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

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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 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.
[redacted]

Sponsor Signatory:
[redacted] MD, PhD, FACC
[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

SPONSOR AGREEMENT

I have read the following protocol and agree to the content as presented:

[redacted]

[redacted], MD, PhD, FACC

[redacted] Date

[redacted]

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 moderate to severe prurigo nodularis experiencing moderate to severe pruritus will be enrolled in this Phase 2a/b study.

Primary Objective

- To evaluate the efficacy of subcutaneous (SC) KPL-716 vs. placebo in reducing pruritus in subjects with moderate to severe prurigo nodularis experiencing moderate to severe pruritus

Secondary Objectives

- To evaluate the effect of SC KPL-716 vs. placebo in improving sleep in subjects with moderate to severe prurigo nodularis experiencing moderate to severe pruritus
- To evaluate the effect of SC KPL-716 vs. placebo in improving quality of life in subjects with moderate to severe prurigo nodularis experiencing moderate to severe pruritus
- To evaluate the effect of SC KPL-716 vs. placebo in reducing disease severity in subjects with moderate to severe prurigo nodularis experiencing moderate to severe pruritus
- To evaluate the safety and tolerability of SC KPL-716 vs. placebo in subjects with moderate to severe prurigo nodularis experiencing moderate to severe pruritus
- To evaluate the pharmacokinetics (PK) of SC KPL-716 in subjects with moderate to severe prurigo nodularis experiencing moderate to severe pruritus
- To evaluate the immunogenicity of SC KPL-716 in subjects with moderate to severe prurigo nodularis experiencing moderate to severe pruritus

Exploratory Objectives

- To evaluate the effect of KPL-716 vs. placebo on skin and blood pharmacodynamics (PD) biomarkers
- To evaluate the correlation between KPL-716 responsiveness and co-morbidities in prurigo nodularis
- To evaluate the pharmacogenomics (PG) of KPL-716 responsiveness

Primary Efficacy Endpoint

- Percent change from baseline in weekly average Worst Itch–Numeric Rating Scale (WI-NRS) at Week 8

Key Secondary Efficacy Endpoints

- Proportion of subjects achieving at least a 4-point reduction from baseline in weekly average WI-NRS at Week 8
- Percent change from baseline in pruritus Visual Analog Scale (VAS) at Week 8

Other Secondary Efficacy Endpoints

Related to pruritus:

- Change and percent change from baseline in weekly average of WI-NRS over time
- Change and percent change from baseline in pruritus (VAS) over time
- Change and percent change from baseline in 5-D Pruritus total score over time
- Proportion of subjects achieving at least a 4-point reduction from baseline in weekly average WI-NRS over time.

Related to sleep:

- Change and percent change from baseline in Sleep Loss VAS over time.
- Change and percent change from baseline in weekly average of difficulty falling asleep NRS over time
- Change and percent change from baseline in weekly average of sleep quality NRS over time

Related to quality of life:

- Change and percent change from baseline in quality of life measures over time

Related to disease severity:

Using Prurigo Nodularis Nodule Assessment Tool (PN-NAT), a novel tool for assessment of nodules in prurigo nodularis

- Change from baseline in PN-NAT over time.

Using Prurigo Nodularis Investigator Global Assessment (PN-IGA), a novel tool for assessment of disease severity in prurigo nodularis

- Proportion of subjects with improvement in PN-IGA by 2 categories over time

Exploratory Endpoints

- Measurement of KPL-716 therapeutic benefit (Patient Benefit Index-Pruritus [PBI-P])
- Change from baseline in skin and blood PD biomarkers over time
- Correlation of co-morbidities with KPL-716 responsiveness
- Correlation of PG characteristics with KPL-716 responsiveness

Safety Parameters

- 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

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

Study Design:

This is a Phase 2a/b randomized, double-blind, placebo-controlled study to investigate the efficacy, safety, tolerability, PK and immunogenicity of KPL-716 administered SC in subjects with moderate to severe prurigo nodularis experiencing moderate to severe pruritus.

The Phase 2a portion of the study will enroll approximately 80 up to 100 subjects with moderate to severe prurigo nodularis experiencing moderate to severe pruritus and will include 2 arms: one active arm and one placebo arm. 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 Study (EOS) visit, thus removing the confounding effect of these therapies on the assessment of KPL-716 efficacy. In the interval between Day 1 through the EOS Visit, should subjects experience an exacerbation of symptoms that is significant enough to warrant intervention, topical corticosteroids (TCS) and/or oral antihistamines may be provided at the discretion of the Investigator in consultation with the Sponsor. The weight of the TCS tube will be measured and the number of anti-histamine tablets will be recorded on the initial day of dispensation and upon each subsequent visit. Acceptable study TCS and oral anti-histamines will be described in the Pharmacy Manual. A total of 8 doses of study drug are planned during the Treatment Period to determine Proof of Concept in PN on endpoints of pruritus, sleep, quality of life, and disease severity, following dosing to achieve maximum or near current practical-maximum exposures. Other secondary endpoints will explore the impact of KPL-716 versus placebo on pruritus, sleep, quality of life and disease severity over time, i.e., at each week of the study treatment period including Week 8, and continuing until EOS visit.

An interim analysis of the Phase 2a portion of the study may be performed after at least 50% of subjects have received at least 4 weeks of study drug to assess for an early signal of efficacy to guide program decision-making. Additional details regarding the interim analysis, if performed, will be provided in the Statistical Analysis Plan (SAP).

Subject enrollment in the Phase 2b portion will depend on Phase 2a results. Subjects enrolled in Phase 2a will remain in Phase 2a.

The Phase 2b portion of the study, if enrolled, will include up to approximately 300 subjects with moderate to severe prurigo nodularis experiencing moderate to severe pruritus and will have 5 arms: 4 active arms and one placebo arm. The Phase 2b study will also utilize a washout monotherapy design. Rescue medications may be administered if needed for acute flares as described above. The primary endpoint of the Phase 2b study will also focus on pruritus at Week 8 with other secondary endpoints evaluating pruritus, sleep, quality of life and disease severity over time. The analysis plan for Phase 2b will be defined in the SAP.

Phase 2a and Phase 2b studies each will have three periods:

Phase 2a subjects already consented into Protocol Version 2 will remain in the 16 week treatment period schedule:

- Screening Period (minimum 14 days and maximum 28 days)
- Treatment Period (Day 1 [Baseline] to Week 16)
- Follow-up Period (Week 16 to Week 24)

Phase 2a subjects consented into Protocol Version 3 will follow the 8 week treatment period schedule**:**

- Screening Period (minimum 14 days and maximum 28 days)
- Treatment Period (Day 1 [Baseline] to Week 8)
- Follow-up Period (Week 8 to Week 16 for Phase 2a)

Phase 2b subjects will follow the 16 week treatment period schedule:

- Screening Period (minimum 14 days and maximum 28 days)
- Treatment Period (Day 1 [Baseline] to Week 16)
- Follow-up Period (Week 16 to Week 24)

Allowable window for Week 1 is ± 1 day and from Week 2 to Week 24 visits is ± 2 days. There must be a minimum of 5 days between doses. . If next week's dose is outside of the window, the dose should be skipped.

Screening Period:

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

During the Screening Visit, 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 10 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. There must be normal appearing skin present in between nodules with the exception of atopic dermatitis. Each arm, each leg, and 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) in the past 24 hours on a numerical rating scale (WI-NRS). In addition, subjects will record their WI-NRS on a daily basis during the Screening Period. The daily recordings can begin any time after the Screening Visit. Subjects will be provided with an e-Diary device for daily electronic recordings if needed. To be eligible for study participation, subjects must have moderate to severe pruritus, defined as WI-NRS ≥ 7 at the Screening Visit and a mean weekly WI-NRS ≥ 5 for each of the 2 consecutive weeks (14 consecutive days) immediately prior to randomization. A minimum of 85% compliance with daily WI-NRS recording during the 14 consecutive days prior to dosing is required for eligibility unless approved by the Sponsor.

During the Screening Visit, 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, medical photographs will be taken of a representative area of disease to be 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 include those related to pruritus (Pruritus VAS, and 5-D Pruritus), sleep (Sleep Loss VAS), quality of life (Dermatology Life Quality Index [DLQI], Hospital Anxiety and Depression Scale [HADS], and ItchyQoL) and disease severity (PN-NAT and PN-IGA). Subjects will be instructed on the required washout for specific excluded medications. Subjects also will be instructed to record daily rating of 2 sleep parameters: difficulty falling asleep NRS and sleep quality NRS during the Screening Period. The daily recordings (WI-NRS, difficulty falling asleep NRS, and sleep quality NRS) continue throughout the study for eligible subjects that proceed to dosing.

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

Treatment Period:

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 adverse events. Clinical laboratory results from the Screening Visit will be reviewed. Compliance with recording of daily WI-NRS for the 14 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, PG (optional), ADA and PD biomarkers. Pregnancy testing will be performed if applicable. Medical photographs will be taken of the representative area of disease identified during the Screening Period and of the biopsy areas prior to collection of the biopsy. 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. Skin biopsies (one lesional and one non-lesional) will be performed. Skin biopsies are optional. Subjects will record their Pruritus VAS, Sleep Loss VAS and complete the 5-D Pruritus questionnaire. Subjects will also complete DLQI, HADS, ItchyQoL, and the PBI-P questionnaires. In addition, subjects' disease severity will be assessed (PN-NAT and PN-IGA). Upon confirmation of subject eligibility and completion of required activities (Appendix 1), the subject will be randomized and proceed to dosing.

Randomization and Dosing:

To minimize investigational treatment bias, subjects will be randomized to receive treatment in a double-blind manner. In Phase 2a, subjects will be randomized 1:1 to receive KPL-716 or placebo. In Phase 2b, subjects will be randomized 1:1:1:1:1 to receive 4 different dosing regimens of KPL-716 or placebo. Subjects will remain in the same treatment arm throughout the End of Treatment Period. Stratification will be performed based on sex and presence of atopy.

A loading dose of KPL-716 (2x maintenance dose) or matching placebo will be administered via up to 2 SC injections within 30 minutes on Day 1 by the Investigator or qualified designee at the study site. All subsequent doses of KPL-716 (maintenance dose) or matching placebo will be administered by the Investigator or qualified designee at the study site via a single SC injection. Subjects will be observed for 3 hours after the loading dose, for 2 hours after the first 2 maintenance doses and for 1 hour after all subsequent doses. Vital signs will be measured every hour during the observation period. The post-dose observation duration may be modified based on emerging safety and tolerability data. In addition, the dose level, dosing regimen, and randomization ratio may be modified based on emerging safety, tolerability, PK, PD and/or

efficacy data. The planned loading and maintenance dose levels for the Phase 2a portion of the study are currently 720 mg and 360 mg, respectively.

Phase 2a: Figure 1

- Arm A: KPL-716, 720 mg loading dose followed by 360 mg every week
- Arm B: Placebo loading dose followed by placebo every week

The loading dose and maintenance dose for Phase 2a will not exceed 720 mg and 360 mg, respectively.

Phase 2b: Figure 2

- Arm A: KPL-716, loading dose (2x dose level A) followed by dose level A every 2 weeks
- Arm B: KPL-716, loading dose (2x dose level B) followed by dose level B every 2 weeks
- Arm C: KPL-716, loading dose (2x dose level C) followed by dose level C every 2 weeks
- Arm D: KPL-716, loading dose (2x dose level D) followed by dose level D every 4 weeks, interspersed with placebo injection every 2 weeks to maintain the blind.
- Arm E: placebo loading dose followed by placebo every 2 weeks

The loading and maintenance dose levels for the Phase 2b portion of the study will be determined prior to start of the Phase 2b portion of the study based upon emerging safety, tolerability, PK, PD and/or efficacy data. The KPL-716 PK data (the single dose study of KPL-716 in subjects with atopic dermatitis [Phase 1b, Part 1] and healthy volunteers [Phase 1b, Part 3], the repeated single dose study in subjects with atopic dermatitis [Phase 1b, Part 4], and the Phase 2a portion of this study in subjects with PN) will be used, as available, to support PK modeling to enable dose selection for Phase 2b. The dose levels and dosing intervals for Phase 2b will be chosen in such a way as to not exceed exposures observed in Phase 2a.

All procedures assigned to dosing days are performed prior to study drug administration. The following activities will take place prior to each maintenance dose:

- Review of concomitant medications, therapies and procedures
- Review of adverse events
- Review of subject compliance
- Vital signs (performed before and after dosing on each dosing day)
- Collection of blood for PK
- Completion of Pruritus VAS, Sleep Loss VAS

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

- Physical examination and ECG
- Collection of safety blood and urine samples
- Urine pregnancy test (if applicable); a serum pregnancy test will be performed if the urine pregnancy test is positive
- Collection of ADA and PD samples
- Medical photography
- Completion of 5-D pruritus questionnaire

- Completion of quality of life questionnaire (DLQI, HADS, ItchyQoL, PBI-P)
- Assessment of disease severity (PN-NAT and PN-IGA)
- Skin biopsies (Skin biopsies are optional and will be performed at select sites)

Adverse events 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. In case of study drug interruption or missed dosing visits, subjects will resume the schedule of activities in accordance with their study day. Study drug will be discontinued if more than 3 consecutive doses are withheld or missed. In case of early withdrawal from the entire study, subjects will complete an EOS Visit. In addition, if early termination occurs prior to the end of treatment period, biopsies should be collected at the EOS visit.

The Follow-up Period:

During the Follow-up Period, subjects will undergo vital signs measurement, review of concomitant medications, therapies and procedure, review of adverse events, monitoring of compliance and PK blood sample collection at every visit. Pruritus VAS, 5-D Pruritus, and Sleep Loss VAS will also be completed at every visit during the Follow Up Period. Physical examination, clinical laboratory tests (including pregnancy testing if applicable), quality of life assessment (DLQI, HADS and ItchyQoL), and evaluation of disease severity (PN-NAT and PN IGA) will be performed at designated visits. Subjects will continue to complete their daily questionnaire on pruritus and sleep throughout the Follow-up Period.

