12. My itchy skin condition limits the types of clothes I can wear.	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
13. My itchy skin condition forces me to buy special soaps, detergents, and lotions.	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
14. I am frustrated by my itchy skin condition.	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
15. I am embarrassed by my itchy skin condition.	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
16. My itchy skin condition drives me crazy/nuts.	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
17. My itchy skin condition makes me angry or irritable.	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
18. My itchy skin condition makes me feel depressed or sad.	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
19. I worry about what other people think about me because of my itchy skin condition.	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
20. I worry that the itching will last forever.	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
21. I feel self-conscious because of my itchy skin condition.	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
22. My personality has changed because of my itchy skin condition.	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

14.12 Appendix 12: Patient Global Impression of Prurigo Nodularis Severity (PGI-PN-S)

Instructions: Please select the box that best describes the severity of your prurigo nodularis right now.

Right now, my prurigo nodularis is:

- ☐$_0$ Absent (No sign or symptom of prurigo nodularis)
- ☐$_1$ Minimal
- ☐$_2$ Mild
- ☐$_3$ Moderate
- ☐$_4$ Severe

14.13 Appendix 13: Summary of Changes (Version 6 compared to Version 5)

The following are changes to the KPL-716-C201 protocol (version 6 versus Version 5), which summarizes major changes to the protocol. Additional minor changes were also made with respect to typos, minor edits for clarification, adding new abbreviations to the list of abbreviations, and updating the table of contents.

Protocol Section	Modification	Rationale
First page + footer	Added/changed to Protocol Version 6, 19 July 2021 and included [redacted] to the Sponsor	New protocol version.
Synopsis	Removed ~~Latin America~~	Removed as Sponsor will not be enrolling subjects in this region.
Synopsis, and Section 3.2	Proportion of subjects achieving 0 or 1 ~~from baseline~~ in PN-IGA at Week 16	Clarified the PN-IGA measures the overall assessment at Week 16.
Synopsis and Section 4.7.2	8. Presence of ~~moderately~~ severe depression as indicated by PHQ-9 total score of ≥~~15~~20 or item 9 score >0 at the Screening Visit or Day 1.	Revised to reduce screen failures. Some screen-failed subjects by PHQ-9 cut-off score of 15 from activated North America sites were confirmed to be non-depressive by psychiatrists. Currently revised to only exclude subjects who scored severe depression by PHQ-9.
Synopsis and Section 8.3	Multiple comparison/Multiplicity ~~There is a multiplicity adjustment planned for efficacy endpoints in Phase 2b. Details will be specified in the SAP.~~ As this is a dose finding study, there is no multiplicity adjustment planned for the comparisons of multiple doses of KPL-716 versus placebo.	As this is a dose-ranging study and not intended to make label claims out of it, so multiplicity is not planned.
Synopsis	An interim analysis for Phase 2b portion may be conducted after at least 50% subjects complete Week 16 Visit. If the interim analysis is conducted in the Phase 2b part, a two-sided alpha of 0.0001 will be spent. The two-sided alpha level for the final Phase 2b efficacy analysis will be 0.05. Additional details regarding the interim analysis, if performed, will be provided in the SAP along with other analysis plans.	Added to align with Section 8.12.
Section 7.3.4	PN-NAT is a novel exploratory tool for the evaluation of disease severity based on estimate of the number of nodules over the whole body, estimate of hardness of nodules ~~over the whole body~~ in representative area, estimate of extent of excoriation over the whole body, distribution of nodules, exact number of nodules in the representative area. There are 5 components to PN-NAT.	Editorial alignment with Appendix 3.

Protocol Section	Modification	Rationale
Section 7.3.13	The PGIC (Appendix 6: Patient Global Impression of Change (PGIC) is a patient-reported survey that assesses the subject's impression of change ~~in~~ on prurigo nodularis since the beginning of the study. Scoring ranges from 1~~3~~: "very much improved" to 7~~3~~: "very much ~~improved~~ worse."	Editorial alignment with Appendix 6.

Signature Page for [redacted]

Approval	[redacted] Clinical 19-Jul-2021 21:48:21 GMT+0000

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