PROTOCOL

KPL-716-C202: A Phase 2 Randomized, Double-Blind, Placebo-Controlled Pilot Study to Investigate the Efficacy, Safety, and Tolerability of KPL-716 in Reducing Pruritus in Diseases Characterized by Chronic Pruritus

Protocol Status: Final
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Study Drug: KPL-716

Protocol Number: KPL-716-C202
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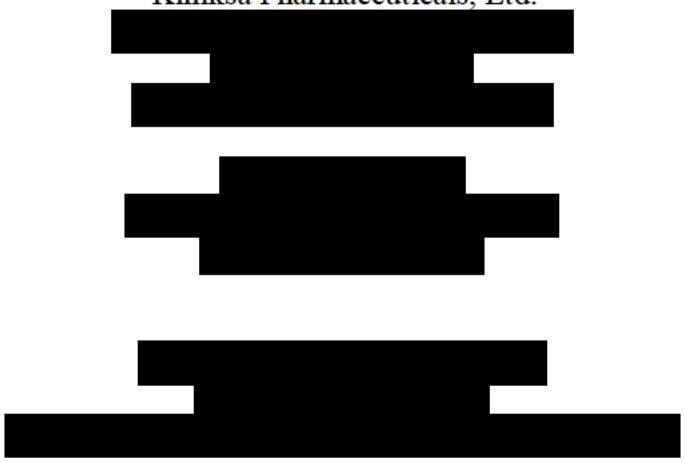
Sponsor:
Kiniksa Pharmaceuticals, Ltd.



INVESTIGATOR AGREEMENT

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

Investigator's Name (Print)

Investigator's Signature Date

SPONSOR AGREEMENT

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

PROTOCOL SYNOPSIS

Title of Study:

A Phase 2 Randomized, Double-Blind, Placebo-Controlled, Pilot Study to Investigate the Efficacy, Safety, and Tolerability of KPL-716 in Reducing Pruritus in Diseases Characterized by Chronic Pruritus

Phase of Clinical Development:

Pilot Phase 2 Study

Study Population:

Subjects with diseases characterized by chronic pruritus experiencing moderate to severe pruritus will be enrolled in this pilot Phase 2 study.

The diseases characterized by chronic pruritus investigated in this pilot study currently include chronic idiopathic urticaria (CIU), chronic idiopathic pruritus (CIP), lichen planus (LP), lichen simplex chronicus (LSC) and plaque psoriasis (PPs).

Primary Objective

- To evaluate the efficacy of subcutaneous (SC) KPL-716 in reducing pruritus in subjects with chronic pruritus experiencing moderate to severe pruritus

Secondary Objectives

- To evaluate the effect of SC KPL-716 in improving sleep in subjects with chronic pruritus experiencing moderate to severe pruritus
- To evaluate the effect of SC KPL-716 in improving quality of life in subjects with chronic pruritus experiencing moderate to severe pruritus
- To evaluate the safety and tolerability of SC KPL-716 in subjects with chronic pruritus experiencing moderate to severe pruritus
- To evaluate the pharmacokinetics (PK) of SC KPL-716 in subjects with chronic pruritus experiencing moderate to severe pruritus
- To evaluate the immunogenicity of SC KPL-716 in subjects with chronic pruritus experiencing moderate to severe pruritus

[redacted]

Primary Efficacy Endpoint

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

Secondary Efficacy Endpoints

Related to pruritus:

- Change and percent change from baseline in weekly average of WI-NRS over time
- Change and percent change from baseline in Pruritus VAS over time
- Change and percent change from baseline in 5-D Pruritus total score over time
- Proportion of subjects achieving at least a 4-point reduction from baseline in weekly average WI-NRS over time
- Change and percent change from baseline in weekly itch severity score, a component of Urticaria Activity Score 7 (UAS7) (CIU only)

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

[redacted]

Safety Parameters

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

[redacted]

Study Design:

This Phase 2 pilot study is comprised of multiple cohorts each for a different study population. Each cohort is an independent randomized, double-blind, placebo-controlled sub-study to investigate the efficacy, safety, tolerability, PK and immunogenicity of KPL-716 administered SC in reducing

pruritus in diseases characterized by chronic pruritus. The following chronic pruritic diseases will be studied.