The EOS Visit includes vital signs, full physical examination, ECG, clinical laboratory blood tests, urinalysis, and urine pregnancy test (if applicable) as well as PK, ADA and PD blood sampling. 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 Study:

The planned study duration per subject for Phase 2a consented into Protocol Version 3 is 20 weeks including a maximum of 4 weeks for the Screening Period, 8 weeks for the Treatment Period, and an 8-week Follow-up Period.

The planned study duration per subject for Phase 2a already consented to Protocol Version 2 and Phase 2b each is 28 weeks including a maximum of 4 weeks for the Screening Period, 16 weeks for the Treatment Period, and an 8-week Follow-up Period.

The minimum duration for the Screening Period will be 14 days.

Study Drug:

Study Drug: KPL-716 or Matching placebo

Active Substance: KPL-716

Strength, Formulation and Route of Administration: 180 mg/ml solution in 20 mM L-histidine, 25 mM L-arginine hydrochloride, 125 mM sodium chloride, 0.05% (w/v) polysorbate 80, pH 6.6, subcutaneous administration.

Matching placebo: 20 mM L-histidine, 25 mM L-arginine hydrochloride, 125 mM sodium chloride, 0.05% (w/v) polysorbate 80, pH 6.6, subcutaneous administration.

Study Treatment:

Subjects will be randomized to receive KPL-716 or matching placebo on Day 1 and will remain in the same treatment arm throughout the study. A loading dose of KPL-716 (2 x maintenance dose) or placebo will be administered via up to 2 SC injections within 30 minutes on Day 1. Maintenance doses of KPL-716 or placebo will be administered via 1 SC injection for the remainder of the Treatment Period. The planned loading and maintenance dose levels for the Phase 2a portion of the study are currently 720 mg and 360 mg, respectively. The dose level and dosing regimen may be modified based on emerging safety, tolerability, PK, PD and/or efficacy data.

Phase 2a: Figure 1

- Arm A:
  - Loading dose of KPL-716 at 720 mg on Day 1 via 2 SC injections
  - Maintenance doses of KPL-716 at 360 mg via a single SC injection weekly starting at Week 1 through Week 15 for subjects already consented into Protocol Version 2, or Week 7 for subjects consented into Protocol Version 3
- Arm B:
  - Loading dose of placebo on Day 1 via 2 SC injections
  - Maintenance doses of placebo via a single SC injection weekly starting at Week 1 through Week 15 for subjects already consented into Protocol Version 2, or Week 7 for subjects consented into Protocol Version 3

Phase 2b: Figure 2

- Arm A:
  - Loading dose of KPL-716 at 2 x dose level A on Day 1 via up to 2 SC injections
  - Maintenance doses of KPL-716 at dose level A via a single SC injection at Week 2, 4, 6, 8, 10, 12 and 14
- Arm B:
  - Loading dose of KPL-716 at 2 x dose level B on Day 1 via up to 2 SC injections
  - Maintenance doses of KPL-716 at dose level B via a single SC injection at Week 2, 4, 6, 8, 10, 12, and 14
- Arm C:
  - Loading dose of KPL-716 at 2 x dose level C on Day 1 via up to 2 SC injections
  - Maintenance doses of KPL-716 at dose level C via a single SC injection at Week 2, 4, 6, 8, 10, 12 and 14

- Arm D:
    - Loading dose of KPL-716 at 2 x dose level D on Day 1 via up to 2 SC injections
    - Maintenance doses of KPL-716 at dose level D via a single SC injection at Week 4, 8, and 12
    - Maintenance doses of placebo via a single SC injection at Week 2, 6, 10, and 14
- Arm E:
    - Loading dose of placebo on Day 1 via up to 2 SC injections
    - Maintenance doses of placebo via a single SC injection at Week 2, 4, 6, 8, 10, 12, and 14

Study Assessments:

Efficacy Assessment:

Efficacy in reduction of pruritus will be assessed via daily recording of WI-NRS as well as on-site assessment of Pruritus VAS and 5-D Pruritus. Efficacy in improvement in sleep will be assessed via daily recording of 2 NRS scales, one for difficulty falling asleep and the other for quality of sleep. Impact on sleep will also be assessed on-site via Sleep Loss VAS. Impact on quality of life will be assessed via on-site PROs: DLQI, HADS, ItchyQoL, and PBI-P. Impact on disease severity will be followed through two novel and exploratory tools: PN-NAT and PN-IGA as per 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 biopsies) will be taken at indicated study visits.

Four skin biopsies will be collected during this study. Skin biopsies are optional. Two 4.5-mm punch biopsies (one from lesional skin and one from adjacent non-lesional skin) will be collected prior to dosing at Day 1, and two 4.5 mm punch biopsies (one lesional and one non-lesional) will be collected at the End of Treatment visit. Skin biopsies will be evaluated for gene expression to assess target engagement and to identify mechanistic and/or predictive biomarkers. 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 at every visit from the baseline visit to EOS. PK samples will be collected pre-dose on dosing days.

PD Assessment:

PD blood samples will be collected from all subjects at Day 1, Weeks 2, and 4 and at End of Treatment and EOS visits, for biomarkers analysis. PD samples will be collected pre-dose on dosing days.

Additional PD blood samples will be collected as follows:

- For Phase 2a subjects consented into Protocol Version 3, at Week 12
- For Phase 2b subjects and Phase 2a subjects already consented into Protocol Version 2, at Weeks 8, 12, and 20

Immunogenicity Assessment:

ADA blood samples will be collected from all subjects at Day 1, Week 2, Week 4 End of Treatment and EOS visits. ADA samples will be collected pre-dose on dosing days.

Additional ADA blood samples for Phase 2b subjects and Phase 2a subjects already consented into Protocol Version 2, will be collected at Week 8

Selection of Study Population:

Inclusion criteria:

1. Male or female aged 18 to 75 years, inclusive, at the time of consent.
2. Have a physician-documented diagnosis of prurigo nodularis that is confirmed by review of medical photography (as outlined in the Study Manual) during the Screening Period. Duration of prurigo nodularis (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 10 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. There must be normal appearing skin present in between nodules with the exception of atopic dermatitis. Each arm, each leg, and trunk are considered different anatomical locations.
4. Subject has moderate to severe pruritus, defined as WI-NRS ≥ 7 at the Screening Visit and a mean weekly WI-NRS ≥ 5 for each of the 2 consecutive weeks immediately prior to randomization.
5. 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 (IUD)
        - intrauterine system (IUS)
        - 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

6. 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. 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.
8. Female of childbearing potential must have a negative serum β-hCG test at the Screening Visit and negative urine pregnancy test on Day 1.
9. 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.
10. Subjects must be on optimized and stable treatment for co-morbidities associated with PN for at least 28 days prior to Day 1.

Exclusion criteria:

1. Use of the following medications within the indicated timeframe from Day 1 and does not agree to refrain from the use of the medications throughout the study treatment and follow up duration:
    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 prurigo nodularis including but not limited to corticosteroids, calcineurin inhibitors, phosphodiesterase inhibitors, retinoids, calcipotriol, capsaicin, camphor, polidocanol, cannabinoids, gabapentin or tars: 2 weeks
    d. Anti-histamines: 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 (JAK) inhibitors: 3 months
    j. Dupilumab: 6 months
    k. Any other marketed biologic: 5 half-lives or until CD19 cell numbers return to normal in case of depleting antibodies such as rituximab
    l. Any investigational biologic drug: 5 half-lives
    m. Any investigational non-biologic drug: 5 half-lives
    n. Phototherapy involving UVA, UVB, or excimer: 4 weeks
    o. Tanning salon use: 4 weeks
2. Has received any investigational biologic or non-biologic drug that targets Oncostatin M, IL-31, or IL-31 receptor α, or Oncostatin M receptor β in the past.

3. Is currently using medication known to cause pruritus (e.g. angiotensin converting enzyme inhibitors) unless timing of onset of pruritus and initiation of medication do not suggest that pruritus was caused by the medication.
4. Has less than 85% compliance with the daily WI-NRS tool during the last 14 days of the Screening Period prior to randomization, unless approved by the Investigator in consultation with the Sponsor.
5. Has a significant flare of pruritus and/or skin eruption during the Screening Period (prior to the study drug administration) that requires a medical intervention.
6. Presence of any inflammatory, pruritic, and/or fibrotic skin condition other than moderate to severe prurigo nodularis or atopic dermatitis unless approved by the Sponsor.
7. History of chronic urticaria with active lesions in the past 2 years.
8. Presence of uncontrolled hyperthyroidism or hypothyroidism or uncontrolled diabetes defined as hemoglobin A1c >7.5%.
9. Presence or history of cancer or lymphoproliferative disease within 5 years prior to Day 1, with the exception of squamous and basal cell carcinoma.
10. Presence or history of any autoimmune disorder.
11. Presence or history of immune deficiency, or opportunistic infections
12. Subject has positive results for hepatitis B surface antigen (HbsAg)
13. Subject has positive results for hepatitis B anti-core antibody (anti-HBc) but negative results for anti-surface antibody (anti-HBs).
14. Subject has positive results for hepatitis C antibody unless patient received curative therapy and a negative viral load is documented.
15. Human immunodeficiency virus (HIV) infection or positive HIV serology.
16. Subject is on hemodialysis or peritoneal dialysis.
17. Psychiatric illness other than stable mild to moderate anxiety and/or depression unless approved by the Sponsor.
18. Hospitalization for a psychiatric illness.
19. Laboratory abnormalities that fall outside the windows below at the Screening Visit:
    a. Alanine aminotransferase > 2 x ULN
    b. Aspartate aminotransferase > 2 x ULN
    c. Gamma-glutamyl transferase > 2 x ULN
    d. Blood bilirubin > 1.5 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 <120,000/ µl
20. Body mass index (BMI) >39 kg/m^2
21. Systolic blood pressure above 150 mm Hg, diastolic blood pressure above 95 mm Hg at the Screening Visit or Day 1 (confirmed by repeat measurement).
22. Hospitalization within 16 weeks prior to Day 1.

23. Major surgery within 12 weeks prior to Day 1 or has a major surgery planned during the study.
24. 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.
25. 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.
26. Has received a live attenuated vaccine within 12 weeks prior to Day 1.
27. Has previously taken part in or withdrawn from this study or has previously received the study drug.
28. Has a known hypersensitivity to KPL-716 or its excipients.
29. 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.
30. 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 Sponsor-approved medication for a stable concomitant condition that explains the positive drug screen result.
31. Current user of nicotine > 3 pack per day or nicotine equivalent/day.
32. Has received blood products within 8 weeks prior Day 1.
33. Has donated blood within 12 weeks prior to Day 1, platelets within 10 weeks prior to Day 1, or plasma within 6 weeks prior to Day 1.
34. Has had a severe allergic reaction to any foods or medications including anaphylactic reactions, unless approved by the Sponsor.

Statistical Methods:

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 (SD), first quartile (Q1), median, third quartile (Q3), 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. Details will be specified in the SAP.

Determination of Sample Size

The sample size calculation is based on the primary efficacy endpoint percentage change from baseline of WI-NRS at Week 8.

Approximately 80 to 100 subjects will be randomized in the Phase 2a portion with a 1:1 allocation ratio. Assuming a weekly average WI-NRS reduction from baseline at week 8 of 60% for the KPL-716 group and 30% for the placebo group and standard deviation of 50% in both treatment groups, a sample size of 50 subjects per group will provide at least 90% power to detect the treatment difference at two-sided alpha of 0.20.

Approximately 300 subjects in total will be equally randomized to the Phase 2b dose groups. As the number of Phase 2b dose groups and dose levels will be determined based on the Phase 2a data,

sample size justification for Phase 2b will not be specified in the protocol. Details for sample size justification will be provided in the SAP and finalized before the database lock.

Randomization strata:

- Sex: Male vs Female
- Presence of atopy: Yes versus No

Analysis Sets

The following analysis sets will be defined separately for the Phase 2a and Phase 2b portions of the study.

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 protocol deviations or violations that may potentially bias statistical 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

All efficacy analyses for the Phase 2a portion of the study will be performed on the mITT analysis set. The analyses of primary and key secondary efficacy endpoints will be repeated using the PP set to assess the sensitivity of the results to deviations and violations of the protocol that could potentially bias the analysis. All efficacy data will be listed by subject.

As the number of Phase 2b dose groups and dose levels will be determined based on the Phase 2a data, analysis of Phase 2b efficacy data is not specified in the protocol. Details for the analysis will be provided in the SAP and finalized before the database lock.

A mixed–effect model repeated measures (MMRM) model will be fitted to the primary efficacy endpoint, the percent change from baseline in weekly average WI-NRS score at Week 8. The model will include fixed effects for treatment, both stratification factors for randomization, baseline weekly average WI-NRS, treatment week (Week 1 through Week 8), and treatment week-by-treatment interaction.

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.

PD Analyses:

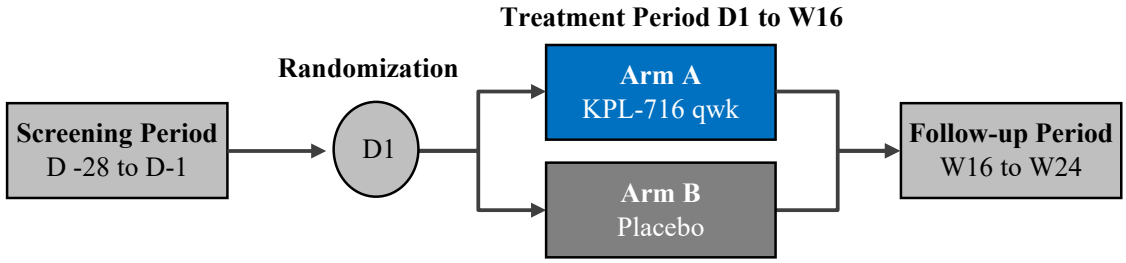
Skin and blood biomarker levels will be compared to placebo adjusted change from baseline over time for each treatment group, and the parameters will be summarized by treatment group and overall using descriptive statistics.

