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Kiniksa Pharmaceuticals, Ltd.

STATISTICAL ANALYSIS PLAN (SAP)

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

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LISTING OF ABBREVIATIONS

Abbreviation	Full Form
ADA	Anti-drug antibodies (anti-KPL-716 antibodies)
AE	Adverse event
ANCOVA	Analysis of covariance
ATC	Anatomical Therapeutic Chemical
BMI	Body mass index
CI	Confidence interval
CMH	Cochran-Mantel-Haenszel
CSR	Clinical study report
DLQI	Dermatology Life Quality Index
DBL	Database lock
ECG	Electrocardiogram
eCRF	Electronic case report form
EDC	Electronic data capture
EOT	End of treatment
EOS	End of study
ET	Early Termination
HR	Heart rate
ICH	International Conference on Harmonization
LOCF	Last observation carried forward
LS	Least squares
MedDRA	Medical Dictionary for Regulatory Activities
MI	Multiple Imputation
mITT	Modified intent-to-treat
MMRM	Mixed model for repeated measures
PBI-P	Patient Benefit Index-Pruritus
PNQ	Patient Needs Questionnaire
PBQ	Patient Benefit Questionnaire
PD	Pharmacodynamic(s)
PK	Pharmacokinetic(s)

Abbreviation	Full Form
PN	Prurigo Nodularis
PN-NAT	Prurigo Nodularis Nodule Assessment Tool
PN-IGA	Prurigo Nodularis Investigator Global Assessment
PP	Per protocol
PT	Preferred term
QoL	Quality of life
QT	Electrocardiographic interval from the beginning of the QRS complex to the end of the T wave
QTcB	QT interval corrected for heart rate using Bazett's method
QTcF	QT interval corrected for heart rate using Fridericia's method
SAE	serious adverse experience/event
SAP	Statistical Analysis Plan
SD	Standard deviation
SE	Standard error
SOC	System organ class
TEAE	Treatment-emergent adverse event
TCS	Topical corticosteroid
VAS	Visual Analog Scale
WHO	World Health Organization
WHODRUG	World Health Organization Drug Dictionary
WI-NRS	Worst Itch Numeric Rating Scale

1. INTRODUCTION

This Statistical Analysis Plan (SAP) contains a detailed description of data presentations, statistical analysis methods, and data reporting specifications for the programming outputs and preparation of the Clinical Study Report (CSR) for the Phase 2a study KPL-716-C201. The SAP addendum will be prepared for study Phase 2b separately.

The SAP is prepared based on the protocol KPL-716-C201 (IND: 132912) Version 3 dated May 13, 2019.

2. STUDY OBJECTIVES AND ENDPOINTS

2.1. Study Objectives

2.1.1. Primary objective(s)

- 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

2.1.2. Secondary objective(s)

- 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

2.1.3. Exploratory objective(s)

- 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

2.2. Study Endpoints

2.2.1. Primary endpoints

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

2.2.2. Key Secondary 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

2.2.3. Other Secondary 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

2.2.4. Exploratory endpoints

- Measurement of KPL-716 therapeutic benefit (Subject 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 pharmacogenomics characteristics with KPL-716 responsiveness

2.2.5. Safety Parameters

- Incidence rate and severity of treatment-emergent adverse events (TEAEs)
- Incidence rate and severity of study drug-related TEAEs
- Clinical laboratory tests, vital signs, and electrocardiogram (ECG) results

2.2.6. Other Parameters

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

3. OVERALL STUDY DESIGN

This is a Phase 2a 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.

Phase 2a three periods:

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

- Screening Period: Minimum 14 days and maximum 28 days (Day -28 to Day -1)
- 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 weeks treatment period schedule:

- Screening Period: Minimum 14 days and maximum 28 days (Day -28 to Day -1)
- Treatment Period; Day 1 [Baseline] to Week 8
- Follow-up Period: Week 8 to Week 16

Phase 2a treatment groups:

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

Randomization:

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. Subjects will remain in the same treatment arm throughout the treatment period. Stratification will be performed based on sex and presence of atopy at baseline.

Efficacy Assessments:

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. Schedules of these efficacy assessments are specified in Appendix 1.

- WI-NRS score: 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 from 14 days prior to dosing through EOS Visit. The WI-NRS questionnaire is provided in Appendix 2: Daily NRS Tool.
- Sleep quality NRS: 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. The sleep quality NRS is provided in Appendix 2: Daily NRS Tool.
- The difficulty falling asleep NRS is provided in the Daily NRS Tool Appendix 2. 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 not difficult at all and 10 indicating extremely difficult. Difficulty falling asleep NRS is provided in Appendix 2: Daily NRS Tool.
- 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 indicating the worst imaginable pruritus. Pruritus VAS scale is provided in Appendix 3: 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. The scale of Sleep Loss VAS can be found in Appendix 3. Visual Analog 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) (S. Elman, etc. 2010). The 5-D Pruritus Scale is administered every two (2) visits. The score of each of the 5 domains is obtained separately and summed together to get the total 5D-pruritus score. The total 5D-pruritus score can range from 0 (no pruritus) to 25 (most severe pruritus).

- For duration, degree and direction, use the number indicated below the response choice in the questionnaire.
- For disability, take the highest score for any of the 4 items (sleep, leisure/social, housework/errands, work/school).
- For distribution, use the following scale:
  - 0-2 areas affected: score 1
  - 3-5 areas affected: score 2
  - 6-10 areas affected: score 3
  - 11-13 areas affected: score 4
  - 14 to 16 areas affected: score 5

5-D Pruritus Scale is specified in Appendix 4.

- DLQI: It is a 10-question questionnaire that considers symptoms and feelings, daily activities, leisure, school, personal relationships, and treatment. Each question except question 7 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), taking into account the previous week. For question 7: Over the last week, has your skin prevented you from working or studying? If answered yes, score=3; If no, a second question will be asked: over the last week how much has your skin been a problem at work or studying? If further answered a lot, score=2; if a little, score=1; if not at all or not relevant, score=0. The DLQI total score is defined as the sum of all 10-quesion scores with minimum of 0 meaning no effect on quality of life and 30 meaning extremely large effect. DLQI questionnaire is provided in Appendix 5.
- ItchyQoL: The 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. The ItchyQoL total score is defined as the sum of all 22-items scores. The ItchyQoL-symptom subscale score is calculated as the sum of question 1-6. The ItchyQoL-functional subscale score is calculated as the sum of question 7-13. The ItchyQoL-emotional subscale score is calculated as the sum of question 14-22. If there is only 1 item skipped in a subscale, the missing item value in the subscale will be calculated as the average of other non-missing item values. If 2 or more items are skipped in any given subscale, the subscale and total scores are set to missing. For other subscales that have less than 2 items skipped, those subscale scores need to be calculated. Total scores can be classified as little (0-30), mild (31-50), moderate (51-80), severe (81-110). ItchyQoL questionnaire is provided in Appendix 6.
- PN-NAT: This 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. Given its exploratory feature, first three components (number of nodules over the whole body, estimate of hardness of nodules over the whole body, estimate of extent of excoriations over the whole body) possess the main interest while distribution of nodules, exact number of nodules in the representative will be exploratory. The formula for the cumulative score will be generated post-hoc and no analysis is planned for total score. Subjects 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. The PN-NAT is provided in Appendix 7.