Each cohort will be enrolled and analyzed independently:

- Cohort 1: Chronic Idiopathic Urticaria (CIU)
- Cohort 2: Chronic Idiopathic Pruritus (CIP)
- Cohort 3: Lichen Planus (LP)
- Cohort 4: Lichen Simplex Chronicus (LSC)
- Cohort 5: Plaque Psoriasis (PPs)

Each cohort will enroll approximately 26 subjects and contain three periods:

- Screening Period (Day-28 to Day-1, minimum 14 days and maximum 28 days)
- Treatment Period (Day 1 [Baseline] to Week 8)
- Follow-up Period (After week 8 to Week 18)

Allowable window for Week 1 is ±1 day and from Week 2 to Week 18 visits is ± 2 days.

In every cohort, a loading dose of KPL-716 at 720 mg SC (or matching placebo) will be followed by maintenance doses of 360 mg SC (or matching placebo) administered every week for 7 additional weekly doses in order to detect an early signal of efficacy on pruritus once exposures approach an expected steady state. In addition, the impact of KPL-716 on sleep and quality of life will be assessed. Furthermore, the impact of KPL-716 on urticaria in CIU (Cohort 1) will be investigated.

Each cohort will utilize a washout design in which concomitant therapies that could impact pruritus will be prohibited from a designated timepoint prior to dosing through the End of Study (EOS) Visit, thus removing the confounding effect of these therapies on the assessment of KPL-716 efficacy. Subjects who use a moisturizer cream/emollient will be instructed to use the same moisturizer cream/emollient at the same frequency throughout the study. Only subjects with CIU (Cohort 1) will be allowed to use H1 antihistamines at approved stable doses from 14 days prior to dosing to EOS Visit. The permitted H1 antihistamines for CIU will be outlined in the Pharmacy Manual. Should subjects in any cohort experience an exacerbation of symptoms that is significant enough to warrant intervention, they will be provided with H1 antihistamines and/or topical corticosteroids (TCS) as rescue medication. The permitted rescue medications for each cohort will be outlined in the Pharmacy Manual.

Accountability for rescue medications will be maintained by the sites. The date, time, and the number of antihistamine tablets will be recorded and the weight of TCS tubes will be measured at dispensation, at every visit, and upon return.

Screening Period:

After the Informed Consent Form (ICF) is signed, subjects will enter the Screening Period for assessment of eligibility.

During the Screening Visit, subject's medical and surgical history will be reviewed including allergic history. Review of medical history will include the specific cohort disease history and history of co-morbidities. Prior and concomitant medications, therapies and procedures will be recorded. Subjects will be instructed on the required washout for specific excluded medications.

Vital signs and body weight will be measured, and subjects will undergo a full physical examination. Clinical laboratory tests and an ECG will be performed. Urine drug screen and pregnancy test (if applicable) will also be performed.

To be eligible for study participation, subjects must have moderate to severe pruritus, defined as WI-NRS ≥ 7 at the Screening Visit and a mean weekly WI-NRS ≥ 5 for each of the 2 consecutive weeks immediately prior to randomization. A minimum of 85% compliance with daily WI-NRS recording during the last 14 days of Screening Period prior to randomization is required for eligibility unless approved by the Sponsor.

At the Screening Visit, subjects will be asked to rate their pruritus severity (WI-NRS) in the previous 24 hours on a numerical rating scale. Subjects also will be instructed to record their daily rating of WI-NRS and two sleep parameters, difficulty falling asleep NRS and sleep quality NRS, from the beginning of screening to Day 1. The daily recordings (WI-NRS, difficulty falling asleep NRS, and sleep quality NRS) will continue throughout the study for eligible subjects that proceed to dosing.