Immunogenicity Analyses:

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

Figure 1 Phase 2a Study Design Diagram

Subjects already consented into Protocol Version 2



Subjects consented into Protocol Version 3

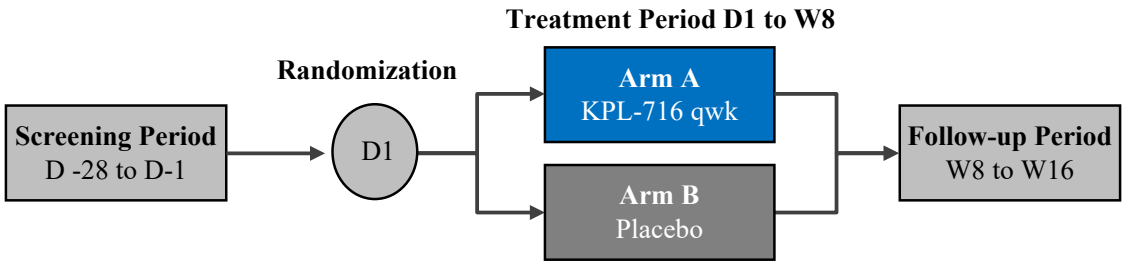
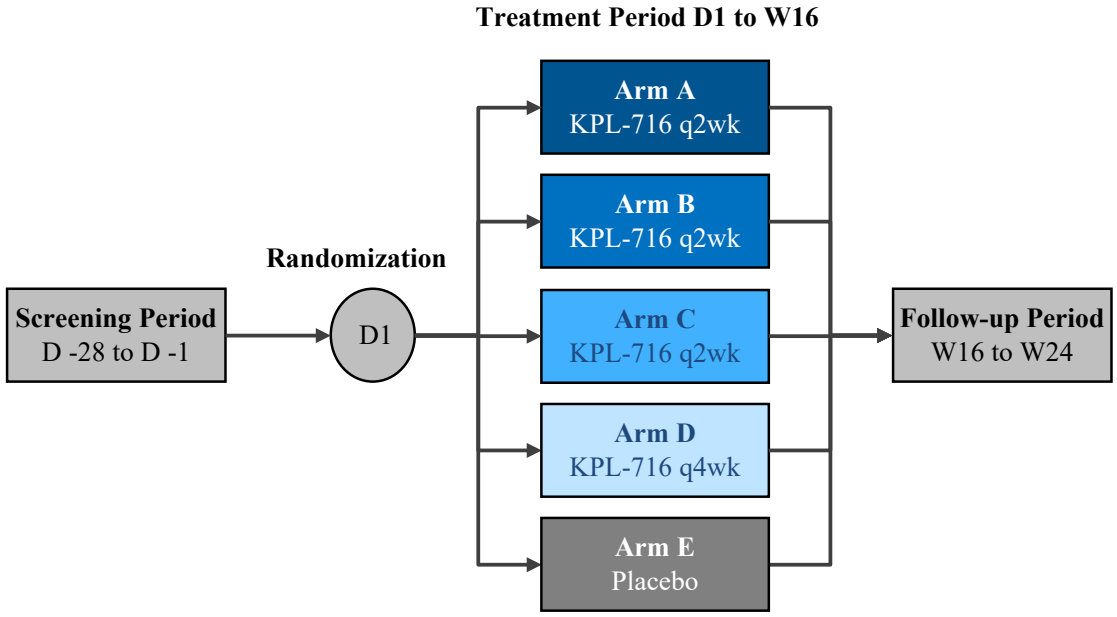


Figure 2 Phase 2b Study Design Diagram



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LIST OF ABBREVIATIONS

ADA	Anti-drug antibodies (anti-KPL-716 antibodies)
AE	Adverse event
Anti-HBc	Hepatitis B core antibody
Anti-HBs	Hepatitis B surface antibody
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
DLQI	Dermatology Life Quality Index
DMC	Data Monitoring Committee
EDC	electronic data capture
ECG	electrocardiogram
e-CRF	electronic Case Report Form
EOS	End of Study
FSH	Follicle-stimulating hormone
HADS	Hospital Anxiety and Depression Scale
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
I/E	inclusion/exclusion
IMP	investigational medicinal product
IRB	Institutional Review Board
ISR	Injection Site Reaction
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
PBI-P	Patient Benefit Index-Pruritus
PD	pharmacodynamic(s)
PG	pharmacogenomic(s)
PK	pharmacokinetic(s)
PN	Prurigo Nodularis
PN-NAT	Prurigo Nodularis Nodule Assessment Tool
PN-IGA	Prurigo Nodularis Investigator Global Assessment
PT	Preferred term
Q	Quartile

QA	Quality Assurance
QTcF	QT interval corrected for heart rate using Fridericia's method
SAE	serious adverse event
SAP	Statistical Analysis Plan
SC	subcutaneous(ly)
SD	standard deviation
SRC	Safety Review Committee
TCS	topical corticosteroids
TEAE	treatment-emergent adverse event
TMF	Trial Master File
ULN	Upper limit of normat
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).

There are 4 published studies to date describing cohorts of PN patients (6, 7, 8, 9). In addition to these studies, 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 focusing in this early stage of development on all comers excluding subjects only on the basis of safety considerations. The secondary objectives are to investigate the impact of KPL-716 on sleep loss, quality of life and disease severity. Clinical response and biomarker studies from this all-comer population 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).

1.2.1 In Vivo

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 simultaneously inhibits signaling of IL-31 and OSM, 2 cytokine pathways important in pruritus, inflammation, hyperkeratosis and fibrosis. KPL-716 does not inhibit signaling of OSM down the 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 many aspects of disease pathology in PN. A clinical effect on pruritus intensity is anticipated at therapeutic doses based on the Phase 1b study results (Protocol KPL-716-C001). 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 2a/b 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. Moderate to severe disease is defined as having at least 10 nodules meeting the above criteria. Moderate to severe pruritus is defined as WI-NRS $\geq$ 7 at the Screening Visit and a mean weekly WI-NRS $\geq$ 5 for the 2 consecutive weeks immediately

prior to randomization. Given the early stage of KPL-716 development, subjects will be excluded if they have co-morbidities that would complicate interpretation of safety data such as infections, malignancies, and rheumatologic diseases. Otherwise, this Phase 2 study is an all-comers study. Randomization will be performed based on 2 strata: sex and atopy. Stratification according to sex is based on preliminary data from the KPL-716-C001 single dose study, which showed a potential sex effect for the anti-pruritic response of KPL-716. Stratification according to presence or absence of atopy is based on the reported high prevalence of atopy in this patient population and the potential impact of atopy in the immunopathologic process in PN. As an exploratory objective, clinical response will be correlated with biomarker changes and pharmacogenomics findings in this all-comer population to understand whether KPL-716 responsiveness is broad or limited to a specific subset of PN patients.

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

1.4 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 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 PD data from Part 1 of KPL-716-C001, please see IB.

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. 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 (secondary endpoint). 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.

As described previously, in the first-in-human study (KPL-716-C001), 50 healthy volunteers (Part 3) and 32 subjects with atopic dermatitis (Part 1) were exposed to single doses of KPL-716 or placebo. There were no deaths, SAEs, or discontinuations due to AEs. There were no infusion reactions or injection site reactions. Drug-related or possibly related treatment-emergent AEs were infrequent. For summary of safety data from KPL-716-C001 Part 1 and Part 3, please see IB.

In Part 4 of KPL-716-C001 (repeated-single-dose study), subjects with moderate to severe atopic dermatitis experiencing moderate to severe pruritus are being randomized 1:1 and administered KPL-716 360 mg or placebo SC once weekly for a total of 12 doses. To date, 45 subjects have been randomized in Part 4, 43 subjects have received at least 1 dose of study

drug, 42 have received at least 5 doses, and 27 have completed the 12-dose treatment regimen. In this blinded study, KPL-716 continues to be well tolerated to date.

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 subjects with moderate to severe PN experiencing moderate to 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 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. 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 conduct of the Phase 2a/b study.

2 OBJECTIVES

2.1 Primary Objective

- To evaluate the efficacy of subcutaneous (SC) KPL-716 vs. placebo in reducing pruritus in subjects with moderate to severe prurigo nodularis experiencing moderate to severe pruritus

2.2 Secondary Objectives

- To evaluate the efficacy of SC KPL-716 vs. placebo in improving sleep in subjects with moderate to severe prurigo nodularis experiencing moderate to severe pruritus
- To evaluate the efficacy of SC KPL-716 vs. placebo in improving quality of life in subjects with moderate to severe prurigo nodularis experiencing moderate to severe pruritus
- To evaluate the efficacy of SC KPL-716 vs. placebo in reducing disease severity in subjects with moderate to severe prurigo nodularis experiencing moderate to severe pruritus
- To evaluate the safety and tolerability of SC KPL-716 vs. placebo in subjects with moderate to severe prurigo nodularis experiencing moderate to severe pruritus
- To evaluate the PK of SC KPL-716 in subjects with moderate to severe prurigo nodularis experiencing moderate to severe pruritus
- To evaluate the immunogenicity of SC KPL-716 in subjects with moderate to severe prurigo nodularis experiencing moderate to severe pruritus

2.3 Exploratory Objectives

- To evaluate the effect of KPL-716 vs. placebo on skin and blood PD biomarkers
- To evaluate the correlation between KPL-716 responsiveness and co-morbidities in prurigo nodularis
- To evaluate the pharmacogenomics (PG) of KPL-716 responsiveness

3 ENDPOINTS

3.1 Primary Efficacy Endpoints

- Percent change from baseline in weekly average WI-NRS at Week 8

3.2 Key Secondary Efficacy Endpoints

- Proportion of subjects achieving at least a 4-point reduction from baseline in weekly average WI-NRS at Week 8
- Percent change from baseline in pruritus VAS at Week 8

3.3 Other Secondary Efficacy Endpoints

Related to pruritus:

- Change and percent change from baseline in weekly average of WI-NRS over time
- Change and percent change from baseline in Pruritus VAS over time
- Change and percent change from baseline in 5-D Pruritus total score over time
- Proportion of subjects achieving at least a 4-point reduction from baseline in weekly average WI-NRS over time.

Related to sleep:

- Change and percent change from baseline in Sleep Loss VAS over time.
- Change and percent change from baseline in weekly average of difficulty falling asleep NRS over time
- Change and percent change from baseline in weekly average of sleep quality NRS over time

Related to quality of life:

- Change and percent change from baseline in quality of life measures over time

Related to disease severity:

Using Prurigo Nodularis Nodule Assessment Tool (PN-NAT, a novel tool for assessment of nodules in prurigo nodularis

- Change from baseline in PN-NAT over time.

Using PN-IGA, a novel tool for assessment of disease severity in prurigo nodularis

- Proportion of subjects with improvement in PN-IGA by 2 categories over time

3.4 Exploratory Endpoints

- Measurement of KPL-716 therapeutic benefit (Patient Benefit Index-Pruritus [PBI-P])
- Change from baseline in skin and blood PD biomarkers over time
- Correlation of co-morbidities with KPL-716 responsiveness
- Correlation of PG characteristics with KPL-716 responsiveness

3.5 Safety Parameters

- Incidence rate and severity of TEAEs
- Incidence rate and severity of study drug-related TEAEs
- Vital signs, ECG, and clinical laboratory test results

3.6 Other Parameters

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

4 INVESTIGATIONAL PLAN

4.1 Study Design

This is a Phase 2a/b randomized, double-blind, placebo-controlled study to investigate the efficacy, safety, tolerability, PK and immunogenicity of KPL-716 administered SC in subjects with moderate to severe prurigo nodularis experiencing moderate to severe pruritus.

The Phase 2a portion of the study will enroll approximately 80 to 100 subjects with moderate to severe prurigo nodularis experiencing moderate to severe pruritus and will include 2 arms: one active arm and one placebo arm. 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 EOS Visit, thus removing the confounding effect of these therapies on the assessment of KPL-716 efficacy. In the interval between Day 1 through the EOS Visit, should subjects experience an exacerbation of symptoms that is significant enough to warrant intervention, TCS and/or oral antihistamines may be provided at the discretion of the Investigator in consultation with the Sponsor. The weight of the TCS tube will be measured and the number of anti-histamine tablets will be recorded on the initial day of dispensation and upon each subsequent visit. Acceptable study TCS and oral anti-histamines will be described in the Pharmacy Manual. A total of 8 doses of study drug are planned during the Treatment Period to determine Proof of Concept in PN on endpoints of pruritus, sleep, quality of life, and disease severity, following dosing to achieve maximum or near current practical maximum exposures. Other secondary endpoints will explore the impact of KPL-716 versus placebo on pruritus, sleep, quality of life and disease severity over time, i.e., at each week of the study treatment period including Week 8 and continuing until EOS visit.

An interim analysis of the Phase 2a portion of the study may be performed after at least 50% of subjects have received at least 4 weeks of study drug to assess for an early signal of efficacy to inform program decision-making. Additional details regarding the interim analysis, if performed, will be provided in the SAP.

Subject enrollment in the Phase 2b portion will depend on Phase 2a results. Subjects enrolled in Phase 2a will remain in Phase 2a. The Phase 2b portion of the study, if enrolled, will include up to approximately 300 subjects with moderate to severe prurigo nodularis experiencing moderate to severe pruritus and will have 5 arms: 4 active arms and one placebo arm. The Phase 2b study will also utilize a washout monotherapy design. Rescue medications may be administered if needed for acute flares as described above. The primary endpoint of the Phase 2b study will also focus on pruritus at Week 8 with other secondary endpoints evaluating pruritus, sleep, quality of life and disease severity over time. The analysis plan for Phase 2b will be defined in the SAP.

Phase 2a and Phase 2b studies each will have three periods.

Phase 2a subjects already consented into Protocol Version 2 will remain in the 16 week treatment period schedule:

- Screening Period (minimum 14 days and maximum 28 days)
- Treatment Period (Day 1 [Baseline] to Week 16)

- Follow-up Period (Week 16 to Week 24)

Phase 2a subjects consented into Protocol Version 3 will follow the 8 week treatment period schedule.

- Screening Period (minimum 14 days and maximum 28 days)
- Treatment Period (Day 1 [Baseline] to Week 8)
- Follow-up Period (Week 8 to Week 16 for Phase 2a)

Phase 2b subjects will follow the 16 week treatment period schedule:

- Screening Period (minimum 14 days and maximum 28 days)
- Treatment Period (Day 1 [Baseline] to Week 16)
- Follow-up Period (Week 16 to Week 24)

Allowable window for Week 1 is ± 1 day and from Week 2 to Week 24 visits is ± 2 days. There must be a minimum of 5 days between doses. If next week's dose is outside of the window, the dose should be skipped.