- 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. It utilizes a 5-point scale that ranges from 0 (clear) to 4 (severe disease). Patients may present with smaller popular 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. The PN-IGA is provided in Appendix 8.
- HADS: It is a general Likert scale used to detect states of anxiety and depression. 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. The HADS total score is defined as the sum of all 14-items scores. The HADS-anxiety subscale score is calculated as the sum of 7-items scores related to anxiety. The HADS-depression subscale score is calculated as the sum of 7-items scores related to depression. HADS questionnaire can be found in Appendix 9.
- PBI-P: Patient Benefit Index-Pruritus. PBI-P includes 2 questionnaires: Patient Needs Questionnaire (PNQ) and Patient Benefit Questionnaire (PBQ). 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). 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). PBI-P will be administered at designated visits. PBI-P questionnaire is provided in Appendix 10.

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 up 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 KPL716 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.

5. STUDY ANALYSIS SETS

The following analysis sets will be defined for Phase 2a.

5.1. Randomized Subjects

Randomized subjects will include all subjects whose date of randomization is not missing. Screen failures will not be included in this population.

5.2. Modified Intent-to-Treat (mITT) Analysis Set

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. All mITT analyses will be based on each subject's randomized treatment assignment.

5.3. Per Protocol (PP) Analysis Set

The PP analysis set includes all mITT subjects who have no important protocol deviations that may potentially bias efficacy analyses of the study. These deviations will be pre-specified prior to study unblinding/database lock.

5.4. Safety Analysis Set

All randomized subjects who received any 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.

5.5. PK Analysis Set

The PK analysis set includes any subjects who received KPL-716 and who had at least one PK sample.

5.6. Study Cohort

Since treatment durations are different per the protocol V2 (Week 16 of treatment) and V3 (Week of treatment), study cohorts of 8 Weeks and 16 Weeks subjects are defined as the following.

- Cohort 16 Weeks includes subjects who consented to protocol V2.
- Cohort 8 Weeks includes subjects who consented to protocol V3.

All descriptive summaries of efficacy and safety endpoints will be performed by the study cohort and combined subjects.

6. GENERAL ASPECTS FOR STATISTICAL ANALYSIS

6.1. General Methods

- All analyses and summaries will be produced using SAS® version 9.4 (or higher).
- For inferential statistical analyses, arms of KPL-716 and placebo within each cohort (8 weeks, 16 weeks, and combined) will be compared respectively. Unless otherwise specified, all tests will be two-tailed using pre-specified levels of significance.
- Descriptive statistics (n, mean, standard deviation (SD), median, minimum, and maximum) will be presented for continuous variables. For continuous efficacy endpoints, standard error (SE) will be provided as well. Where specified, 80 and 95% Confidence Interval (CI) of the mean will be calculated.
- For categorical variables (including binary variables), counts and percentages will be presented. Where specified, 80% and 95% 2-sided CI for proportions and the odds ratio will be calculated with Cochran-Mantel-Haenszel (CMH) Test.
- Subject listings in all randomized subjects, except the listing for screen failures, will be provided for all efficacy and safety data. In general, the subject listings will be sorted by treatment group, subject number and assessment date (and time, if applicable).
- In general, months will be defined as 30.4375 days (365.25 days/12 months).

6.2. Baseline Value and Change from Baseline

In general, baseline is defined as the last non-missing value obtained immediately prior to the first SC injection otherwise specified.

For daily collected efficacy endpoints (WI-NRS, difficulty falling asleep NRS, sleep quality NRS), baseline is calculated as weekly average of non-missing scores from 7 days prior to Day 1 to Day 1, the day when the first SC injection is administered. For those daily collected efficacy endpoints, weekly average will be calculated based on every 7 days starting on the day after the start of injection (Day 1). Change and percent change from baseline in weekly averages will be summarized and compared between KPL-716 and placebo.

6.3. Study Day

Study day is defined as the number of days from the first date of treatment to the event/visit date. It is calculated as follows:

- If the event date falls on the date of treatment, or after the date of treatment,

  Study Day = Event or Visit Date – 1st SC injection Date + 1

- If the event date falls before the date of 1st SC injection,

  Study Day = Event or Visit Date – 1st SC injection Date

6.4. Analysis Visits

All data will be organized and analyzed according to the scheduled times as outlined in the protocol and by the visit denoted on the electronic case report form (eCRF), except for unscheduled and early termination (ET) visits during the treatment period. For unscheduled and early termination visits, analysis visits will be assigned to closest planned visits per protocol. The visit will be assigned to the later CRF collected visit if equally close to two scheduled visits. For multiple records on the same visit, CRF collected records will be used for the analysis. Summary by analysis visits will not include unscheduled analysis visits (after reassignment). However, unscheduled analysis visits will be included to define baseline, worst post baseline, or minimum, maximum post baseline and listings.

6.5. Time on study

Time on study will be defined as time from randomization date to the end of study. For ongoing subjects, cutoff dates will be used.

6.6. Missing Data Handling

No imputations will be performed for missing data for safety endpoints, unless otherwise specified. Missing data handling for efficacy endpoints are specified in Section 9.

7. STUDY SUBJECTS

7.1. Subject Disposition

The subject disposition will be summarized by treatment and overall. All information will be presented in numbers and percentages in a summary table. The following information will be presented in subject disposition table:

- Screened subjects
- Randomized subjects
- Safety analysis set
- mITT analysis set
- Subjects who completed study phase 2a
- Subjects discontinued treatment and the primary reasons for Treatment discontinuation
- Subjects discontinued study and the primary reasons for Study discontinuation

7.2. Protocol Deviations

A protocol deviation can be defined as any deviation from the study protocol that does not materially affect the safety of the subjects and/or the conduct of the study and/or its evaluation.

Important protocol deviations will be based upon the eCRF database and determined for all subjects by either medical review processes or programming based on the inclusion/exclusion criteria or other criteria presented in the protocol.