Furthermore, subjects with CIU will be instructed to also complete on a daily basis the UAS7 questionnaire (on itch and hives severity) from the beginning of screening to Day 1. Daily completion of the UAS7 questionnaire will continue throughout the study for eligible CIU subjects that proceed to dosing.

Additional assessments at the Screening Visit include those related to pruritus (Pruritus VAS, and 5-D Pruritus), sleep (Sleep Loss VAS) and quality of life (DLQI and ItchyQoL).

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

Treatment Period:

The treatment period will last 8 weeks.

Pre-dose:

Eligibility must be confirmed prior to dosing on Day 1. Subjects will have the following procedures performed prior to dosing on Day 1:

- Review of medical and surgical history
- Review of prior and concomitant medications
- Review of adverse events
- Review of compliance with recording of daily WI-NRS
- Review of clinical laboratory results from the Screening Visit
- Full physical examination
- Vital signs and weight
- ECG (if more than 30 days since screening ECG)
- Subjects will record their Pruritus VAS, Sleep Loss VAS and complete the 5-D Pruritus, DLQI and ItchyQoL questionnaires.
- Collection of laboratory blood tests
- Collection of urine for urinalysis
- Pregnancy test (if applicable)
- Collection of [redacted] PK [redacted] blood samples

[redacted]

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

Dosing:

A loading dose of KPL-716 720 mg (2x maintenance dose) or matching placebo will be administered via 2 SC injections within 30 minutes on Day 1 by the Investigator or qualified designee at the study sites.

All subsequent doses of KPL-716 (360 mg maintenance dose) or matching placebo will be administered by the Investigator or qualified designee at the study sites via a single SC injection.

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

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

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

- Physical examination
- Collection of safety blood and urine samples
- Urine pregnancy test (if applicable); a serum pregnancy test will be performed if the urine pregnancy test is positive

[redacted]

- Completion of 5-D pruritus questionnaire
- Completion of quality of life questionnaire (DLQI and ItchyQoL)

[redacted]

Subjects will be observed for 3 hours after completion of the loading dose, for 2 hours after the first 2 maintenance doses and for 1 hour after all subsequent doses. Vital signs will be measured every hour during the observation period. The post-dose observation period duration may be modified based on emerging safety and tolerability data.

Adverse events and concomitant medications will be collected throughout the study. Subjects will continue to complete their daily questionnaire on pruritus (WI-NRS) and sleep until the EOS Visit. CIU subjects will continue to complete their daily UAS7 questionnaire (on itch and hives severity) until the EOS Visit.

In case of study drug discontinuation, subjects will continue to follow the schedule of activities for each visit minus study drug administration. [redacted]

[redacted] In case of study drug interruption or missed dosing visits, subjects will resume the schedule of activities in accordance with their study day. Study drug will be discontinued if more than three consecutive doses are withheld or missed.

In case of early withdrawal from the entire study, subjects will complete an EOS Visit.

Follow-up Period:

During the Follow-up Period, subjects will undergo vital signs measurement, review of concomitant medications, therapies and procedure, review of adverse events, and monitoring of compliance at every visit. Pruritus VAS, 5-D Pruritus, and Sleep Loss VAS will also be completed at every visit during the Follow Up Period. Physical examination, clinical laboratory blood tests, urinalysis, and quality of life assessment (DLQI and ItchyQoL), will be performed at designated visits. Subjects will continue to complete their daily questionnaire on pruritus and sleep throughout the Follow-up Period. CIU subjects will continue to complete their daily UAS7 questionnaire (on itch and hives severity) throughout the Follow-up Period.