4.1.1 Screening Period

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

During the Screening Visit, 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 10 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. There must be normal appearing skin present in between nodules with the exception of atopic dermatitis. Each arm, each leg, and 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) in the past 24 hours on a numerical rating scale (WI-NRS). In addition, subjects will record their WI-NRS on a daily basis during the Screening Period. The daily recordings can begin any time after the Screening Visit. Subjects will be provided with an e-Diary device for daily electronic recordings if needed. To be eligible for study participation, subjects must have moderate to severe pruritus, defined as WI-NRS ≥ 7 at the Screening Visit and a mean

weekly WI-NRS ≥ 5 for each of the 2 consecutive weeks (14 consecutive days) immediately prior to randomization. A minimum of 85% compliance with daily WI-NRS recording during the 14 consecutive days prior to dosing is required for eligibility unless approved by the Sponsor.

During the Screening Visit, 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, medical photographs will be taken of a representative area of disease to be 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 include those related to pruritus (Pruritus VAS, and 5-D Pruritus), sleep (Sleep Loss VAS), quality of life (DLQI, HADS, and ItchyQoL) and disease severity (PN-NAT and PN-IGA). Subjects will be instructed on the required washout for specific excluded medications. Subjects also will be instructed to record daily rating of 2 sleep parameters: difficulty falling asleep NRS and sleep quality NRS during the Screening Period. The daily recordings (WI-NRS, difficulty falling asleep NRS, and sleep quality NRS) continue throughout the study for eligible subjects that proceed to dosing.

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

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 adverse events. Clinical laboratory results from the Screening Visit will be reviewed. Compliance with recording of daily WI-NRS for the 14 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, PG (optional), ADA and PD biomarkers. Pregnancy testing will be performed if applicable. Medical photographs will be taken of the representative area of disease identified during the Screening Period and of the biopsy areas prior to collection of the biopsy. 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. Skin biopsies (one lesional and one non-lesional) will be performed. Skin biopsies are optional. Subjects will record their Pruritus VAS, Sleep Loss VAS and complete the 5-D Pruritus questionnaire. Subjects will also complete DLQI, HADS, ItchyQoL, and the PBI-P questionnaires. In addition, subjects' disease severity will be assessed (PN-NAT and PN-IGA). Upon confirmation of subject eligibility and completion of required activities (Appendix 1), the subject will be randomized and proceed to dosing.

4.1.2.2 Randomization and Dosing

To minimize investigational treatment bias, subjects will be randomized to receive treatment in a double-blind manner. In Phase 2a, subjects will be randomized 1:1 to receive KPL-716 or placebo. In Phase 2b, subjects will be randomized 1:1:1:1:1 to receive 4 different dosing regimens of KPL-716 or placebo. Subjects will remain in the same treatment arm throughout the End of Treatment Period. End of Treatment Period is at Week 8 for Phase 2a subjects consented into Protocol Version 3, at Week 16 for Phase 2a subjects already consented into Protocol Version 2 and for Phase 2b subjects. Stratification will be performed based on sex and presence of atopy.

A loading dose of KPL-716 (2x maintenance dose) or matching placebo will be administered via up to 2 SC injections within 30 minutes on Day 1 by the Investigator or qualified designee at the study site. All subsequent doses of KPL-716 (maintenance dose) or matching placebo will be administered by the Investigator or qualified designee at the study site via a single SC injection. Subjects will be observed for 3 hours after the loading dose, for 2 hours after the first 2 maintenance doses and for 1 hour after all subsequent doses. Vital signs will be measured every hour during the observation period. The post-dose observation duration may be modified based on emerging safety and tolerability data. In addition, the dose level, dosing regimen, and randomization ratio may be modified based on emerging safety, tolerability, PK, PD and/or efficacy data. The planned loading and maintenance dose levels for the Phase 2a portion of the study are currently 720 mg and 360 mg, respectively.

Phase 2a: **Figure 1**

- Arm A: KPL-716, 720 mg loading dose followed by 360 mg every week
- Arm B: Placebo loading dose followed by placebo every week

The loading dose and maintenance dose for Phase 2a will not exceed 720 mg and 360 mg, respectively.

Phase 2b: **Figure 2**

- Arm A: KPL-716, loading dose (2x dose level A) followed by dose level A every 2 weeks
- Arm B: KPL-716, loading dose (2x dose level B) followed by dose level B every 2 weeks
- Arm C: KPL-716, loading dose (2x dose level C) followed by dose level C every 2 weeks
- Arm D: KPL-716, loading dose (2x dose level D) followed by dose level D every 4 weeks, interspersed with placebo injection every 2 weeks to maintain the blind.
- Arm E: placebo loading dose followed by placebo every 2 weeks

The loading and maintenance dose levels for the Phase 2b portion of the study will be determined prior to study start based upon emerging safety, tolerability, PK, PD and/or

efficacy data. All KPL-716 PK data (the single dose study of KPL-716 in subjects with atopic dermatitis [Phase 1b Part 1] and healthy volunteers [Phase 1b, Part 3], the repeated single dose study in subjects with atopic dermatitis [Phase 1b, Part 4], and the Phase 2a portion of this study in subjects with PN), as available, will be used to support PK modeling to enable dose selection for Phase 2b. The dose levels and dosing intervals for Phase 2b will be chosen in such a way as to not exceed exposures observed in Phase 2a.

All procedures assigned to dosing days are performed prior to study drug administration. The following activities will take place prior to each maintenance dose:

- Review of concomitant medications, therapies and procedures
- Review of adverse events
- Review of subject compliance
- Vital signs (performed before and after dosing on each dosing day)
- Collection of blood for PK
- Completion of Pruritus VAS, Sleep Loss VAS

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

- Physical examination and ECG
- Collection of safety blood and urine samples
- Urine pregnancy test (if applicable); a serum pregnancy test will be performed if the urine pregnancy test is positive
- Collection of ADA and PD samples
- Medical photography
- Completion of 5-D pruritus questionnaire
- Completion of quality of life questionnaire (DLQI, HADS, ItchyQoL, PBI-P)
- Assessment of disease severity (PN-NAT and PN-IGA)
- Skin biopsies (Skin biopsies are optional and will be performed at select sites)

Adverse events 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. In case of study drug interruption or missed dosing visits, subjects will resume the schedule of activities in accordance with their study day. Study drug will be discontinued if more than 3 consecutive doses are withheld or missed. In case of early withdrawal from the entire study, subjects will complete an EOS Visit. In addition, if the early termination occurs prior to Week 8, biopsies should be collected at the EOS visit.

4.1.3 The Follow-up Period

During the Follow-up Period, subjects will undergo vital signs measurement, review of concomitant medications, therapies and procedure, review of adverse events, monitoring of compliance and PK blood sample collection at every visit. Pruritus VAS, 5-D Pruritus, and Sleep Loss VAS will also be completed at every visit during the Follow Up Period. Physical examination, clinical laboratory tests (including pregnancy testing if applicable), quality of life assessment (DLQI, HADS and ItchyQoL), and evaluation of disease severity (PN-NAT and PN IGA) will be performed at designated visits. Subjects will continue to complete their daily questionnaire on pruritus and sleep throughout the Follow-up Period.

The EOS Visit (Week 16 for subjects in Phase 2a consented into Protocol Version 3, or Week 24 for subjects in Phase 2a already consented into Protocol Version 2 and subjects in Phase 2b) includes vital signs, full physical examination, ECG, clinical laboratory blood tests, urinalysis, and urine pregnancy test (if applicable) as well as PK, ADA and PD blood sampling. 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 Study Duration

The planned study duration per subject for Phase 2a consented into Protocol Version 3 each is 20 weeks including a maximum of 4 weeks for the Screening Period, 8 weeks for the Treatment Period, and an 8-week Follow-up Period.

The planned study duration per subject for Phase 2a already consented into Protocol Version 2 and Phase 2b each is 28 weeks including a maximum of 4 weeks for the Screening Period, 16 weeks for the Treatment Period, and an 8-week Follow-up Period.

The minimum duration for the Screening Period will be 14 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

Subjects will be randomized to receive KPL-716 or matching placebo on Day 1 and will remain in the same treatment arm throughout the study. A loading dose of KPL-716 (2 x maintenance dose) or placebo will be administered via up to 2 SC injections within 30 minutes on Day 1. Maintenance doses of KPL-716 or placebo will be administered via 1 SC injection for the remainder of the Treatment Period. The planned loading and maintenance dose levels for the Phase 2a portion of the study are currently 720 mg and 360 mg, respectively. The dose level and dosing regimen may be modified based on emerging safety, tolerability, PK, PD and/or efficacy data.

Phase 2a: Figure 1

- Arm A:
    - Loading dose of KPL-716 at 720 mg on Day 1 via 2 SC injections
    - Maintenance doses of KPL-716 at 360 mg via a single SC injection weekly starting at Week 1 through Week 15 for subjects already consented into Protocol Version 2, or Week 7 for subjects consented into Protocol Version 3
- Arm B:
    - Loading dose of placebo on Day 1 via 2 SC injections
    - Maintenance doses of placebo via a single SC injection weekly starting at Week 1 through Week 15 for subjects already consented into Protocol Version 2, or Week 7 for subjects consented into Protocol Version 3

Phase 2b: Figure 2

- Arm A:
    - Loading dose of KPL-716 at 2 x dose level A on Day 1 via up to 2 SC injections
    - Maintenance doses of KPL-716 at dose level A via a single SC injection at Week 2, 4, 6, 8, 10, 12 and 14
- Arm B:
    - Loading dose of KPL-716 at 2 x dose level B on Day 1 via up to 2 SC injections
    - Maintenance doses of KPL-716 at dose level B via a single SC injection at Week 2, 4, 6, 8, 10, 12, and 14

- Arm C:
    - Loading dose of KPL-716 at 2 x dose level C on Day 1 via up to 2 SC injections
    - Maintenance doses of KPL-716 at dose level C via a single SC injection at Week 2, 4, 6, 8, 10, 12 and 14
- Arm D:
    - Loading dose of KPL-716 at 2 x dose level D on Day 1 via up to 2 SC injections
    - Maintenance doses of KPL-716 at dose level D via a single SC injection at Week 4, 8, and 12
    - Maintenance doses of placebo via a single SC injection at Week 2, 6, 10, and 14
- Arm E:
    - Loading dose of placebo on Day 1 via up to 2 SC injections
    - Maintenance doses of placebo via a single SC injection at Week 2, 4, 6, 8, 10, 12, and 14

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 SD 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 C_{max} of 217 µg/ml and $AUC_{0-\infty}$ 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. In the absence of sufficient number of subjects at the lower dose level arms, it is difficult to ascertain a precise C_{eff} for the antipruritic response. 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 AtD 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 weekly SC dosing regimen is proposed to ensure subsequent doses are administered before a significant decline in blood concentrations has occurred so as to achieve initial KPL-716 exposure levels similar to those achieved with 7.5 mg/kg IV as a single dose. A loading dose of 720 mg is administered in this Phase 2a study in order to achieve blood concentrations that are likely to provide clinical benefit sooner. The 720 mg SC loading dose represents an incremental increase from the SC 360 mg dose used in Part 4 of KPL-716-C001 (repeated-single-dose study). A loading dose of 720 mg was chosen since the peak concentration levels from this dose are anticipated to be less than those achieved with 7.5 mg/kg IV, which showed acceptable safety and tolerability in the single dose study. A loading dose that is twice the maintenance dose is typical, in particular to minimize the risk of dosing errors.

Based on PK modeling, the expected C_{max} from a loading dose of 720 mg SC followed by 7 weekly SC doses at 360 mg is expected to be approximately 200 μg/ml, with trough levels of approximately 120 μg/ml. These are exposure levels similar to those anticipated to be achieved with 12 weekly doses of 360 mg SC, which has shown acceptable safety and tolerability to date in KPL-716-C001 Part 4.

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 (up to 16) and the dose level (720 mg loading dose and 360 mg weekly dose or 10 mg/kg and 5 mg/kg in a 72 kg adult, respectively) in this Phase 2a study fall well under 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 32 subjects with atopic dermatitis (Part 1) were exposed to single doses of KPL-716 or placebo IV or SC. There were no deaths, SAEs, or discontinuations due to AEs. There were no infusion reactions or injection site reactions. Drug-related or possibly related treatment-emergent AEs were infrequent. In Part 4 of KPL-716-C001 (repeated-single-dose study), subjects with moderate to severe atopic dermatitis experiencing moderate to severe pruritus are being randomized 1:1 and administered KPL-716 360 mg or placebo SC once weekly for a total of 12 doses. Based on PK modeling, steady state exposures are achieved after approximately 5 doses of 360 mg SC. To date, 45subjects have been randomized in Part 4, 43 have received at least 1 dose of study drug, 42 have received 5 doses and 27 have completed the 12-dose treatment regimen. In this blinded study, safety and tolerability have been acceptable to date in Part 4. For summary of safety data from KPL-716-C001 Part 1 and Part 3, please see IB. The 720 mg SC loading dose represents an incremental increase from the SC 360 mg dose. The anticipated C_{max} from a 720 mg SC loading dose is anticipated to be lower than that seen with 10 mg/kg in the Phase 1 study, which showed acceptable safety and tolerability in healthy volunteers when administered as a single IV dose.

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 1:1:1:1:1 to receive 4 different dosing regimens of KPL-716 or placebo SC. Maintenance doses of KPL-716 or placebo will be administered via 1 SC injection during the Treatment Period. A loading dose of KPL-716 (2x maintenance dose) or placebo will be administered via up to 2 SC injections within 30 minutes on Day 1 in order to achieve efficacious levels more quickly. The dose levels for each arm will be chosen based on emerging safety, tolerability, PK, PD, ADA and efficacy data. KPL-716 PK data (the single dose study of KPL-716 in subjects with atopic dermatitis [Phase 1b, Part 1] and healthy volunteers [Phase 1b, Part 3], the repeated single dose study in subjects with atopic dermatitis [Phase 1b, Part 4], and the Phase 2a portion of this study in subjects with PN), as available, will be used to support PK modeling to enable dose selection for Phase 2b. The dose levels and dosing intervals for Phase 2b will be chosen in such a way as to not exceed exposures observed in Phase 2a. Dosing regimen and randomization schedule may also be modified as needed based on emerging data.