Current ICH GCP guidelines list the important protocol deviations that must be listed in the clinical report. Important protocol deviations are a subset of protocol deviations that may significantly impact the completeness, accuracy, and/or reliability of key study data or that may significantly affect a subject's rights, safety, or well-being. These may include, but are not limited to:

- Subjects that are dosed on the study despite not satisfying the inclusion criteria;
- Subjects that develop withdrawal criteria whilst on the study but are not withdrawn;
- Subjects that receive the wrong treatment or an incorrect dose;
- Subjects that receive an excluded concomitant medication.

A summary table will be provided as the number (%) of subjects with at least one important protocol deviation and the number (%) of subjects in each category.

8. DEMOGRAPHICS AND BASELINE CHARACTERISTICS

The demographics and baseline characteristics data will be summarized for the mITT, and safety populations. Descriptive statistics will be provided for continual variables. Numbers and percentages of subjects will be tabulated for categorical variables.

8.1. Demographics

The following demographic variables will be summarized:

Age (years), calculated as the number of years between the date of birth and the date of signing the Informed Consent form.

- Age (years)
- Sex (Male or Female)
- Childbearing potential status (Of childbearing potential, Postmenopausal, Surgically sterile)
- Race (White, Black or African American, Asian, American Indian or Alaska Native, Native Hawaiian or Other Pacific Islander, Other)
- Ethnicity (Hispanic or Latino, Not Hispanic or Latino, Not reported, Unknown)
- Height (cm)
- Weight (kg)
- BMI (kg/m^2) = $Weight(kg)/Height(m)^2$

8.2. Screening and Baseline Disease Characteristics

The following baseline characteristics will be summarized.

- Presence of Atopy (Yes, No)
- Elevated IgE (Yes: IgE >200 IU/mL, No: IgE ≤200 IU/mL)

- Historical allergy (Yes, No):
  - Historical Asthma (Yes, No)
  - Historical Atopic Dermatitis (Yes, No)
  - Historical Allergic Rhinitis (Yes, No)
  - Historical Allergic Conjunctivitis (Yes, No)
  - Other Historical allergies (food, drug, bee sting, environmental, etc.) (Yes, No)
- Years since first PN nodules (calculated relative to first dose date)
- Years since diagnosis (calculated relative to first dose date)
- Co-morbidities includes history of atopy, anxiety or depression , allergy, dermatologic conditions other than AD, lipid disorders, hypertension, type 2 diabetes.
- Screening visits and baseline efficacy endpoints

8.3. Medical History

The medical history is coded using Medical Dictionary for Regulatory Activities (MedDRA version 21.1). The summary of medical history will be presented with number (%) by System Organ Class (SOC) and Preferred Term (PT). Each subject will be counted only once for each preferred term within a SOC per cohort. Similarly, for determination of MedDRA SOC incidences, subjects who experience multiple medical conditions under the same SOC will be counted only once for that SOC.

8.4. Prior and Concomitant Medications

All medications will be coded using the World Health Organization (WHO) drug dictionary. The WHO drug dictionary version B3 September 2018.

Prior medications are defined as medications that started before the first dose of study drug. Concomitant medications are defined as medications that (1) started before the first dose of study drug and continued into the treatment period, or (2) started on or after the date of the first dose of study drug. The number (%) of subjects who took prior and concomitant medications will be summarized on the anatomical class (ATC level 3) and preferred term (PT) by treatment and overall subjects.

For analysis purpose, topical corticosteroids [TCS], oral antihistamines, and/or systemic corticosteroids, which were used on and after first dose date and have significant impact on efficacy interpretation, are defined as rescue medications. TCS which are deemed to have minimum impact on efficacy interpretation are not considered as rescue medications. For example, TCS used for injection site reaction are not considered as rescue medication. Identification of rescue medications will be based on medical review. Number and percentage of subjects who used rescue medications will be summarized. Time to 1st usage of any rescue medication, rescue TCS/systemic steroid, oral antihistamine will be tabulated as well. The amount used of TCS and oral antihistamine based on the drug accountability and usage days of rescue medications will be summarized descriptively.

Prior TCS regardless of indication, systemic steroid, and oral antihistamine will be summarized as well, of which identification will be based on medical review.

Prohibited medications include, but not limited to, calcineurin inhibitors, phosphodiesterase inhibitors, Jak inhibitors, any other immunosupressives and antihistamines used after first dose date, which are subject to medical review. Number and percentage of subjects who used prohibited medications will be summarized as well if any data available. Identification of prohibited medication will be based on medical review.

8.5. Prior and concomitant procedures

The procedures are coded using Medical Dictionary for Regulatory Activities (MedDRA version 21.1). The prior and concomitant procedures are defined similarly as the prior and concomitant medications. The summary of prior and concomitant procedures will be presented with number (%) by System Organ Class (SOC) and Preferred Term (PT). Each subject will be counted only once for each preferred term within a SOC. Similarly, for determination of MedDRA SOC incidences, subjects who experience multiple procedures under the same SOC will be counted only once for that SOC.

9. EFFICACY ANALYSES

All efficacy analyses will be performed in the mITT analysis set. The statistical analyses of the primary and key secondary endpoints will be repeated in PP analysis set. Analysis based on the mITT set will be the primary analysis and the analyses based on other analysis sets will be considered as the supportive analyses. Line plots of Mean (SE) in percent change from baseline overtime will be presented and bar charts for responder analyses will be provided as well if needed for selected endpoints.

To minimize confounding effect on the efficacy endpoints caused by rescue medications, efficacy assessments collected in the following intervals will be set to missing:

1. Systemic corticosteroids: from first date and afterward;
2. TCS except indication of injection site reaction from start date to end date plus 2 days if duration ≤2 days, plus 7 days if duration ≥3 days;
3. Oral antihistamine, from start date to end date plus 1 day.

9.1. Analyses of change and percent change endpoints

There are two types of analysis models planned for continuous endpoints: Mixed-effect Model Repeated Measures (MMRM) and Analysis of Covariance (ANCOVA). MMRM will include treatment, sex, atopy, baseline, week (1-8), and week-by-treatment interaction as fixed effect and subject as random effect based on unstructured covariance matrix and Kenward-Roger corrected degree of freedom. ANCOVA will include treatment as fix effect, randomization stratification factors of sex and atopy and corresponding baseline value as covariates. Least square (LS) mean and standard error (SE) with 80% and 95% CIs, and p-value for differences between-treatment comparisons of treatment with placebo are calculated.

Three sets of analyses are planned for continuous endpoints in terms of missing data handling. Analysis based on the last observation carried forward (LOCF) will be used as the primary analysis. Analyses based on the observed values and multiple imputation (MI) will be conducted as sensitivity analyses.

For analysis with LOCF, data assessments are set to missing if collected in rescue medication intervals specified above. Then all missing data including those due to early discontinuation will be imputed by LOCF method up to the end of the period with last non-missing CRF collected data or cutoff date whichever is first. For daily assessments, last non-missing daily value will be carried forward, and then weekly average will be calculated with 50% rule applied to the last week. If 50% or more data are missing for weekly average calculation, the week will be set to missing.