The EOS Visit includes vital signs and weight, full physical examination, ECG, clinical laboratory blood tests, urinalysis, and urine pregnancy test (if applicable) as well as all efficacy assessments for pruritus, sleep, and quality of life. All subjects will complete an EOS Visit.

Duration of Study:

The planned study duration per subject is approximately 20 to 22 weeks. This includes a maximum of 4 weeks for the Screening Period, 8 weeks for the Treatment Period, and a 10-week Follow-up Period. The minimum duration for the Screening Period will be 14 days.

Study Drug and Treatment:

Study Drug: KPL-716 or matching placebo

Active Substance: Fully-human monoclonal antibody against Oncostatin M Receptor beta (OSMRβ)

Strength [redacted] and Route of Administration:

KPL-716: 180 mg/mL solution [redacted]

A loading dose of KPL-716 (2x maintenance dose) or matching placebo will be administered via up to 2 SC injections within 30 minutes on Day 1. Maintenance doses of KPL-716 or matching placebo will be administered via 1 SC injection for the remainder of the Treatment Period. The planned loading and maintenance dose levels are currently 720 mg and 360 mg weekly, respectively.

Study Assessments:

Efficacy Assessment:

Efficacy in reduction of pruritus will be assessed via daily recording of WI-NRS as well as on-site assessment of Pruritus VAS and 5-D Pruritus. Improvement in sleep will be assessed via daily recording of two (2) NRS scales, one for difficulty falling asleep and the other for quality of sleep.

Impact on sleep will also be assessed via on-site Sleep Loss VAS. Impact on quality of life will be assessed via on-site PROs: DLQI and ItchyQoL. Impact on pruritus and disease severity for subjects with CIU will be assessed via daily completion of UAS7 questionnaire. Efficacy assessments will be performed as per Schedule of Activities (Appendix 1).

[redacted]

Safety Assessments:

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

PK Assessments:

PK blood samples will be collected from all subjects at every visit from the baseline visit to EOS. PK samples will be collected pre-dose on dosing days.

[redacted]

Selection of Study Population:

Inclusion criteria:

1. Male or female, aged 18 to 75 years, inclusive, at the time of consent.
2. Has a physician-documented diagnosis of the specified chronic pruritic disease. Duration of disease must be at least 6 months. The study dermatologist or the study allergist/immunologist confirms the diagnosis of the specified chronic pruritic disease. The duration of disease (at least 6 months) can be documented as affirmed by the subject.
    - Pruritus associated with these diagnoses must be refractory to treatment with H1 antihistamines and must have been present for at least 6 weeks prior to Day 1
    - Subjects with CIU must have had pruritus and hives for at least 6 consecutive weeks prior to Day 1. In subjects with CIU, urticarial eruptions must typically last less than 24 hours
3. Has moderate to severe pruritus, defined as WI-NRS ≥ 7 at the Screening Visit and a mean weekly WI-NRS ≥ 5 for each of the two consecutive weeks immediately prior to randomization.

4. Sexually active female subjects must be:
    - postmenopausal, defined as at least 12 consecutive months post cessation of menses (without an alternative medical cause) and confirmed by a follicular stimulating hormone (FSH) test, or
    - surgically sterile following documented hysterectomy, bilateral salpingectomy, bilateral oophorectomy, or
    - nonpregnant, nonlactating, and having agreed to use a highly effective method of contraception from the Screening Visit until 16 weeks after final study drug administration
        - Note: highly effective methods of contraception include:
            - hormonal contraceptives associated with inhibition of ovulation (stable dose for at least 4 weeks prior to first dose)
            - intrauterine device (IUD)
            - intrauterine system (IUS)
            - double barrier methods of contraception (barrier methods include male condom, female condom, cervical cap, diaphragm, contraceptive sponge) in conjunction with spermicide
            - tubal ligation
            - vasectomized male partner
5. Sexually active male subjects must have documented vasectomy or must agree to use a highly effective method of contraception as defined above with their partners of childbearing potential from first dose until 16 weeks after final study drug administration.
6. Male subjects must agree to refrain from donating sperm from first dose until 16 weeks after the last study drug administration. Female subjects must agree to refrain from donating eggs from first dose until 16 weeks after the last study drug administration.
7. Female subjects of childbearing potential must have a negative serum β-hCG test at the Screening Visit and negative urine pregnancy test on Day 1.
8. Able to comprehend and willing to sign an Informed Consent Form and able to abide by the study restrictions and comply with all study procedures for the duration of the study.