4.6 Study Assessments

4.6.1 Efficacy Assessment

Efficacy in reduction of pruritus will be assessed via daily recording of WI-NRS as well as on-site assessment of Pruritus VAS and 5-D Pruritus. Efficacy in improvement in sleep will be assessed via daily recording of 2 NRS scales, one for difficulty falling asleep and the other for quality of sleep. Impact on sleep will also be assessed on-site via Sleep Loss VAS. Impact on quality of life will be assessed via on-site PROs: DLQI, HADS, ItchyQoL, and PBI-P. Impact on disease severity will be followed through two novel and exploratory tools: PN-NAT and PN-IGA as per 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 biopsies) will be taken at indicated study visits.

Four skin biopsies will be collected during this study. Skin biopsies are optional. Two 4.5-mm punch biopsies (one from lesional skin and one from adjacent non-lesional skin) will be collected prior to dosing at Day 1 and two 4.5 mm punch biopsies (one lesional and one non-lesional) will be collected at End of Treatment visit. Skin biopsies will be evaluated for gene expression to assess target engagement and to identify mechanistic and/or predictive biomarkers. 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 at every visit from the baseline visit to EOS. PK samples will be collected pre-dose on dosing days.

4.6.4 PD Assessments

PD blood samples will be collected from all subjects on Day 1, Weeks 2, and 4, and at End of Treatment and EOS visits, for biomarkers analysis. PD samples will be collected pre-dose on dosing days.

Additional PD blood samples will be collected as follows:

- For Phase 2b subjects and Phase 2a subjects already consented into Protocol Version 2, at Weeks 8, 12, and 20
- For Phase 2a subjects consented into Protocol Version 3, at Week 12

4.6.5 Immunogenicity Assessments

ADA blood samples will be collected from all subjects at Day 1, Weeks 2, and 4, and at End of Treatment and EOS visits. ADA samples will be collected pre-dose on dosing days. Additional ADA blood samples for Phase 2b subjects and Phase 2a subjects already consented into Protocol Version 2, will be collected at Week 8.

4.7 Selection of Study Population

4.7.1 Inclusion Criteria

1. Male or female aged 18 to 75 years, inclusive, at the time of consent.
2. Have a physician-documented diagnosis of prurigo nodularis that is confirmed by review of medical photography (as outlined in the Study Manual) during the Screening Period. Duration of prurigo nodularis (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 10 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. There must be normal appearing skin present in between nodules with the exception of atopic dermatitis. Each arm, each leg, and trunk are considered different anatomical locations.

4. Subject has moderate to severe pruritus, defined as WI-NRS ≥ 7 at the Screening Visit and a mean weekly WI-NRS ≥ 5 for each of the 2 consecutive weeks immediately prior to randomization.

5. 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 (IUD)

            - intrauterine system (IUS)

            - 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

6. 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. 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.

8. Female of childbearing potential must have a negative serum β-hCG test at the Screening Visit and negative urine pregnancy test on Day 1.

9. 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.

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

4.7.2 Exclusion Criteria

1. Use of the following medications within the indicated timeframe from Day 1 and does not agree to refrain from the use of the medications throughout the study treatment and follow up duration:

    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 prurigo nodularis including but not limited to corticosteroids, calcineurin inhibitors, phosphodiesterase inhibitors, retinoids, calcipotriol, capsaicin, camphor, polidocanol, cannabinoids, gabapentin or tars: 2 weeks

    d. Anti-histamines: 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 (JAK) inhibitors: 3 months

    j. Dupilumab: 6 months

k. Any other marketed biologic: 5 half-lives or until CD19 cell numbers return to normal in case of depleting antibodies such as rituximab

l. Any investigational biologic drug: 5 half-lives

m. Any investigational non-biologic drug: 5 half-lives

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

o. Tanning salon use: 4 weeks

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

3. Is currently using medication known to cause pruritus (e.g. angiotensin converting enzyme inhibitors) unless timing of onset of pruritus and initiation of medication do not suggest that pruritus was caused by the medication.

4. Has less than 85% compliance with the daily WI-NRS tool during the last 14 days of the Screening Period prior to randomization, unless approved by the Investigator in consultation with the Sponsor.

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

6. Presence of any inflammatory, pruritic, and/or fibrotic skin condition other than moderate to severe prurigo nodularis or atopic dermatitis unless approved by the Sponsor.

7. History of chronic urticaria with active lesions in the past 2 years.

8. Presence of uncontrolled hyperthyroidism or hypothyroidism or uncontrolled diabetes defined as hemoglobin A1c >7.5%.

9. Presence or history of cancer or lymphoproliferative disease within 5 years prior to Day 1, with the exception of squamous and basal cell carcinoma.

10. Presence or history of any autoimmune disorder.

11. Presence or history of immune deficiency, or opportunistic infections

12. Subject has positive results for hepatitis B surface antigen (HbsAg)

13. Subject has positive results for hepatitis B anti-core antibody (anti-HBc) but negative results for anti-surface antibody (anti-HBs).

14. Subject has positive results for hepatitis C antibody unless patient received curative therapy and a negative viral load is documented.

15. Human immunodeficiency virus (HIV) infection or positive HIV serology.

16. Subject is on hemodialysis or peritoneal dialysis.

17. Psychiatric illness other than stable mild to moderate anxiety and/or depression unless approved by the Sponsor.

18. Hospitalization for a psychiatric illness.

19. Laboratory abnormalities that fall outside the windows below at the Screening Visit:

    a. Alanine aminotransferase > 2 x ULN

    b. Aspartate aminotransferase > 2 x ULN

    c. Gamma-glutamyl transferase > 2 x ULN

    d. Blood bilirubin > 1.5 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 <120,000/ µl

20. Body mass index (BMI) >39 kg/m^2

21. Systolic blood pressure above 150 mm Hg, diastolic blood pressure above 95 mm Hg at the Screening Visit or Day 1 (confirmed by repeat measurement).

22. Hospitalization within 16 weeks prior to Day 1.

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

24. 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.

25. 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.

26. Has received a live attenuated vaccine within 12 weeks prior to Day 1.

27. Has previously taken part in or withdrawn from this study or has previously received the study drug.

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

29. Has a known history of drug or alcohol abuse in the last 2 years prior to Day 1. 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

30. 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 Sponsor-approved medication for a stable concomitant condition that explains the positive drug screen result.

31. Current user of nicotine > 3 pack per day or nicotine equivalent/day.

32. Has received blood products within 8 weeks prior Day 1.

33. Has donated blood within 12 weeks prior to Day 1, platelets within 10 weeks prior to Day 1, or plasma within 6 weeks prior to Day 1.

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

4.8 Subject Number and Identification

Each subject that signs the ICF and enters the Screening Visit will be assigned a unique 3-digit screening number provided (e.g., 001, 002, 003). 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 e-CRF.

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

Study drug will be permanently discontinued if more than 3 consecutive doses are withheld or missed. 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 IRB/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.

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 of 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 2a, subjects will be randomized 1:1 to receive KPL-716 or placebo. In Phase 2b, subjects will be randomized 1:1:1:1:1 to receive 4 different dosing regimens of KPL-716 or placebo.

A loading dose of KPL-716 (2x maintenance dose) or matching placebo will be administered via up to 2 SC injections within 30 minutes on Day 1 by the Investigator or designee at the study site. All subsequent doses of KPL-716 (maintenance dose) or matching placebo will be

administered by the Investigator or designee via a single SC injection. The planned loading and maintenance dose levels for the Phase 2a portion of the study are currently 720 mg and 360 mg, respectively.

Phase 2a: Figure 1

- Arm A: KPL-716, 720 mg loading dose followed by 360 mg every week
- Arm B: Placebo loading dose followed by placebo every week

Phase 2b: Figure 2

- Arm A: KPL-716, loading dose (2 x dose level A) followed by dose level A every 2 weeks
- Arm B: KPL-716, loading dose (2x dose level B) followed by dose level B every 2 weeks
- Arm C: KPL-716, loading dose (2x dose level C) followed by dose level C every 2 weeks
- Arm D: KPL-716, loading dose (2x dose level D) followed by dose level D every 4 weeks, interspersed with placebo injection every 2 weeks to maintain the blind.
- Arm E: placebo loading dose followed by placebo every 2 weeks

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 presence of atopy.

An Interactive Web Response System (IWRS) will issue a unique treatment code to each subject, which will assign the treatment for the subject. Prior to each dosing, medical ID number of the vial to be administered will be obtained from (IWRS) based on the computer-generated treatment randomization schedule. The study drug will be prepared and administered according to instructions in the Pharmacy Manual. In Part 2b, an unblinded pharmacist or an unblinded nurse will complete any of these steps as needed.

5.4 Blinding

This will be a double-blind, placebo-controlled study. As such, the Investigator, the Sponsor, and remaining clinical site staff will be blinded to treatment.

The unblinded treatment assignment for each individual subject may be made available to the Investigator through the web-based randomization system 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.
- 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 study monitor. In Phase 2b this activity may be performed by a separate 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 last Follow-up Visit. The following medications are prohibited from designated timepoints before Day 1 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 including but not limited to corticosteroids, calcineurin inhibitors, phosphodiesterase inhibitors, retinoids, calcipotriol, capsaicin, camphor, polidocanol, cannabinoids, gabapentin or tars

d. Anti-histamines

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 (JAK) inhibitors

j. Dupilumab

k. Any other marketed biologic

l. Any investigational biologic drug

m. Any investigational non-biologic drug

n. Phototherapy involving UVA, UVB, or excimer

o. Tanning salon use

Topical corticosteroids and anti-histamines may be provided in consultation with the Sponsor 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 or the inability to comply with nicotine restrictions of the study site 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 child bearing 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 (IUD)
    - intrauterine system (IUS)
    - 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

7.1.1 Pharmacokinetic Blood Sample Collection and Processing

Pharmacokinetic 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

7.2.1 Immunogenicity Blood Sample Collection and Processing

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 as well as recording of Pruritus VAS and 5-D Pruritus at each study visit. Sleep will be assessed using daily recording of difficulty falling asleep NRS and sleep quality NRS as well as recording of Sleep Loss VAS at each study visit. Quality of life will be followed via DLQI, HADS, ItchyQoL and PBI-P. Disease severity will be evaluated using PN-NAT and PN-IGA, two novel exploratory tools, 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 4 contains 3 numerical rating scales to assess subjects' pruritus and sleep on a daily basis. The Daily NRS tool will be used during the Screening Period through the EOS Visit. The daily recordings can begin any time after the Screening Visit. Please see Sections 7.3.1.1, 7.3.1.2 and 7.3.1.3.

7.3.1.1 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 Worst-Itch NRS is provided in the Daily NRS Tool Appendix 4.

7.3.1.2 Difficulty falling asleep Numerical Rating Scale

Subjects will be asked to assign a numerical score to the intensity of their difficulty falling asleep last night due to itch using a scale from 0 to 10, with 0 indicating no difficulty and 10

indicating extremely difficult. This NRS will be used to assess subjects' level of difficulty falling asleep during the Screening Period through EOS Visit. The difficulty falling asleep NRS is provided in the Daily NRS Tool Appendix 4.

7.3.1.3 Quality of Sleep Numerical Rating Scale

Subjects will be asked to assign a numerical score to the quality of their sleep in the previous night using a scale from 0 to 10, with 0 indicating best possible sleep and 10 indicating worst possible sleep. This NRS tool will be used to assess subjects' quality of sleep during the Screening Period through the EOS Visit. The sleep quality NRS is provided in the Daily NRS Tool Appendix 4.

7.3.2 Pruritus Visual Analog Scale (Pruritus VAS)

Subjects will be asked to place a line perpendicular to the VAS line at the point that represents the intensity of their average pruritus experienced over the previous 3 days using a scale from 0 to 10, with 0 indicating no pruritus and 10 indication the worst imaginable pruritus (24). The Pruritus VAS is administered at every visit.

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 is administered at every visit.

7.3.4 5-D Pruritus Scale

The 5-D Pruritus Scale evaluates pruritus in five domains: duration, degree, direction, disability and distribution. Duration, degree and direction each consist of one item. The disability domain contains four items and the distribution domain includes 16 items. The first four domains are measured on a five-point Likert scale. The scores from each domain are added together to obtain a total 5-D score ranging from 5 (no pruritus) and 25 (most severe pruritus) (25). The 5-D Pruritus Scale is administered every 2 visits.

7.3.5 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 over the whole body, 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 compartment based on the appearance of the disease at the time of the evaluation without referring to the baseline state. A cumulative score will be calculated from the scoring of each compartment. The formula for the cumulative score will be generated post-hoc. PN-NAT is provided in Appendix 5. The PN-NAT tool is administered at designated visits.

7.3.6 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 size of the nodules as defined by their elevation. The IGA will be performed by the Investigator. The IGA utilizes a 5-point scale that ranges from 0 (clear) to 4 (severe disease) Appendix 5. 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 5. The PN-IGA tool is administered at designated visits.

7.3.7 Medical Photographs

Standardized medical photographs will include photographs of the whole body, of the most representative area (as established in 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 Treatment, and the EOS Visits (). The representative areas of the subject's disease will be photographed at the following timepoints: Screening Visit, at Day 1, Week 4, End of Treatment, and EOS Visits. Photographs of representative areas will also be collected at Weeks 8 and 12 for subjects in Phase 2a who already consented to Protocol Version 2 and subjects in Phase 2b. Sites of lesional and non-lesional biopsies will be photographed before dosing at Day 1 and at End of Treatment visit, 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 Manual.

7.3.8 Dermatology Life Quality Index

The DLQI is a 10-question questionnaire that considers symptoms and feelings, daily activities, leisure, school, personal relationships, and treatment. Each question is answered on a scale of 0 to 3 (0 for not at all, 1 for a little, 2 for a lot, and 3 for very much) or with a yes or no, taking into account the previous week. The scores are added with minimum of 0 meaning no effect on quality of life and 30 meaning extremely large effect (26). DLQI will be administered at designated visits.

7.3.9 Hospital Anxiety and Depression Scale

The HADS is a general Likert scale used to detect states of anxiety and depression (27). The 14 items on the questionnaire include 7 that are related to anxiety and 7 that are related to depression. Each item on the questionnaire is scored on a scale of 0 to 3 with a possible total score between 0 and 21 for each parameter. HADS will be administered at designated visits.