For the analysis based on the observed data, no imputation will be done for missing values. Weekly average will be derived based on the non-missing daily values. If 50% or more values are missing, weekly average will be set to missing. However, to minimize the missing baseline values, this rule will not be applicable to the derivation of baseline weekly average. MMRM models will be fitted for combined cohorts with data up to week 8 while ANCOVA model will be fit for 8 weeks and 16 weeks cohorts with all data. For combined cohorts, if MMRM models cannot be converged, ANCOVA models will be implemented.

For analysis based on multiple imputation, data will be set to missing if the assessments are collected in the intervals of rescue medication specified as above. Then all post baseline missing values up to week 8 will be imputed using multiple imputation (see below for details) method. For daily NRS, daily assessments will be set to missing if rescue medication used (see above) and weekly averages will be calculated using the 50% rule. Then missing values will be imputed using MI method. MMRM models will be fitted for combined cohorts while ANCOVA for 8 weeks and 16 weeks cohorts. For combined cohorts, if MMRM models cannot be converged, ANCOVA models will be implemented. LS mean and SE will be obtained using the SAS PROC MIANALYZE procedure.

Continuous endpoints with different analysis methods are listed in Table 1.

Multiple imputation

Intermediate missing and tail missing will be imputed with separate steps as below.

1. Fill in intermediate missing values by predicted mean match regression (RegPMM) under PROC MI FCS procedure, then only keep the imputed values for intermediate missing values by treatment arm and merge back to the original dataset. Variables in FCS include sex, atopy, baseline value, week 1-8 scores. 200 iterations will be run.
2. Define placebo completer as subjects who have non missing scores at week 8.
3. Impute all tail missing values sequentially by RegPMM under PROC MI FCS procedure by iterations, e.g. week 1 regressed on sex, atopy, baseline; week 2 on sex, atopy, baseline, week 1; week 3 on sex, atopy, baseline, week 1, week 2, and so on. For each regression, placebo completers will be included as model input.
4. Imputed data will be fitted with either MMRM or ANCOVA and results will be pooled with PROC MIANALYZE.

Programming details will be specified with ADaM specifications.

Table 1: Statistical Analyses for Change and Percent Change Endpoints

Change and percent change from baseline for Efficacy Endpoints	LOCF	As Observed	Multiple imputation
Primary endpoint: • in weekly average WI-NRS score at Week 8	X	X	X
Key secondary endpoint: • in pruritus VAS at Week 8	X	X	
Other secondary endpoints:			
Related to pruritus: • in weekly average of WI-NRS over time • in pruritus (VAS) over time • in 5-D Pruritus total score and subscales over time	X X X	X X X	
Related to sleep: • in sleep loss VAS over time • in weekly average of difficulty falling asleep NRS over time • in weekly average of sleep quality NRS over time	X X X	X X X	
Related to quality of life: • in DLQI total score over time • in HADS total score over time • Itchy QoL (total score, symptom subscale, functional subscale, emotional subscale) over time	X X X	X X X	
Related to disease severity: • in PN-NAT Estimate of the Number of Nodules Over the Whole Body over time • in PN-NAT Estimate of Hardness of Nodules Over the Whole Body over time • in PN-NAT Estimate of Extent of Excoriations Over the Whole Body over time • in Sub-total of Number of Nodules, Hardness of Nodules, and Extent of Excoriations Over the Whole Body over time • in PN-IGA score over time	X X X X X	X X X X X	

9.2. Responder analyses

For binary responder analyses, responders will be defined based on observed data and LOCF imputed data for missing values and rescue medications as described as continuous endpoints above. Subjects with baseline score < cutoff values should be excluded from the analysis for the corresponding endpoint.

For statistical inference, all these three sets of analyses will be analyzed with Cochran-Mantel-Haenszel (CMH) Test adjusted by the randomization stratification variables (sex and atopy).

Odds ratios, 80% and 95% CIs and p-value will be displayed for the comparison of treatment groups.

Endpoints with responder analysis are listed in Table 2.

Table 2: Statistical analyses for responders

Responder analysis endpoints	LOCF	As observed
Related to pruritus: • Weekly average WI-NRS with a ≥4-point reduction	X	X
Related to sleep: • Difficulty falling asleep NRS with a ≥4-point reduction • Sleep quality NRS with a ≥4-point reduction	X X	X X
Related to quality of life: • DLQI total score with a ≥4-point reduction	X	X
Related to disease severity: • PN-IGA with a ≥1-point reduction • PN-IGA with a ≥2-point reduction • Proportion of 0 or 1 PN-IGA score	 X X X	 X X X
Exploratory: • Proportions of subjects achieving a 4-<5, 5-<6, 6-<7, 7-<8, 8-<9, 9-10-point reduction in Weekly average WI-NRS from baseline over time	X (no CMH test)	X (no CMH test)

9.3. Shift table for selected efficacy endpoints

Shift from baseline to post baseline visits in the categories of ItchyQoL total scores (little, mild, moderate, severe) will be presented based on data with LOCF and as observed.

Below PN-NAT endpoints will be presented with shift from baseline to post baseline visits in the categories of scores (0, 1, 2, 3) with LOCF and as observed method:

- Estimate of the Number of Nodules Over the Whole Body
- Estimate of Hardness of Nodules Over the Whole Body
- Estimate of Extent of Excoriations Over the Whole Body

9.4. Exploratory Endpoints

The summary of the following exploratory endpoints will be provided as descriptive statistics by visit.

- Measurement of KPL-716 therapeutic benefit (Subject Benefit Index-Pruritus [PBI-P]) will be summarized as continuous variable at visits as planned in the protocol using as observed data.
- Correlation of co-morbidities with KPL-716 responsiveness will be analyzed as appropriated. See section 16 for subgroup analysis.
- Change from baseline in skin and blood PD biomarkers over time will be analyzed and reported separately.
- Correlation of pharmacogenomics (PG) characteristics with KPL-716 responsiveness will be analyzed and reported separately.
- Change and percent change from baseline in PN-NAT (novel tool for assessment of nodules in prurigo nodularis) overtime.
- Proportion of subjects with improvement in PN-IGA (a novel tool for assessment of disease severity in prurigo nodularis) by 2 categories over time.

10. MULTIPLICITY ADJUSTMENT

The type I error will be adjusted under a hierarchical procedure with the pre-specified testing order for primary and key secondary efficacy endpoints in the mITT analysis set rather than the PP analysis set. The multiplicity will not be adjusted for the sensitivity analyses.