Exclusion criteria:

1. Has used the following medications within the indicated timeframe prior to Day 1 or does not agree to refrain from the use of the medications throughout the study treatment and Follow up Period:
    a. Systemic corticosteroids (IV/IM/oral): 8 weeks for IV/IM, 4 weeks for oral; Note: Intranasal corticosteroids, eye drops containing corticosteroids, and inhaled corticosteroids for stable medical conditions are allowed.
    b. Intralesional corticosteroids and intra-articular corticosteroids: 8 weeks
    c. Topical treatments including but not limited to corticosteroids, calcineurin inhibitors, phosphodiesterase inhibitors, retinoids, calcipotriol, capsaicin, camphor, polidocanol or tars: 2 weeks
    d. Antihistamines: 1 week

- Subjects with CIU (Cohort 1) may use H1 antihistamine at approved and stable doses. The acceptable H1 antihistamines will be defined in the Pharmacy Manual

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

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

g. Cannabinoids: 2 weeks

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

i. Janus Kinase (JAK) inhibitors: 3 months

j. Dupilumab and ustekinumab: 6 months

k. Any other marketed biologic: 3 months or until cell numbers return to normal in case of depleting antibodies such as rituximab

l. Any investigational biologic drug: 6 months

m. Any investigational non-biologic drug: 3 months

n. Phototherapy involving Ultraviolet A (UVA), Ultraviolet B (UVB), or excimer: 4 weeks

o. Tanning salon use: 4 weeks

2. Has received any investigational biologic or non-biologic drug that targets Oncostatin M, IL-31, or IL-31 receptor α, or Oncostatin M receptor β in the past.
3. Is currently using medication known to cause pruritus (e.g., angiotensin converting enzyme inhibitors) unless timing of onset of pruritus and initiation of medication do not suggest that pruritus was caused by the medication.
4. Has a diagnosis of LP and is currently using medication known to cause lichenoid reaction (e.g., angiotensin converting enzyme inhibitors and/or beta blockers) unless timing of onset of lichenoid skin changes and initiation of medication do not suggest that lichenoid reaction was caused by the medication.
5. Has less than 85% compliance with the daily WI-NRS tool during the last 14 days of the Screening Period prior to randomization, unless approved by the Sponsor.
6. Has had a significant flare of pruritus and/or skin eruption during the Screening Period (prior to the study drug administration) that requires a medical intervention.
7. Has any inflammatory, pruritic, and/or fibrotic skin condition other than the diagnosis that defines the cohort unless approved by the Sponsor. For example:
    a. Has urticarial vasculitis, urticaria pigmentosa, systemic mastocytosis, familial cold urticaria or hereditary or acquired angioedema due to C1 inhibitor deficiency.
    b. Has a clear cause of urticaria including but not limited to cold, heat, solar, pressure, and delayed pressure. Has contact urticaria, aquagenic urticaria or cholinergic urticaria.
    c. Has pustular psoriasis, erythrodermic/exfoliative psoriasis, drug-induced psoriasis, or psoriatic arthritis
    d. Has atopic dermatitis
8. Has significant severe xerosis that persists despite the regular use of an emollient unless approved by the Sponsor.