7.3.10 ItchyQoL questionnaire

The ItchyQoL tool 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 (28). ItchyQoL will be administered at designated visits.

7.3.11 Patient Benefit Index-Pruritus

PBI-P consists of 2 questionnaires:

Patient Needs Questionnaire (PNQ) contains 27 items on treatment needs and is administered prior to first dose. PNQ is scored using a 5-point Likert scale ranging from 0 (not at all important or does not apply to me) to 4 (very important)

Patient Benefit Questionnaire (PBQ) contains the same items but patients rate the extent to which their treatment needs have been achieved by therapy. PBQ is scored using a 5-point Likert scale ranging from 0 (treatment didn't help at all) to 4 (treatment helped a lot).

PBI is calculated by dividing each rating on a need item by the sum of all ratings in the PNQ, multiplying this fraction with the respective benefit rating in the PBQ and summing these products. PBI can range from 0 (no benefit) to 4 (maximal benefit) (29). PBI-P will be administered at designated visits.

7.4 Pharmacodynamic Assessments

7.4.1 Pharmacodynamic Blood Sample Collection and Processing

Blood samples will be collected by venipuncture at the times indicated in Appendix 1. Blood protein biomarker profiles will be analyzed. Skin gene expression analyses will be performed and may include target genes related to pruritus, inflammation, and/or fibrosis. Unused or partly-used samples will be archived for potential future analysis.

7.4.2 Pharmacodynamic Skin Biopsy Collection and Processing

Subjects will undergo skin biopsy sampling for gene expression analysis at the times indicated in Appendix 1. Skin biopsies are optional. A total of four skin biopsies will be collected during the study. Two 4.5-mm skin biopsies will be obtained pre-dose on Day 1, and two 4.5 mm skin biopsies will be obtained at End of Treatment visit.

One biopsy at each time point will be from lesional skin and one from non-lesional skin. The lesional biopsy will be taken from a representative PN nodule in an area with at least 2 nodules. Every effort will be made to obtain the non-lesional skin biopsy from an area of skin that is completely disease free, is in the same anatomical location as the lesional biopsy and is as far from diseased skin as possible. Lesional biopsies will be performed from the center of nodules.

Post-treatment (End of Treatment Visit) lesional biopsy will be obtained from a nodule in the same anatomical location as the pre-treatment lesional biopsy. If no nodules are present in the same anatomic location, the lesional biopsy will be taken from an area 2-5 cm from the location of pre-treatment lesional biopsy. In case of early treatment discontinuation, biopsies will be performed at the earliest possible visit. In addition, in case of early termination that occurs prior to Week 8, biopsies should be collected at the EOS visit.

Specifics instructions will be provided in a separate manual.

7.5 Pharmacogenomic Assessments

A single blood sample for pharmacogenomic analysis will be collected on Day 1. Specifics of the analytical method will be provided in the Laboratory Sample Management Plan.

7.6 Safety and Tolerability Assessments

7.6.1 Adverse Events

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 adverse event (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 (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 serious adverse events (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 through the Study Manual.

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

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.

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.

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

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 Reporting

Investigator Reporting Responsibilities to the Sponsor

SAEs 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:

The event must also be recorded on the standard AE e-CRF. 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.

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.

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.

7.6.2 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. A serum pregnancy test will be performed if urine pregnancy is positive. 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.

7.6.3 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.

7.6.4 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 >450 ms in men and >470 ms in 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.

7.6.5 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.

7.6.6 Safety Data Review

During KPL-716-C201, periodic reviews of safety and tolerability data will be conducted by a safety data review committee consisting of Investigators from active sites and a Sponsor physician representative. In addition, the Sponsor will review internally emerging safety and tolerability data periodically.

For the Phase 2b portion of the study a Data Monitoring Committee (DMC) comprised of members with appropriate scientific and medical expertise to monitor the study will be convened before the study is opened. A charter describing the composition and conduct of the DMC will be issued by the Sponsor and agreed to by all DMC members prior to the DMC's initial meeting. A DMC chairperson will be appointed who will be responsible for the overall operation of the DMC. Minutes from each meeting will be recorded and archived. The DMC will meet by teleconference at regular intervals, approximately once every 3 months, or more frequently if needed, and depending on speed of subject enrollment and amount of new data generated. The DMC will be charged with review of all unexpected treatment-related SAEs following notification by the Sponsor.

It will be the responsibility of the Sponsor or Sponsor's designee to provide the members of the DMC with safety data and any other relevant information necessary for the members to conduct a comprehensive safety review and assessment of the ongoing study. The Sponsor will promptly contact the chairperson of the DMC about all serious unexpected AEs (i.e., unexpected in nature and /or in severity). The DMC will have the right to recommend modifications to the ongoing study or halt the study at any time due to concerns for the safety of the subjects.

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, SD, 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 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. Details for the analyses including handling subjects randomized to different treatment durations (16 weeks for the original protocol and 8 weeks for the Protocol Version 3) 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

Multiplicity adjustment will be done for the analyses of the primary efficacy endpoint and key secondary efficacy endpoints in Phase 2a and the primary efficacy endpoint in Phase 2b. Details will be specified in the SAP.

8.4 Determination of Sample Size

The sample size calculation is based on a two-sample t-test for the primary efficacy endpoint percentage change from baseline of WI-NRS at Week 8.

Approximately 80 to 100 subjects will be randomized in the Phase 2a part with a 1:1 allocation ratio. Assuming a weekly average WI-NRS reduction from baseline at week 8 of 60% for the KPL-716 group and 30% for the placebo group and standard deviation of 50% in both treatment groups, a sample size of 50 subjects per group will provide at least 90% power to detect the treatment difference at two-sided alpha of 0.20.

Approximately 300 subjects in total will be equally randomized to the Phase 2b dose groups. As the number of Phase 2b dose groups and dose levels will be determined based on the Phase 2a data, sample size justification for Phase 2b will not be specified in the protocol. Details for sample size calculation will be provided in the SAP and finalized before the database lock.

8.5 Analysis Populations

The following analysis sets will be defined separately for the Phase 2a and Phase 2b portions 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 post-baseline efficacy assessment 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 Analysis Sets

All mITT subjects who have no protocol deviations or violations that may potentially bias statistical 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 analyses of primary and key secondary efficacy endpoints will be repeated using the PP set to assess the sensitivity of the results to major violations of the protocol. All efficacy data will be listed by subject.

As the number of Phase 2b dose groups and dose levels will be determined based on the Phase 2a data, analysis of Phase 2b efficacy data is not specified in the protocol. Details for the analysis will be provided in the SAP and finalized before the database lock.

8.6.1 Analysis of Primary Efficacy Endpoint in Phase 2a

A mixed–effect model repeated measures (MMRM) model will be fitted to the primary efficacy endpoint, the percent change from baseline in weekly average WI-NRS score at Week 8. The model will include fixed effects for treatment, both stratification factors for randomization, baseline weekly average WI-NRS, treatment week (Week 1 through Week 8), and treatment week-by-treatment interaction. Details for the modeling will be specified in the SAP. The LS mean estimates for average WI-NRS score at Week 8 based on this model will be used for comparisons of treatment groups for the primary endpoint analysis. The corresponding p-value and 95% CI for the treatment mean difference will be displayed.

8.6.2 Analysis of Key Secondary Endpoints in Phase 2a

A similar MMRM model will be fitted to the key secondary efficacy endpoint, the percent change from baseline in Pruritus VAS assessed at Week 8. The model will include fixed effects for treatment, both stratification factors for randomization, baseline Pruritus VAS, treatment visit, and treatment visit-by-treatment interaction. The LS mean estimates for Pruritus VAS assessed at Week 8 visit based on this model will be used for comparisons of treatment groups for this secondary endpoint analysis. The corresponding p-value and 95% CI for the treatment mean difference will be displayed.

The number and proportion of subjects achieving at least a 4-point reduction from baseline in weekly average WI-NRS at week 8 will be summarized for each treatment group. The difference of proportions and the corresponding 95% CI for the difference of proportions will be displayed. Treatment groups will be compared using a CMH test controlling for the randomization stratification variables. Logistic regression using randomization stratification factors and baseline WI-NRS value as covariates might be done as a sensitivity analysis.

8.6.3 Analysis of Other Efficacy Endpoints in Phase 2a

The continuous efficacy endpoints are changes and percent changes over time (weekly until Week 8 for subjects treated for 8 weeks and Week 16 for subjects treated for 16 weeks) either in weekly averages of daily measurements or in by-visit assessments of efficacy-related measures. These endpoints will be analyzed descriptively by treatment group. The analyses will include two-sided 95% CIs for the difference of treatment means by week or by visit, as appropriate.

The responder endpoints will also be analyzed descriptively by treatment group over time. Frequencies and proportions of responders for each treatment group as well as the two-sided 95% CIs for the difference of proportions will be displayed, by week or by visit, as appropriate.

For selected variables, MMRM models may be employed for longitudinal comparisons of the treatment groups and these analyses will be fully described in the SAP.

8.7 Analysis of Safety

All safety analyses will be conducted based on the Safety Analysis Set. 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 treatment emergent AEs (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 preferred term (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 Immunogenicity Analyses

Serum ADA will be listed and summarized. The effect of serum KPL-716 antibodies on PK parameters and KPL-716 concentrations may also be evaluated as appropriate. No formal statistical analyses are planned. Additional details on immunogenicity analyses will be provided in the SAP.

8.10 Pharmacogenomic and Gene Expression Analyses

Blood samples will be used to identify genetic polymorphisms for target-related genes. Protein biomarker profiles will be analyzed from blood samples. Gene expression will also be analyzed from skin biopsy specimens. Other genetic and gene expression analyses may be performed for target genes related to pruritus, inflammation, and/or fibrosis as determined by the Sponsor.

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

8.11 Interim Analyses

An interim analysis of the Phase 2a portion of the study may be performed after at least 50% of subjects have received at least 4 weeks of study drug to assess for an early signal of efficacy. Additional details regarding the interim analysis, if performed, will be provided in the Statistical Analysis Plan (SAP).___

Subject enrollment in the Phase 2b portion will depend on Phase 2a results. Subjects enrolled in Phase 2a will remain in Phase 2a. If the interim analysis is conducted in the Phase 2a part, a two-sided alpha of 0.0001will be spent. The two-sided alpha level for the final Phase 2a efficacy analysis will be 0.20.

9 QUALITY CONTROL AND QUALITY ASSURANCE

9.1 Auditing

The study may be audited or reviewed by Kiniksa Quality Assurance (QA) 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, e-CRF 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 Clinical Research Organization (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 (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 Case Report Forms or EDC by staff at the study site. Following data entry, the e-CRF 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.

PG samples and skin biopsies are optional in this study.

11.4 Subject Confidentiality

The results from Screening and data collected during the study will be recorded in the CRF. To maintain confidentiality, the subjects will be identified only by a unique subject identification number.

Subject medical information obtained by this study is confidential and may only be disclosed to third parties as permitted by the ICF signed by the subject, unless permitted or required by law.

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 A Schedule of Activities for subjects in Phase 2a already consented into Protocol Version 2

Study Visits	**Screening**	**Treatment Period**																	**Follow-up Period**		
Week (W)	**W-4 to W0**	**Baseline**	**W1**	**W2**	**W3**	**W4**	**W5**	**W6**	**W7**	**W8**	**W9**	**W10**	**W11**	**W12**	**W13**	**W14**	**W15**	**W16**	**W18**	**W20**	**W24 (EOS)**
Day (D)	**D -28 to -1**	**D1**	**D8**	**D15**	**D22**	**D29**	**D36**	**D43**	**D50**	**D57**	**D64**	**D71**	**D78**	**D85**	**D92**	**D99**	**D106**	**D113**	**D127**	**D141**	**D169**
Study Procedures	Windows (D)	0	±1	±2	±2	±2	±2	±2	±2	±2	±2	±2	±2	±2	±2	±2	±2	±2	±2	±2	±2
Informed consent	X																				
Demographics	X																				
Medical and surgical history	X	X																			
Prior medications, therapies, procedures	X	X																			
Eligibility Assessment	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	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
ECG (12-lead)[3]	X	X								X								X			X

Study Visits	**Screening**	**Treatment Period**																	**Follow-up Period**		
Week (W)	**W-4 to W0**	**Baseline**	**W1**	**W2**	**W3**	**W4**	**W5**	**W6**	**W7**	**W8**	**W9**	**W10**	**W11**	**W12**	**W13**	**W14**	**W15**	**W16**	**W18**	**W20**	**W24 (EOS)**
Day (D)	**D -28 to -1**	**D1**	**D8**	**D15**	**D22**	**D29**	**D36**	**D43**	**D50**	**D57**	**D64**	**D71**	**D78**	**D85**	**D92**	**D99**	**D106**	**D113**	**D127**	**D141**	**D169**
Study Procedures	Windows (D)	0	±1	±2	±2	±2	±2	±2	±2	±2	±2	±2	±2	±2	±2	±2	±2	±2	±2	±2	±2
Adverse events monitoring	From the Screening Visit through EOS Visit (Week 24)																				
Concomitant meds/therapies/ procedures monitoring	From the Screening Visit through EOS Visit (Week 24)																				
Compliance assessment	From the Screening Visit through EOS Visit (Week 24)																				
Laboratory Tests																					
Clinical laboratory blood tests	X	X		X		X		X		X				X				X			X
Urinalysis	X	X				X				X				X				X			X
Pregnancy test[4]	X	X								X								X			X
Serology (HIV, HBV, HCV)	X																				
Urine Drug of Abuse screen[5]	X	X																			
Dosing																					
Randomization		X																			
Study drug[6] administration		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X				