The endpoints will be first tested starting with the primary endpoint. If the 2-sided p-value is <0.05 and the efficacy benefits to the treatment group, the study will be claimed positive, and the key secondary endpoints will be tested using the Hochberg procedure specified as the following:

To control the family-wise Type I error rate at 5%. The Hochberg procedure starts with the larger p-value and proceeds as follows:

1. If the larger p-value is ≤ 0.05 and the efficacy benefits the treatment group, then both key secondary endpoints will be positive; otherwise, the endpoint with the larger p-value is not positive and the procedure will continue with the smaller p-value.
2. If the smaller p-value is $\leq 0.05/2$ and the efficacy benefits the treatment group, then the key secondary endpoint with the smaller p-value is positive; otherwise, none of the key secondary efficacy endpoints is claimed positive.

No multiplicity adjustment will be performed for the other secondary efficacy endpoints.

11. SAFETY ANALYSES

Safety analyses will consist of data summaries for clinical and laboratory parameters, vital sign, and for adverse events (AEs). Adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA version 21.1). Laboratory parameters, vital signs, and ECG data will be summarized as descriptive statistics by treatment and visit.

11.1. Treatment Exposure and Compliance

Descriptive statistics will be provided for the following.

- Duration of treatment calculated as [min (last dose date+6, end of study date) – first dose date+1]/7.
- Number of doses received per subjects will be summarized as 1 dose, 2 doses, … 16 doses. The loading dose is comprised of two injections of maintenance dose.
- Treatment compliance is 100*total study drugs received (mg)/total planned doses (mg) on treatment. For early discontinued subjects, total planned doses on treatment will be counted from first dose date to last dose date.
- Number of dose interruptions (dose skipped) per subjects.
- Number of dose interruptions (dose skipped) per subjects due to AE.

All study drug exposure data will be listed including reasons for dose not administered.

11.2. Adverse Events

Adverse events will be mapped to preferred term (PT) and system organ class (SOC) using the most up to date Medical Dictionary (MedDRA) version 21.1. Treatment emergent AEs (TEAEs) are defined as all AEs started or after the first dose date. Furthermore, if an AE cannot be determined as treatment-emergent due to incomplete/missing data, conservatively, it will be considered as treatment emergent and included in the summary tables.

11.2.1. Adverse events

The following AE or TEAE summaries will be generated for the safety analysis set.

- Overview of AEs, summarizing number (%) of subjects with any:
  - Any AEs
  - Any TEAEs
  - Drug-related TEAEs
  - Serious TEAEs
  - Injection site reaction
  - Drug related serious TEAEs

  - TEAEs leading to dose interruption
  - Drug-related TEAEs leading to dose interruption
  - TEAEs leading to treatment discontinuation
  - Drug-related TEAEs leading to treatment discontinuation
  - TEAEs leading to study discontinuation
  - Drug-related TEAEs leading to study discontinuation
  - Death
- Summary of TEAEs by primary SOC, PT, and maximum severity (mild, moderate, or severe)
- Summary of TEAEs by SOC, PT, and drug-relationship (not related, unlikely related, possibly related, or related)
- Summary of drug related TEAEs by primary SOC, PT, maximum severity
- Summaries of TEAEs presented by PT
- Summary of injection site reaction by SOC, PT

11.2.2. Serious TEAEs

The following serious TEAEs summaries will be generated:

- Summary of serious TEAEs by primary SOC, PT
- Summary of drug related serious TEAE by SOC, PT

11.2.3. TEAEs leading to dose interruption

- Summary of TEAEs leading to dose interruption by SOC, PT
- Summary of drug related TEAEs leading to dose interruption by SOC, PT

11.2.4. TEAEs leading to treatment discontinuation

- Summary of TEAEs leading to treatment discontinuation by SOC, PT
- Summary of drug related TEAEs leading to treatment discontinuation by SOC, PT

11.2.5. TEAEs leading to study discontinuation

- Summary of TEAEs leading to study discontinuation by SOC, PT
- Summary of drug related TEAEs leading to study discontinuation by SOC, PT

11.2.6. Disease exacerbation

- Summary of subjects with disease exacerbation
- Summary of time to onset of disease exacerbation in days

- Summary of disease exacerbation by primary SOC, PT

11.3. Clinical Laboratory Tests

During the study period from screening to the end of treatment, clinical laboratory tests in Appendix 2 will be performed. The data collected in different units were converted in SI units (the International System of Units) for summary.

The following summaries will be provided by laboratory category of chemistry, hematology, and urinalysis, urine microscopy.

- Numeric laboratory values will be summarized as descriptive statistics for both actual value and change from baseline (post baseline minus baseline) by week. If lab values are recorded as <xx, the limits of xx will be used for summary. If lab values are recorded as TNTC (too many to count), correspondingly maximum values per confirmation by vendors will be used for summary.
- Categorical laboratory values will be summarized with frequency or shift tables.
- Shift table summarizing subject incidence of laboratory normal range (Low, Normal, High) at baseline contrasted with individual visits and minimum or maximum post baseline. For parameters with bidirectional abnormality (low and high) will be presented by post baseline minimum and maximum.
- Serology, Endocrinology and Drug Screening will be listed. For convenience, IgE will be summarized along with chemistry parameters.
- Vital signs (systolic and diastolic blood pressure, pulse, respiration, temperature) and weight will be summarized in descriptive manner by visit for both actual values and changes from baseline (post baseline minus baseline) for each visit. At any visit and timepoint, if the test is repeated, the average will be used for the analysis at this visit.
- All vital signs including weight, pulse rate, body temperature, respiration rate, and systolic and diastolic blood pressure, as well as weight will be summarized. Descriptive statistics will be presented for the observed value and the change from baseline by treatment and visit. For repeated assessments at a visit, the average of these values will be taken for the summary at the visit. Incidence of clinically relevant vital signs noted post-baseline will also be summarized by treatment and visit. Clinical relevance is based on the following criteria (Table 3).

Table 3: Criteria for Clinically Relevant Vital Signs Post-Baseline

Parameter	Clinically Relevant Criteria
Systolic Blood Pressure (mmHg)	• Hypertension: Any post-baseline value of 120-139, 140-159, ≥160 • Hypotension: Any post-baseline value ≤90 or post-baseline value ≥30 decrease from baseline
Diastolic Blood Pressure (mmHg)	• Hypertension: Any post-baseline value of 80-89, 90-99, ≥100 • Hypotension: Any post-baseline value ≤60 Pulse
Pulse Rate (bpm)	• Any post-baseline value >100 or ≥20 increase from baseline • Any post-baseline value <60 or post-baseline value ≥20 decrease from baseline
Respiratory Rate (breaths/min)	• Any post-baseline value >24 • Any post-baseline value <10
Body Temperature (°C)	• Any post-baseline value ≥38 • Any post-baseline value ≤36

11.4. Electrocardiograms

Numeric 12-lead ECG parameters will be summarized. Descriptive statistics will be presented for the observed value and the change from baseline at each scheduled visit. Incidence of a normal to abnormal shift for overall ECG interpretation will also be summarized at each scheduled visit and worst post baseline. Findings of other categorical parameters will be listed. For repeated assessment, if interpretations are the same, the last value will be taken for numerical assessment for summaries. If interpretations are different, the last value with the abnormal interpretation will be used for summary.