9. Has uncontrolled hyperthyroidism or hypothyroidism. Has insulin-dependent diabetes or uncontrolled diabetes defined as hemoglobin A1c >7.5%.
10. Has had cancer or lymphoproliferative disease within 5 years prior to Day 1
11. Has had any autoimmune disorder other those under investigation in this study
12. Has had a severe allergic reaction to any foods or medications including anaphylactic reactions unless approved by the Sponsor.
13. Has had systemic amyloidosis
14. Has had immune deficiency, or opportunistic infections
15. Has positive results for hepatitis B surface antigen (HbsAg)
16. Has positive results for hepatitis B anti-core antibody (anti-HBc) but negative results for anti-surface antibody (anti-HBs)
17. Has positive results for hepatitis C antibody
18. Has human immunodeficiency virus (HIV) infection or positive HIV serology
19. Has psychiatric illness other than stable mild to moderate anxiety and/or depression unless approved by the Sponsor
20. Has been hospitalized for a psychiatric illness
21. Has laboratory abnormalities that fall outside the windows below at the Screening Visit:
    a. Alanine aminotransferase > 1.5 x Upper limit of normal (ULN)
    b. Aspartate aminotransferase > 1.5 x ULN
    c. Gamma-glutamyl transferase > 1.5 x ULN
    d. Blood bilirubin > 1.25 x ULN
    e. Hemoglobin more than 1g/dL below the lower limit of normal for sex per the laboratory in which screening lab is performed.
    f. Platelet count <120,000/ µl
    g. Creatinine > 1.25 x ULN
22. Has a body mass index (BMI) of <16 kg/m^2 or >38 kg/m^2
23. Has systolic blood pressure above 150 mm Hg, diastolic blood pressure above 95 mm Hg at the Screening Visit or Day 1 (confirmed by repeat measurement).
24. Has been hospitalized within 12 weeks prior to Day 1
25. Has had major surgery within 12 weeks prior to Day 1 or has a major surgery planned during the study
26. Has had an active infection including skin infection, requiring systemic treatment within 4 weeks and/or topical treatment within 2 weeks of Day 1. Has an active or chronic parasitic infection.
27. Has any medical (heart, lung, kidney, liver, metabolic) or psychiatric condition which, in the opinion of the Investigator or the Sponsor, may place the subject at increased risk as a result of study participation, interfere with study participation or study assessments, affect compliance with study requirements, or complicate interpretation of study results.
28. Has received a live attenuated vaccine within 12 weeks prior to Day 1

29. Has previously taken part in or withdrawn from this study or has previously received the study drug. Screen failures may be rescreened at the discretion of the Investigator.
30. Has a known hypersensitivity to KPL-716 or its excipients
31. Has a known history of drug or alcohol abuse in the last 2 years prior to Day 1. Has more than eight drinks (5 ounces of wine, 12 ounces of beer or 1.5 ounces of liquor) weekly for females and 15 drinks weekly for males
32. Has a positive urine drug screen for opiates, opioids, methadone, cocaine, phencyclidine, or amphetamines at the Screening Visit. Exceptions may be made if a subject is on a Sponsor-approved medication for a stable concomitant condition that explains the positive drug screen result.
33. Has received blood products within 8 weeks prior to Day 1
34. Has donated blood within 12 weeks prior to Day 1, platelets within 10 weeks prior to Day 1, or plasma within 6 weeks prior to Day 1

Statistical Methods:

All clinical study data will be presented in subject data listings. Descriptive statistics will be presented for all endpoints and will include number of subjects (n), mean, standard deviation (SD), first quartile (Q1), median, third quartile (Q3), minimum and maximum for continuous variables, and frequency and percentage for categorical and ordinal variables.

Statistical analyses of efficacy endpoints will be conducted separately for each cohort.