Study Visits	**Screening**	**Treatment Period**																	**Follow-up Period**		
Week (W)	**W-4 to W0**	**Baseline**	**W1**	**W2**	**W3**	**W4**	**W5**	**W6**	**W7**	**W8**	**W9**	**W10**	**W11**	**W12**	**W13**	**W14**	**W15**	**W16**	**W18**	**W20**	**W24 (EOS)**
Day (D)	**D -28 to -1**	**D1**	**D8**	**D15**	**D22**	**D29**	**D36**	**D43**	**D50**	**D57**	**D64**	**D71**	**D78**	**D85**	**D92**	**D99**	**D106**	**D113**	**D127**	**D141**	**D169**
Study Procedures	Windows (D)	0	±1	±2	±2	±2	±2	±2	±2	±2	±2	±2	±2	±2	±2	±2	±2	±2	±2	±2	±2
Study drug accountability		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 sleep[7]	From the Screening Visit through EOS Visit (Week 24)																				
Pruritus VAS	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Sleep Loss VAS	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
5-D pruritus scale	X	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	X
PN-IGA	X	X		X		X		X		X		X		X		X		X	X	X	X
ItchyQoL	X	X		X		X		X		X				X				X			X
DLQI	X	X		X		X		X		X				X				X			X
HADS	X	X		X		X		X		X				X				X			X
PBI-P		X								X								X			
Medical photographs[8]	X	X				X				X				X				X			X
Skin biopsies[9]		X																X			
Blood PD samples		X		X		X				X				X				X		X	X

Study Visits	Screening	Treatment Period																	Follow-up Period		
Week (W)	**W-4 to W0**	**Baseline**	**W1**	**W2**	**W3**	**W4**	**W5**	**W6**	**W7**	**W8**	**W9**	**W10**	**W11**	**W12**	**W13**	**W14**	**W15**	**W16**	**W18**	**W20**	**W24 (EOS)**
Day (D)	**D -28 to -1**	**D1**	**D8**	**D15**	**D22**	**D29**	**D36**	**D43**	**D50**	**D57**	**D64**	**D71**	**D78**	**D85**	**D92**	**D99**	**D106**	**D113**	**D127**	**D141**	**D169**
Study Procedures	Windows (D)	0	±1	±2	±2	±2	±2	±2	±2	±2	±2	±2	±2	±2	±2	±2	±2	±2	±2	±2	±2
Pharmacogenomics		X																			
PK and Immunogenicity evaluation																					
PK samples[10]		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
ADA samples		X		X		X				X								X			X

ADA= anti-drug antibodies; DLQI=Dermatology Life Quality Index; ECG=electrocardiogram; HADS= Hospital Anxiety and Depression Scale; HBV=hepatitis B virus; HCV=hepatitis C virus; HIV=human immunodeficiency virus; WI-NRS=Worst itch numeric rating scale; PBI-P=Patient Benefit Index-Pruritus; PD=pharmacodynamic; PK=pharmacokinetics; PN-NAT=Prurigo nodularis Nodule Assessment Tool; PN-IGA=Prurigo Nodularis Investigator Global Assessment; ItchyQoL=Itchy Quality of Life; VAS=Visual Analog Scale. 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 and at the EOS Visit (Week 24), 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, an abbreviated physical examination will be performed consisting of cardiovascular, respiratory, and abdominal systems and as indicated based on subjects' symptoms. A physical examination 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 beta-human chorionic gonadotropin (βhCG) pregnancy test is performed at the Screening Visit. A urine βhCG test is performed at all later time points. A serum βhCG test is performed if urine βhCG test is positive.

[5]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.

[6] On dosing days, all blood samples (safety, PK, ADA, PG (optional), PD biomarkers, serum pregnancy if indicated), all urine samples (urinalysis, pregnancy, urine drug screen if indicated), all efficacy assessments (Pruritus VAS, Sleep Loss VAS, 5-D Pruritus, PN-NAT, IGA), all patient reported outcomes (DLQI, HADS, ItchyQoL, PBI-P), all medical photography, ECG and 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 at the study site for 3 hours after the loading dose and for 2 hours after the first 2 maintenance doses and for 1 hour after all subsequent doses. Vital signs will be measured every hour during the observation period and adverse events will be recorded if any. In case study drug treatment is interrupted or discontinued, subject continues with study visits as outlined in the Schedule of Activities minus dosing. In case of Early withdrawal, subjects will complete the EOS Visit.

[7] At the Screening Visit, subjects will be instructed to evaluate the intensity of their WI-NRS and the quality of their sleep (difficulty falling sleep NRS and sleep quality) on a daily basis during the Screening Period. The daily recordings can begin any time after the Screening Visit. Eligible subjects will continue daily recording of their pruritus and sleep NRS from Day 1 through the EOS Visit.

[8] At the Screening Visit, medical photographs will be taken of an area representative of subject's disease. 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 prurigo nodularis will be performed by review of medical photographs (Refer to Study Manual). At Day 1, whole body photographs and images of the same representative area and locations of biopsies (prior to biopsies) will be captured. Whole body photographs will be repeated at Week 16 and the EOS Visit (Week 24). Photographs of the same representative area will be taken at Week 4, 8, 12, 16 and 24. Location of biopsies will be photographed prior to biopsies at Week 16.

[9] A total of four skin biopsies will be collected during the study. Skin biopsies are optional. Two 4.5-mm skin biopsies (one from lesional skin and one from non-lesional skin) will be obtained prior to dosing at Day 1. Two 4.5-mm skin biopsies (one from lesional skin and one from non-lesional skin) will be obtained at Week 16. Lesional biopsies will be performed in the center of nodules. Post-treatment (Week 16) lesional biopsy will be obtained from a nodule in the same anatomical location as the pre-treatment lesional biopsy. If no nodules are present in the same anatomical location, the lesional biopsy will be taken from an area in the vicinity of the location of the pre-treatment lesional biopsy. In case study drug is discontinued, post-treatment biopsies will be performed at the earliest possible visit. In addition, in case of early termination that occurs prior to Week 8 and unscheduled drug discontinuation, biopsies should be collected at the EOS visit. Every effort will be made to obtain the non-lesional skin biopsy from an area of skin that is completely disease free, in the same anatomical location as the lesional biopsy and as far from diseased skin as possible.

[10] PK blood samples will be collected prior to study drug administration on dosing days during the Treatment Period. PK blood samples will also be collected at every visit during the follow-up period.

Table B Schedule of Activities for subjects in Phase 2a consented into Protocol Version 3

Study Visits	**Screening**	**Treatment Period**									**Follow-up Period**		
Week (W)	**W-4 to W0**	**Baseline**	**W1**	**W2**	**W3**	**W4**	**W5**	**W6**	**W7**	**W8**	**W10**	**W12**	**W16 (EOS)**
Day (D)	**D -28 to -1**	**D1**	**D8**	**D15**	**D22**	**D29**	**D36**	**D43**	**D50**	**D57**	**D71**	**D85**	**D113**
Study Procedures	Windows (D)	0	±1	±2	±2	±2	±2	±2	±2	±2	±2	±2	±2
Informed consent	X												
Demographics	X												
Medical and surgical history	X	X											
Prior medications, therapies, procedures	X	X											
Eligibility Assessment	X	X											
Safety Assessments													
Physical examination[1]	X	X		X		X		X		X		X	X
Vital signs[3]	X	X	X	X	X	X	X	X	X	X	X	X	X
Body weight, height, BMI[2]	X	X		X		X		X		X			X
ECG (12-lead)[3]	X	X								X			X

Study Visits	**Screening**	**Treatment Period**									**Follow-up Period**		
Week (W)	**W-4 to W0**	**Baseline**	**W1**	**W2**	**W3**	**W4**	**W5**	**W6**	**W7**	**W8**	**W10**	**W12**	**W16 (EOS)**
Day (D)	**D -28 to -1**	**D1**	**D8**	**D15**	**D22**	**D29**	**D36**	**D43**	**D50**	**D57**	**D71**	**D85**	**D113**
Study Procedures	Windows (D)	0	±1	±2	±2	±2	±2	±2	±2	±2	±2	±2	±2
Adverse events monitoring	From the Screening Visit through EOS Visit (Week 16)												
Concomitant meds/therapies/ procedures monitoring	From the Screening Visit through EOS Visit (Week 16)												
Compliance assessment	From the Screening Visit through EOS Visit (Week 16)												
Laboratory Tests													
Clinical laboratory blood tests	X	X		X		X		X		X			X
Urinalysis	X	X				X				X			X
Pregnancy test[4]	X	X								X			X
Serology (HIV, HBV, HCV)	X												
Urine Drug of Abuse screen[5]	X	X											
Dosing													
Randomization		X											
Study drug[6] administration		X	X	X	X	X	X	X	X				

Study Visits	**Screening**	**Treatment Period**									**Follow-up Period**		
Week (W)	**W-4 to W0**	**Baseline**	**W1**	**W2**	**W3**	**W4**	**W5**	**W6**	**W7**	**W8**	**W10**	**W12**	**W16 (EOS)**
Day (D)	**D -28 to -1**	**D1**	**D8**	**D15**	**D22**	**D29**	**D36**	**D43**	**D50**	**D57**	**D71**	**D85**	**D113**
Study Procedures	Windows (D)	0	±1	±2	±2	±2	±2	±2	±2	±2	±2	±2	±2
Study drug accountability		X	X	X	X	X	X	X	X				
Efficacy and PD measures													
Daily NRS Tool for assessment of pruritus and sleep[7]	From the Screening Visit through EOS Visit (Week 16)												
Pruritus VAS	X	X	X	X	X	X	X	X	X	X	X	X	X
Sleep Loss VAS	X	X	X	X	X	X	X	X	X	X	X	X	X
5-D pruritus scale	X	X		X		X		X		X	X	X	X
PN-NAT	X	X		X		X		X		X	X	X	X
PN-IGA	X	X		X		X		X		X	X	X	X
ItchyQoL	X	X		X		X		X		X			X
DLQI	X	X		X		X		X		X			X
HADS	X	X		X		X		X		X			X
PBI-P		X								X			
Medical photographs[8]	X	X				X				X			X
Skin biopsies[9]		X								X			
Blood PD samples		X		X		X				X		X	X

Study Visits	Screening	Treatment Period									Follow-up Period		
Week (W)	**W-4 to W0**	**Baseline**	**W1**	**W2**	**W3**	**W4**	**W5**	**W6**	**W7**	**W8**	**W10**	**W12**	**W16 (EOS)**
Day (D)	**D -28 to -1**	**D1**	**D8**	**D15**	**D22**	**D29**	**D36**	**D43**	**D50**	**D57**	**D71**	**D85**	**D113**
Study Procedures	Windows (D)	0	±1	±2	±2	±2	±2	±2	±2	±2	±2	±2	±2
Pharmacogenomics		X											
PK and Immunogenicity evaluation													
PK samples[10]		X	X	X	X	X	X	X	X	X	X	X	X
ADA samples		X		X		X				X			X

ADA= anti-drug antibodies; DLQI=Dermatology Life Quality Index; ECG=electrocardiogram; HADS= Hospital Anxiety and Depression Scale; HBV=hepatitis B virus; HCV=hepatitis C virus; HIV=human immunodeficiency virus; WI-NRS=Worst itch numeric rating scale; PBI-P=Patient Benefit Index-Pruritus; PD=pharmacodynamic; PK=pharmacokinetics; PN-NAT=Prurigo nodularis Nodule Assessment Tool; PN-IGA=Prurigo Nodularis Investigator Global Assessment; ItchyQoL=Itchy Quality of Life; VAS=Visual Analog Scale. 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 and at the EOS Visit (Week 16), 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, an abbreviated physical examination will be performed consisting of cardiovascular, respiratory, and abdominal systems and as indicated based on subjects' symptoms. A physical examination 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 beta-human chorionic gonadotropin (βhCG) pregnancy test is performed at the Screening Visit. A urine βhCG test is performed at all later time points. A serum βhCG test is performed if urine βhCG test is positive.

[5]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.

[6] On dosing days, all blood samples (safety, PK, ADA, PG (optional), PD biomarkers, serum pregnancy if indicated), all urine samples (urinalysis, pregnancy, urine drug screen if indicated), all efficacy assessments (Pruritus VAS, Sleep Loss VAS, 5-D Pruritus, PN-NAT, IGA), all patient reported outcomes (DLQI, HADS, ItchyQoL, PBI-P), all medical photography, ECG and 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 at the study site for 3 hours after the loading dose and for 2 hours after the first 2 maintenance doses and for 1 hour after all subsequent doses. Vital signs will be measured every hour during the observation period and adverse events will be recorded if any. In case study drug treatment is interrupted or discontinued, subject continues with study visits as outlined in the Schedule of Activities minus dosing. In case of Early withdrawal, subjects will complete the EOS Visit.

[7] At the Screening Visit, subjects will be instructed to evaluate the intensity of their WI-NRS and the quality of their sleep (difficulty falling sleep NRS and sleep quality) on a daily basis during the Screening Period. The daily recordings can begin any time after the Screening Visit. Eligible subjects will continue daily recording of their pruritus and sleep NRS from Day 1 through the EOS Visit.

[8] At the Screening Visit, medical photographs will be taken of an area representative of subject's disease. 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 prurigo nodularis will be performed by review of medical photographs (Refer to Study Manual). At Day 1, whole body photographs and images of the same representative area and locations of biopsies (prior to biopsies) will be captured. Whole body photographs will be repeated at Week 8 and the EOS Visit (Week 16). Photographs of the same representative area will be taken at Week 4, Week 8 and 16,. Location of biopsies will be photographed prior to biopsies at Week 8.

[9] A total of four skin biopsies will be collected during the study. Skin biopsies are optional. Two 4.5-mm skin biopsies (one from lesional skin and one from non-lesional skin) will be obtained prior to dosing at Day 1. Two 4.5-mm skin biopsies (one from lesional skin and one from non-lesional skin) will be obtained at Week 8. Lesional biopsies will be performed in the center of nodules. Post-treatment (Week 8) lesional biopsy will be obtained from a nodule in the same anatomical location as the pre-treatment lesional biopsy. If no nodules are present in the same anatomical location, the lesional biopsy will be taken from an area in the vicinity of the location of the pre-treatment lesional biopsy. In case study drug is discontinued, post-treatment biopsies will be performed at the earliest possible visit. In addition, in case of early termination that occurs prior to Week 8 and unscheduled drug discontinuation, biopsies should be collected at the EOS visit. Every effort will be made to obtain the non-lesional skin biopsy from an area of skin that is completely disease free, in the same anatomical location as the lesional biopsy and as far from diseased skin as possible.

[10] PK blood samples will be collected prior to study drug administration on dosing days during the Treatment Period. PK blood samples will also be collected at every visit during the follow-up period.