QT interval corrected for heart rate using Fridericia's method - Below incidence will be summarized:

- QTcF interval >450 msec in men
- QTcF interval >470 msec in women
- QTcF change from the baseline (pre-dose) is >60 msec

11.5. 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.

12. PHARMACOKINETIC (PK) ANALYSIS

The PK analysis plan and report will be done separately.

13. PD BIOMARKER ANALYSIS

The PD analysis plan and report will be done separately.

14. IMMUNOGENICITY ANALYSIS

Pre-dose anti-drug antibody (ADA) blood samples will be collected according to Appendix 1.

Analysis of ADA will be performed for KPL-716 group in the immunogenicity analysis set. The number and percentage of subjects with positive antibodies will be summarized by visit. All ADA data will be listed by subject to show if the result is positive or negative, and if positive, the titer will also be provided for active treatment group.

Endpoints below will be summarized by visits.

- Number and percentage of subjects with confirmed positive ADA;
- Titer for confirmed positive ADA;
- Number and percentage of subjects with positive neutralizing antibody for confirmed positive ADA;

Correlation between ADA and clinical efficacy may be explored based on prevalence of ADA.

15. PHARMACOGENOMIC AND GENE EXPRESSION ANALYSIS

The analysis plan and report will be done separately.

16. SUBGROUP ANALYSIS

The primary and key secondary efficacy endpoints may be summarized as descriptive statistics by subgroups in Table 4 in the mITT analysis set.

Table 4: Subgroups Defined at Baseline

Subgroup	Categories
Age group	<65 years, ≥65 years
Sex	Female, Male
Race	White, Non-white (American Indian or Alaska Native, Asian, Black or African American, Native Hawaiian or Other Pacific Islander, Other)
Atopy	Yes, No
Any of Anxiety or depression	Yes, No

17. 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 to

guide program decision-making. The interim analysis will be performed by an unblinded independent biostatistician; unblinded results and anonymized subject data will be communicated to selected sponsor members who are not involved with the conduct of the study. Investigators and subjects will remain blinded to the interim results until an appropriate time, as determined by sponsor.

If the interim analysis is conducted in the Phase 2a part, a two-sided alpha of 0.0001 will be spent. The two-sided alpha level for the final Phase 2a efficacy analysis will be 0.20.

18. GENERAL CONVENTIONS FOR OUTPUTS

18.1. Format Decimals

Means and medians will be reported to one decimal place more than the precision of the recorded data. Standard deviations will be reported to two decimal places more than the recorded data. Minimum and maximum values will be reported to the same number of decimal places displayed on the eCRF or by the laboratory/vendor. If too many decimals, adjustments may be applied per request. Percentages will be reported to one decimal place.

18.2. Missing/Partial Date Handlings

Imputation rules for the missing AE onset date:

For the partial date (missing day and/or month) of AE start date, the following imputation rules will be applied:

- If AE Start Date year is equal to the year of the first dose and the AE end date is not before (<) the first dose, then the day and month will be imputed with the day and month of the first study dose date. Note: Partial missing / missing AE End date is considered as 'not before/on first dose'. Otherwise, the month and day is imputed as the first day of the year (01 Jan).
- If only day is missing, and if the year and month are equal to the first dose date and AE end date is not before (<) the first dose, the AE start date will be imputed as the first dose date. Note: Partial missing / missing AE End date is considered as 'not before/on first dose'. Otherwise, the day will be imputed as "01".

Imputation rules for the missing Con-med (CM) or Medical History (MH) onset date:

For partially missing CM or MH dates (missing day and/or month), the following imputation rules will be applied:

- If CM or MH start date day and month are missing, the start date is imputed as the first day of the year (01 Jan) and impute the end date as the last day of the year (Dec 31).
  - If only day is missing, the start date is imputed as the first day of the month (01).

Impute the end date as the last day of the month (28, 30 or 31 depending on month). Consider leap year.

19. CHANGE FROM ANALYSIS PLANNED IN PROTOCOL

Planned Analysis in Protocol	Change	Reason for Change
MMRM model to be used as the primary analysis and ANCOVA model to be used as a sensitivity analysis for the primary efficacy endpoint and key secondary efficacy endpoints.	ANCOVA model to be used as the primary analysis and MMRM model to be used as a sensitivity analysis for the primary efficacy endpoint and key secondary efficacy endpoints.	To avoid potential coverage issues caused by the small sample size of this POC study.

20. REFERENCES

The 5-Ditch scale: a new measure of pruritus, S. Elman, L.S. Hynan, V. Gabriel, and M.J. Mayo, Br J Dermatol. 2010 March; 162(3): 587-593. doi:10.1111/j.1365-2133.2009.09586.x.

21. APPENDICES

APPENDIX 1. SCHEDULE OF ACTIVITIES

Appendix 1A 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

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
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 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																					

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
Randomization		X																			
Study drug[6] administration		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X				
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			

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
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	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 judgment.

[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.

Appendix 1B 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			

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
Blood PD samples		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

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 judgment.

[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.

APPENDIX 2. 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**

APPENDIX 3. VISUAL ANALOG SCALE

Subject ID #: _____ Subject Initials: ___ ___ ___
Visit Day: _____ Visit Date (dd-mmm-yyyy):_____

Pruritus assessment (itching) (average during the past 3 days)

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

0 1 2 3 4 5 6 7 8 9 10

Measure: _____cm Subject Initials : _____

Sleep Loss Assessment (average during the past 3 nights)

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

0 1 2 3 4 5 6 7 8 9 10

Measure: _____cm Subject Initials : _____

APPENDIX 4. 5-D PRURITUS SCALE

5-D Pruritus Scale

1. Duration: During the last 2 weeks, how many hours a day have you been itching?

Less than 6hrs/day	6-12 hrs/day	12-18 hrs/day	18-23 hrs/day	All day
☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

2. Degree: Please rate the intensity of your itching over the past 2 weeks

Not present	Mild	Moderate	Severe	Unbearable
☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

3. Direction: Over the past 2 weeks has your itching gotten better or worse compared to the previous month?

Completely resolved	Much better, but still present	Little bit better, but still present	Unchanged	Getting worse
☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

4. Disability: Rate the impact of your itching on the following activities over the last 2 weeks

	Never affects sleep	Occasionally delays falling asleep	Frequently delays falling asleep	Delays falling asleep and occasionally wakes me up at night	Delays falling asleep and frequently wakes me up at night
Sleep	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

	N/A	Never affects this activity	Rarely affects this activity	Occasionally affects this activity	Frequently affects this activity	Always affects this activity
Leisure/Social	☐	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
Housework/ Errands	☐	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
Work/School	☐	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

5. Distribution: Mark whether itching has been present in the following parts of your body over the last 2 weeks. If a body part is not listed, choose the one that is closest anatomically.