Determination of Sample Size:

This is a double-blind study. Each cohort will be independently analyzed. A total of approximately 26 subjects will be randomized in each cohort. The first 12 subjects will be randomized to the KPL-716 and the placebo arms in a 3:1 randomization ratio. The rest of the 14 subjects will be randomized in a 1:1 randomization ratio. There will be approximately 16 subjects and 10 subjects randomized to the KPL-716 arm and the placebo arm respectively. Based on a two-sample t-test for the primary efficacy endpoint, change from baseline in weekly average of WI-NRS at Week 8, assumed mean changes of 4 for the KPL-716 arm and 1.5 for the placebo arm, a total sample size of 26 subjects per cohort will provide about 80% power to detect a 2.5-point mean difference with a standard deviation of 2.8, given a two-sided alpha of 0.2. Given the exploratory nature of this pilot study, the precision attained with the above cohort samples size is acceptable for early signal of efficacy assessments.

Safety Analysis Set:

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

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.

Per Protocol (PP) Analysis Set:

All mITT subjects who have no protocol deviations that may potentially bias statistical analyses of the study will be included in the PP set. Protocol deviations that may potentially bias statistical analyses will be defined in the SAP before database lock.

Efficacy Analyses:

All efficacy analyses for each disease cohort will be done separately based on the mITT analysis set. The analyses of primary and selected secondary efficacy endpoints will be repeated using the PP set to assess the sensitivity of the results to deviations of the protocol that could potentially bias the analysis. All efficacy data will be listed by subject. The primary efficacy endpoint, change from baseline in weekly average WI-NRS score at Week 8, will be analyzed using ANCOVA. The model will include treatment as the independent variable and baseline WI-NRS as covariate. In addition, randomization ratio and gender might be considered as covariates. Missing data will be imputed using the last observation carried forward (LOCF) method. Analysis details will be specified in the Statistical Analysis Plan (SAP).

Safety Analyses:

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

PK Analyses:

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

[redacted]

[redacted]

Interim Analysis:

Unblinded efficacy data endpoint review and unblinded interim analyses may be performed by the Sponsor for individual cohorts while enrollment is ongoing; one possible unblinded interim analysis for a given cohort may be conducted, for example, when approximately 12 subjects have been randomized in the cohort and treated for at least 8 weeks. The purpose of the interim analysis is to assess for potential early signals of efficacy to inform updates of the clinical development plan. The interim analysis will be performed by an unblinded independent biostatistician; unblinded results and anonymized subject data will be communicated to select Sponsor members

not involved with the conduct of the study. Investigators and subjects will remain blinded to treatment assignment until after database lock and completion of clinical study report (CSR) as defined in the SAP. Details of the unblinded interim analysis plan will be specified in the SAP.