Table C Schedule of Activities for Phase 2b

Study Visits	Screening	Treatment Period									Follow-up Period		
Week (W)	**W-4 to W0**	**Baseline**	**W2**	**W4**	**W6**	**W8**	**W10**	**W12**	**W14**	**W16**	**W18**	**W20**	**W24 (EOS)**
Day (D)	**D -28 to -1**	**D1**	**D15**	**D29**	**D43**	**D57**	**D71**	**D85**	**D99**	**D113**	**D127**	**D141**	**D169**
Study Procedures	Windows (D)	0	±2	±2	±2	±2	±2	±2	±2	±2	±2	±2	±2
Informed consent	X												
Demographics	X												
Medical and surgical history	X	X											
Prior medications, therapies, procedures	X	X											
Eligibility Assessment	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	X
Body weight, height, BMI[2]	X	X	X	X	X	X	X	X	X	X			X
ECG (12-lead)[3]	X	X				X				X			X
Adverse event monitoring	From the Screening Visit through the EOS Visit (Week 24)												
Concomitant meds/therapies/ procedures	From the Screening Visit through the EOS Visit (Week 24)												
Compliance assessment	From the Screening Visit through the EOS Visit (Week 24)												
Laboratory Tests													

Study Visits	Screening	Treatment Period									Follow-up Period		
Week (W)	**W-4 to W0**	**Baseline**	**W2**	**W4**	**W6**	**W8**	**W10**	**W12**	**W14**	**W16**	**W18**	**W20**	**W24 (EOS)**
Day (D)	**D -28 to -1**	**D1**	**D15**	**D29**	**D43**	**D57**	**D71**	**D85**	**D99**	**D113**	**D127**	**D141**	**D169**
Study Procedures	Windows (D)	0	±2	±2	±2	±2	±2	±2	±2	±2	±2	±2	±2
Clinical laboratory blood tests	X	X	X	X	X	X		X		X			X
Urinalysis	X	X		X		X		X		X			X
Pregnancy test[4]	X	X				X				X			X
Serology (HIV, HBV, HCV)	X												
Urine Drug of Abuse screen[5]	X	X											
Dosing													
Randomization		X											
Study drug[6] administration		X	X	X	X	X	X	X	X				
Study drug accountability		X	X	X	X	X	X	X	X				
Efficacy and PD measures													
Daily NRS Tool for assessment of pruritus and sleep[7]	From the Screening Visit through the EOS Visit (Week 24)												
Pruritus VAS	X	X	X	X	X	X	X	X	X	X	X	X	X
Sleep Loss VAS	X	X	X	X	X	X	X	X	X	X	X	X	X
5-D pruritus scale	X	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	X
PN-IGA	X	X	X	X	X	X	X	X	X	X	X	X	X
ItchyQoL	X	X	X	X	X	X	X	X	X	X	X	X	X

Study Visits	Screening	Treatment Period									Follow-up Period		
Week (W)	**W-4 to W0**	**Baseline**	**W2**	**W4**	**W6**	**W8**	**W10**	**W12**	**W14**	**W16**	**W18**	**W20**	**W24 (EOS)**
Day (D)	**D -28 to -1**	**D1**	**D15**	**D29**	**D43**	**D57**	**D71**	**D85**	**D99**	**D113**	**D127**	**D141**	**D169**
Study Procedures	Windows (D)	0	±2	±2	±2	±2	±2	±2	±2	±2	±2	±2	±2
DLQI	X	X	X	X	X	X	X	X	X	X	X	X	X
HADS	X	X	X	X	X	X	X	X	X	X	X	X	X
PBI-P		X				X				X			
Medical photographs[8]	X	X		X		X		X		X			X
Skin biopsies[9]		X								X			
Blood PD samples		X	X	X		X		X		X		X	X
Pharmacogenomics		X											
PK and Immunogenicity evaluation													
PK samples[10]		X	X	X	X	X	X	X	X	X	X	X	X
ADA samples		X	X	X		X				X			X

ADA= anti-drug antibodies; DLQI=Dermatology Life Quality Index; ECG=electrocardiogram; HADS= Hospital Anxiety and Depression Scale; HBV=hepatitis B virus; HCV=hepatitis C virus; HIV=human immunodeficiency virus; WI-NRS=Worst itch numeric rating scale; PBI-P=Patient Benefit Index-Pruritus; PD=pharmacodynamic; PK=pharmacokinetics; PN-NAT=Prurigo nodularis Nodule Assessment Tool; PN-IGA=Prurigo Nodularis Investigator Global Assessment; ItchyQoL=Itchy Quality of Life; VAS=Visual Analog Scale. 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.

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[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 beta-human chorionic gonadotropin (βhCG) pregnancy test is performed at the Screening Visit. A urine βhCG test is performed at all later time points. A serum βhCG test is performed if urine βhCG test is positive.

[5]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.

[6] On dosing days, all blood samples (safety, PK, ADA, PG (optional), PD biomarkers, serum pregnancy if indicated), all urine samples (urinalysis, pregnancy, urine drug screen if indicated), all efficacy assessments (Pruritus VAS, Sleep Loss VAS, 5-D Pruritus, PN-NAT, IGA), all patient reported outcomes (DLQI, HADS, ItchyQoL, PBI-P), all medical photography, ECG and 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 at the study site for 3 hours after the loading dose and for 2 hours after the first 2 maintenance doses and for 1 hour after all subsequent doses. Vital signs will be measured every hour during the observation period and adverse events will be recorded if any. In case study drug treatment is interrupted or discontinued, subject continues with study visits as outlined in the Schedule of Activities minus dosing. In case of Early withdrawal, subjects will follow the schedule for the EOS Visit (Week 24).

[7] At the Screening Visit, subjects will be instructed to evaluate the intensity of their WI-NRS and the quality of their sleep (difficulty falling sleep NRS and sleep quality) on a daily basis during the Screening Period. The daily recordings can begin any time after the Screening Visit. Eligible subjects will continue daily recording of their pruritus and sleep NRS from Day 1 through the EOS Visit.

[8] At the Screening Visit, medical photographs will be taken of an area representative of subject's disease. 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 prurigo nodularis will be performed by review of medical photographs (Refer to Study Manual). At Day 1, whole body photographs and images of the same representative area and locations of biopsies (prior to biopsies) will be captured. Whole body photographs will be repeated at Week 16 and the EOS Visit (Week 24). Photographs of the same representative area will be taken at Week 4, 8, 12, 16 and 24. Location of biopsies will be photographed prior to biopsies at Week 16.

[9] A total of four skin biopsies will be collected during the study. Skin biopsies are optional. Two 4.5-mm skin biopsies (one from lesional skin and one from non-lesional skin) will be obtained prior to dosing at Day 1. Two 4.5-mm skin biopsies (one from lesional skin and one from non-lesional skin) will be obtained at Week 16. Lesional biopsies will be performed in the center of nodules. Post-treatment (Week 16) lesional biopsy will be obtained from a nodule in the same anatomical location as the pre-treatment lesional biopsy. If no nodules are present in the same anatomical location, the lesional biopsy will be taken from an area in the vicinity of the location of the pre-treatment lesional biopsy. In case study drug is discontinued, post-treatment biopsies will be performed at the earliest possible visit. In addition, in case of early termination that occurs prior to Week 8 and unscheduled drug discontinuation, biopsies should be collected at the EOS visit. Every effort will be made to obtain the non-lesional skin biopsy from an area of skin that is completely disease free, in the same anatomical location as the lesional biopsy and as far from diseased skin as possible.

[10] PK blood samples will be collected prior to study drug administration on dosing days during the Treatment Period. PK blood samples will also be collected at every visit during the follow-up period.

14.2 Appendix 2: Clinical Laboratory Tests

Clinical chemistry:	**Hematology:**	**Urinalysis:**
Alanine aminotransferase	Hematocrit	Bilirubin
Albumin	Hemoglobin	Blood
Alkaline phosphatase	Mean corpuscular hemoglobin	Color and appearance
Aspartate aminotransferase	Mean corpuscular hemoglobin concentration	Glucose
Blood urea nitrogen	Mean cell volume	Ketones
Calcium	Platelet count	Leukocyte esterase
Carbon dioxide	Red blood cell (RBC) count	Nitrite
Chloride	RBC distribution width	pH
Cholesterol	White blood cell (WBC) count	Protein
Creatinine	WBC differential (total and percentage):	Specific gravity
Gamma-glutamyl transferase	Basophils	Urobilinogen
Glucose	Eosinophils	Microscopic examination (for cells, cellular debris, crystals and bacteria, completed only if abnormal findings upon macroscopic examination)
High-density lipoprotein	Lymphocytes	
Lactate dehydrogenase	Monocytes	
Low-density lipoprotein	Neutrophils	
Potassium	Prothrombin time	
Sodium	Partial thromboplastin time	
Total bilirubin	International normalized ratio	
Total protein	Fibrinogen	
Triglycerides	D-dimer (if abnormal fibrinogen levels)	
Uric acid		
Serology[a]:	**Drug screen[b]:**	**Other:**
Hepatitis B surface antigen	Including but not limited to:	Serum βhCG test[c]
Hepatitis B core antibody	Amphetamines/methamphetamines	Urine βhCG test[c]
Hepatitis B surface antibody	Cocaine (metabolite)	FSH
Hepatitis C virus antibody	Methadone	Total IgE
Human immunodeficiency antibodies (type 1 and 2)	Phencyclidine	
	Opiates	
	Opioids	

[a] Analyzed only at the Screening Visit

[b] Analyzed only at the Screening Visit and Day 1; may be analyzed at later timepoints at the discretion of the Investigator.

[c] A serum beta-human chorionic gonadotropin (βhCG) pregnancy test is performed at the Screening Visit for all females of childbearing potential. A urine βhCG test is performed at all later time points. A serum βhCG test is performed if urine βhCG test is positive.

14.3 Appendix 3: Total Blood Volume

Phase 2a, subjects consented into Protocol Version 2: The following approximate blood volumes will be obtained from each subject.

	Volume per blood sample (ml)	Maximum number of blood samples	Approximate total amount of blood (ml)
Safety laboratory tests	15	9	135
Pregnancy test[a]	3	5	15
Serology	10	1	10
Pharmacokinetics	3	20	60
Pharmacodynamics	4	7	28
Pharmacogenomics	5	1	5
Immunogenicity	5	6	30
Total:		49	283

[a] Females only

Phase 2a, subjects consented into Protocol Version 3: The following approximate blood volumes will be obtained from each subject.

	Volume per blood sample (ml)	Maximum number of blood samples	Approximate total amount of blood (ml)
Safety laboratory tests	15	7	105
Pregnancy test[a]	3	5	15
Serology	10	1	10
Pharmacokinetics	3	12	36
Pharmacodynamics	4	6	24
Pharmacogenomics	5	1	5
Immunogenicity	5	5	25
Total:		49	220

[a] Females only

Phase 2b: The following approximate blood volumes will be obtained from each subject.

	Volume per blood sample (ml)	**Maximum number of blood samples**	**Approximate total amount of blood (ml)**
Safety laboratory tests	15	9	135
Pregnancy test[a]	3	5	15
Serology	10	1	10
Pharmacokinetics	3	12	36
Pharmacodynamics	4	7	28
Pharmacogenomics	5	1	5
Immunogenicity	5	6	30
Total:		41	259

14.4 Appendix 4: Daily NRS tool

Daily Assessment of Itch and Sleep in Prurigo Nodularis

Instructions: Please select the box that best describes your experience with prurigo nodularis ***over the past 24 hours.***

1. Over the **past 24 hours,** how would you rate your **most severe itch**?	0 ☐ **No itch**	1 ☐	2 ☐	3 ☐	4 ☐	5 ☐	6 ☐	7 ☐	8 ☐	9 ☐	10 ☐ **Worst imaginable itch**
Instructions: The next two questions are about your sleep ***last night*****.**											
2. How **difficult was it to fall asleep last night** due to itch?	0 ☐ **Not difficult at all**	1 ☐	2 ☐	3 ☐	4 ☐	5 ☐	6 ☐	7 ☐	8 ☐	9 ☐	10 ☐ **Extremely difficult**
3. Please describe your sleep quality last night.	0 ☐ **Best possible sleep**	1 ☐	2 ☐	3 ☐	4 ☐	5 ☐	6 ☐	7 ☐	8 ☐	9 ☐	10 ☐ **Worst possible sleep**

14.5 Appendix 5: Novel Disease Scoring Tools

Prurigo Nodularis Nodule Assessment Tool (PN-NAT)	
Instructions: The purpose of this tool is to 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.**	
Estimate of the Number of Nodules Over the Whole Body	
Score	
0	0 nodules
1	1 to 9 nodules
2	10 to 50 nodules
3	More than 50 nodules
Estimate of Hardness of Nodules Over the Whole Body	
Score	
0	No nodules are hard
1	Up to one-third of nodules are hard
2	One-third to two-thirds of nodules are hard
3	More than two-thirds of nodules are hard
Estimate of Extent of Excoriations Over the Whole Body	
Score	
0	No nodules are excoriated
1	Up to one-third of nodules are excoriated
2	One-third to two-thirds of nodules are excoriated
3	More than two-thirds of nodules are excoriated
Distribution of Nodules	
Select all body parts with nodules	Upper arm • right • left Lower arm including hand • right • left Upper leg • right • left Lower leg including foot • right • left Trunk including neck, groin and buttocks • front • back
Number of body parts with nodules	☐

Exact Nodule Count In Representative Area	
Select the Representative Area	Upper arm • right • left Lower arm including hand • right • left Upper leg • right • left Lower leg including foot • right • left Trunk including neck, groin and buttocks • front • back
Exact number of nodules in representative area	
Total Score:	

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

Instructions: The purpose of this tool is to guide the physician's global assessment of a patient's prurigo nodularis based on the: (a) presence/absence of nodules, and (b) 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 the score that best describes the patient's prurigo nodularis **right now.**

Score	Grade	Morphological Descriptor
0	Clear	No nodules
1	Almost Clear	Nodules are present, few of these nodules are moderately raised
2	Mild	Nodules are present, many of these nodules are moderately raised
3	Moderate	Nodules are present, most of these nodules are moderately raised
4	Severe	Nodules are present, most of these nodules are prominently raised