	Present		Present
Head/Scalp	☐	Soles	☐
Face	☐	Palms	☐
Chest	☐	Tops of Hands/Fingers	☐
Abdomen	☐	Forearms	☐
Back	☐	Upper Arms	☐
Buttocks	☐	Points of Contact w/ Clothing	
Thighs	☐	(e.g waistband, undergarment)	☐
Lower legs	☐	Groin	☐
Tops of Feet/Toes	☐		

APPENDIX 5. DERMATOLOGY LIFE QUALITY INDEX

DLQI

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

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

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

	or **relatives**?	Not at all	☐	Not relevant ☐
9.	Over the last week, how much has your skin caused any **sexual difficulties**?	Very much A lot A little Not at all	☐ ☐ ☐ ☐	 Not relevant ☐
10.	Over the last week, how much of a problem has the **treatment** for your skin been, for example by making your home messy, or by taking up time?	Very much A lot A little Not at all	☐ ☐ ☐ ☐	 Not relevant ☐

APPENDIX 6. ITCHING QUALITY OF LIFE SURVEY

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

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

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

APPENDIX 7. 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:	

APPENDIX 8. 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

APPENDIX 9. HOSPITAL ANXIETY AND DEPRESSION SCALE (HADS)

Hospital Anxiety and Depression Scale (HADS)

Name:_____ Date: _____

FOLD HERE

Clinicians are aware that emotions play an important part in most illnesses. If your clinician knows about these feelings he or she will be able to help you more.

This questionnaire is designed to help your clinician to know how you feel. Read each item below and **underline the reply** which comes closest to how you have been feeling in the past week. Ignore the numbers printed at the edge of the questionnaire.

Don't take too long over your replies, your immediate reaction to each item will probably be more accurate than a long, thought-out response.

FOLD HERE

A	D			A	D
		I feel tense or 'wound up'	**I feel as if I am slowed down**		
3		Most of the time	Nearly all the time		3
2		A lot of the time	Very often		2
1		From time to time, occasionally	Sometimes		1
0		Not at all	Not at all		0
		I still enjoy the things I used to enjoy	**I get a sort of frightened feeling like 'butterflies' in the stomach**		
	0	Definitely as much	Not at all	0	
	1	Not quite so much	Occasionally	1	
	2	Only a little	Quite often	2	
	3	Hardly at all	Very often	3	
		I get a sort of frightened feeling as if something awful is about to happen	**I have lost interest in my appearance**		
3		Very definitely and quite badly	Definitely		3
2		Yes, but not too badly	I don't take as much care as I should		2
1		A little, but it doesn't worry me	I may not take quite as much care		1
0		Not at all	I take just as much care as ever		0
		I can laugh and see the funny side of things	**I feel restless as if I have to be on the move**		
	0	As much as I always could	Very much indeed	3	
	1	Not quite so much now	Quite a lot	2	
	2	Definitely not so much now	Not very much	1	
	3	Not at all	Not at all	0	
		Worrying thoughts go through my mind	**I look forward with enjoyment to things**		
3		A great deal of the time	As much as I ever did		0
2		A lot of the time	Rather less than I used to		1
1		Not too often	Definitely less than I used to		2
0		Very little	Hardly at all		3
		I feel cheerful	**I get sudden feelings of panic**		
	3	Never	Very often indeed	3	
	2	Not often	Quite often	2	

1	Sometimes	Not very often	1
0	Most of the time	Not at all	0

	I can sit at ease and feel relaxed	**I can enjoy a good book or radio or television program**	
0	Definitely	Often	0
1	Usually	Sometimes	1
2	Not often	Not often	2
3	Not at all	Very seldom	3

Now check that you have answered all the questions

	A	**D**
TOTAL		

APPENDIX 10. PBI-P – PATIENT BENEFIT INDEX, PRURITUS VERSION

Importance of Treatment Goals

With the help of the following questions, we'd like to know how important the goals mentioned below are to you personally in the **current treatment** of your skin disease.

For each of the following statements, please mark **how important** this treatment goal is to you.
If a statement does not apply to you, for example because you are not experiencing pain, please mark "*does not apply to me*".

	As a result of therapy, how important is it for you to ...	**not at all**	**somewhat**	**moderately**	**quite**	**very**	*does not apply to me*
1	...be free of pain	O	O	O	O	O	O
2	...be free of itching	O	O	O	O	O	O
3	...no longer have burning sensations on your skin	O	O	O	O	O	O
4	...be healed of all skin defects	O	O	O	O	O	O
5	...concentrate better	O	O	O	O	O	O
6	...be less nervous	O	O	O	O	O	O
7	...be able to wear all types of clothing	O	O	O	O	O	O
8	...be able to bathe and shower normally	O	O	O	O	O	O
9	...sleep better	O	O	O	O	O	O
10	...feel less depressed	O	O	O	O	O	O
11	...experience greater enjoyment of life	O	O	O	O	O	O
12	...have no fear that the disease will get worse	O	O	O	O	O	O
13	...lead a normal everyday life	O	O	O	O	O	O
14	...be more productive in everyday life	O	O	O	O	O	O

15	...be less of a burden to relatives and friends	O	O	O	O	O	O
16	...engage in normal leisure activities	O	O	O	O	O	O
17	...be able to lead a normal working life	O	O	O	O	O	O
18	...be able to have more contact with other people	O	O	O	O	O	O
19	…be more comfortable showing yourself in public	O	O	O	O	O	O
20	...be less burdened in your partnership	O	O	O	O	O	O
21	...be able to have a normal sex life	O	O	O	O	O	O
22	...be less dependent on doctor and clinic visits	O	O	O	O	O	O
23	...need less time for daily treatment	O	O	O	O	O	O
24	...have fewer out-of-pocket treatment expenses	O	O	O	O	O	O
25	...have fewer side effects	O	O	O	O	O	O
26	...find a clear diagnosis and therapy	O	O	O	O	O	O
27	...have confidence in the therapy	O	O	O	O	O	O

Please recheck your answers to make sure you have clearly marked each statement with an "x".
Thank you very much for your cooperation!

Treatment Benefits

When the treatment began, you indicated in a questionnaire how important various goals were in the treatment of your skin disease.

Please mark each of the following statements according to the extent to which those treatment goals **were achieved**, indicating if the treatment has benefited you. If a statement did not apply to you, for example because you did not experience any pain, please mark "*did not apply to me*".

	The current treatment has helped me to …	**not at all**	**somewhat**	**moderately**	**quite**	**very**	*does not apply to me*
1	...be free of pain	O	O	O	O	O	O
2	...be free of itching	O	O	O	O	O	O
3	...no longer have burning sensations on my skin	O	O	O	O	O	O
4	...be healed of all skin defects	O	O	O	O	O	O
5	...concentrate better	O	O	O	O	O	O
6	...be less nervous	O	O	O	O	O	O
7	...be able to wear all types of clothing	O	O	O	O	O	O
8	...be able to bathe and shower normally	O	O	O	O	O	O
9	...sleep better	O	O	O	O	O	O
10	...feel less depressed	O	O	O	O	O	O
11	...experience greater enjoyment of life	O	O	O	O	O	O
12	...have no fear that the disease will get worse	O	O	O	O	O	O
13	...lead a normal everyday life	O	O	O	O	O	O
14	...be more productive in everyday life	O	O	O	O	O	O
15	...be less of a burden to relatives and friends	O	O	O	O	O	O
16	...engage in normal leisure activities	O	O	O	O	O	O
17	...be able to lead a normal working life	O	O	O	O	O	O

18	...be able to have more contact with other people	O	O	O	O	O	O
19	…be more comfortable showing myself in public	O	O	O	O	O	O
20	...be less burdened in my partnership	O	O	O	O	O	O
21	...be able to have a normal sex life	O	O	O	O	O	O
22	...be less dependent on doctor and clinic visits	O	O	O	O	O	O
23	...need less time for daily treatment	O	O	O	O	O	O
24	...have fewer out-of-pocket treatment expenses	O	O	O	O	O	O
25	...have fewer side effects	O	O	O	O	O	O
26	...find a clear diagnosis and therapy	O	O	O	O	O	O
27	...have confidence in the therapy	O	O	O	O	O	O

Please recheck your answers to make sure you have clearly marked each statement with an "x".
Thank you very much for your cooperation!

APPENDIX 11. CLINICAL LABORATORY TESTS

Chemistry	**Hematology**	**Urinalysis**	**Urine microscopy**
Albumin	Baso	Appearance	Erythrocytes
Alkaline phosphatase	Baso (%)	Color	Leucocytes
ALT	Eosino	Bilirubin (urine)	Bacteria
AST	Eosino (%)	Blood (urine)	Epithelial cells
Bicarbonate	Hematocrit	Glucose (urine)	Cast:
Total bilirubin	Hemoglobin	Ketones (urine)	-Hyaline
Urea	Lympho	Leucocytes (urine)	-Granular
Calcium	Lympho (%)	Nitrite (urine)	-Waxy
Chloride	MCH	pH (urine)	-Red Blood Cells
Creatinine	MCHC	Protein (urine)	-White blood cells
GGT	MCV	Specific gravity	Crystals:
Glucose (random)	Mono	Urobilinogen (urine)	-Triple phosphate
LDH	Mono (%)		-Amorphous phos.
Potassium	Neutro		-Uric acid
Sodium	Neutro (%)		-Calcium oxalate
Total protein	Platelet		-Amorphous urates
Uric acid	Red blood cell		-Bilirubin
Cholesterol	RDW		-Calcium carbonate
HDL-cholesterol	White blood cell		-Ammonium biurate
LDL-cholesterol	aPTT		-Cholesterol
Triglycerides	PT		Mucus
	PT-INR		
	Fibrinogen		
	D--Dimer		
	HbA1c		
Serology	**Drug Screening**	**Endocrinology**	**Immunoglobulins**
HBsAg	Amphetamines	FSH	IgE
Anti-HCV	Cocaine (metabolites)	Pregnancy Test (serum)	
Anti-HBc	Methadone		
Anti-HBs	Opiates		
Anti-HIV I/II	Phencyclidine		
Anti-HCV Confirmation	Oxycodone		
	Propoxyphene		
	Urine Drug Screen Dipstick		

APPENDIX 12. SAS SAMPLE CODES

- **Multiple Imputation**

1) For daily NRS, daily scores will be set to missing if daily assessments fall in the interval of rescue medications (see section 9). Then weekly average will be calculated with 50% rules applied. Only baseline and first 8 weeks values will be included for multiple imputation. For pruritus VAS, weekly score will be set to missing if assessments fall in the interval of rescue medication. Then scores up to week 8 will be included for imputation.
2) Transpose data as horizontal and fill in intermediate missing value with FCS regpmm procedure:

```
proc mi data=DATAIN out=DATAOUT nimpute=200 seed=xxx;
  class trt sex atopy;
     var sex atopy BASE WK1 WK2 … WK8;
     fcs regpmm;
     by trt;
  run;
```

3) Only keep those imputed values for intermediate missing values, and merge back to the original transposed data.
4) Define placebo subjects with week 8 values as placebo completers which will be used as input for model establishment in second round multiple imputation.

```
proc mi data=DATAIN out=DATAOUT nimpute=1 seed=xxx;
   class completer sex atopy;
  var sex atopy BASE WK1 WK2 … WK8;
  fcs regpmm (WeeK1=sex atopy _0);
  MNAR model (WK1/modelobs=(completer="Y"));
  Fcs regpmm (WK2=sex atopy _0 WK1);
  MNAR model (WK2/modelobs=(completer="Y"));
  ……
 fcs regpmm (WK8=sex atopy Baseline WK1 WK2 WK3 WK4 WK5 WK6_WK7);
 MNAR model (WK8/modelobs=(completer="Y"));
 By _IMPUTATION_;
```

5) Transpose the imputed data back into a vertical structure and fit MMRM or ANCOVA by _IMPUTATION_.

6) Utilize the PROC MIANALYZE procedure to combine the estimates together for table presentation.

```
PROC MIANALYZE DATA=datain;
   BY week;
   MODELEFFECTS estimate;
   STDERR;
run;
```

- **Mixed Model for Repeated Measures (MMRM) Based on Observed Data**

Sample code for MMRM modeling

```
**********************************************************************;
proc mixed data=eff;
   class treatment sex atopy week usubjid;
```

```
    model chg = treatment sex atopy week base treatment*week / ddfm=kr;
    repeated week / type=un sub=usubjid;
    lsmean treatment*week / diff cl;
    ods output
        diffs=outdiff
        tests3=outpval
        lsmeans=outlsmean;
run;
```

- **CMH Test**

```
    proc freq data=data noprint;
            tables sex*atopy*treatment*resp/ CMH relrisk riskdiff;
            output out=dataout CMH;
    run;
```