Figure 1 Cohort Study Design Diagram

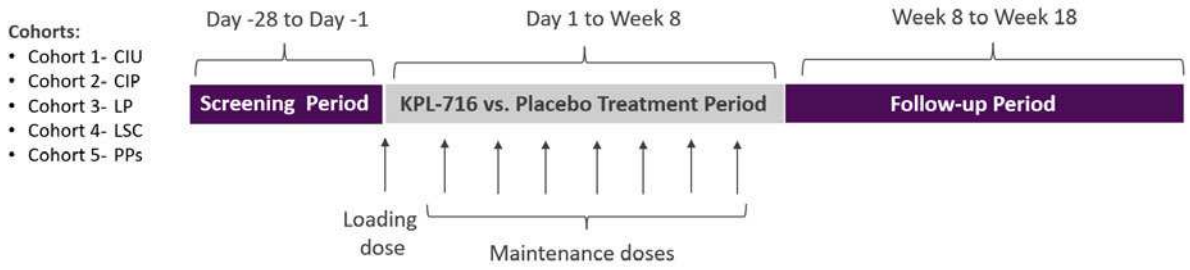


TABLE OF CONTENTS

LIST OF IN-TEXT FIGURES

LIST OF ABBREVIATIONS

[redacted]	[redacted]
AE	Adverse event
Anti-HBc	Hepatitis B core antibody
Anti-HBs	Hepatitis B surface antibody
$AUC_{0-\infty}$	Area under the concentration-time curve from time zero to infinity
β-hCG	β-human Chorionic Gonadotropin
BMI	Body mass index
C_{eff}	Efficacious concentration
CIU	Chronic Idiopathic Urticaria
CIP	Chronic Idiopathic Pruritus
C_{max}	Maximum concentration
CRO	Clinical Research Organization
CSR	Clinical Study Report
C_{trough}	Trough concentration
EDC	electronic data capture
ECG	electrocardiogram
e-CRF	electronic Case Report Form
EOS	End of Study
FSH	Follicle-stimulating hormone
DLQI	Dermatology Life Quality Index
HBV	Hepatitis B virus
HbsAg	Hepatitis B surface antigen
HCV	Hepatitis C virus
HIV	Human immunodeficiency virus
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Council for/Conference on Harmonization
IEC	Independent Ethics Committee
IMP	investigational medicinal product
IRB	Institutional Review Board
ISR	Injection Site Reaction
ItchyQoL	Itchy Quality of Life
LIFR	Leukemia Inhibitory Factor Receptor
LP	Lichen Planus
LSC	Lichen Simplex Chronicus
MedDRA	Medical Dictionary for Regulatory Activities
mITT	Modified Intent-to-Treat
NOAEL	no observed adverse effect level
NRS	Numerical Rating Scale
OSM	Oncostatin M
OSMRβ	Oncostatin M Receptor beta
[redacted]	[redacted]
PK	pharmacokinetic(s)
PPs	Plaque Psoriasis
PT	Preferred term

Q	Quartile
QA	Quality Assurance
QTcF	QT interval corrected for heart rate using Fridericia's method
SAE	serious adverse event
SAP	Statistical Analysis Plan
SC	subcutaneous(ly)
SD	standard deviation
SOC	System Organ Class
TCS	topical corticosteroids
TEAE	treatment-emergent adverse event
UAS7	Urticaria Activity Score/over 7 days
ULN	Upper limit of normal
UVA	Ultraviolet A
UVB	Ultraviolet B
VAS	Visual Analog Scale
WHO	World Health Organization
WI-NRS	Worst Itch Numeric Rating Scale

1 INTRODUCTION

1.1 Background

Chronic pruritus, defined as pruritus lasting for more than 6 weeks, is a common and often debilitating condition associated with a wide range of diagnoses.[1] In chronic idiopathic urticaria (CIU), also called chronic spontaneous urticaria, chronic pruritus occurs in the context of recurrent hives that have no identifiable triggers.[2] Chronic pruritus is the defining feature of chronic idiopathic pruritus (CIP), which disproportionately affects the elderly.[3] Patients with lichen planus (LP) experience chronic pruritus along with polygonal, flat-topped, violaceous papules and plaques.[4] Lichenified plaques develop on accessible body areas in response to constant rubbing from intense chronic pruritus in lichen simplex chronicus (LSC).[5] Chronic pruritus affects up to 60-90% of patients with plaque psoriasis (PPs) who present with symmetrical, erythematous, silvery and scaly plaques commonly located on scalp, trunk, and extremities.[6, 7]

Chronic pruritus is estimated to occur in approximately 20% (lifetime prevalence) of the population.[1] Diagnoses associated with chronic pruritus are common diagnoses that affect a large number of patients. The prevalence of CIU is estimated at up to 1%[8], LP at 0.22 to 5%[9], LSC up to 12%[10] and psoriasis up to 4% in Western Countries[11]. CIP is estimated to occur in 11.5 to 41% in the elderly.[12] Chronic pruritus leads to lack of sleep, fatigue, diminished productivity, anxiety, depression and overall diminished quality of life.

Inflammatory cell infiltration and hyperkeratosis are common features seen in skin biopsies of patients with chronic pruritus. Histologic examination of skin biopsies from CIU patients demonstrates lymphocytes, eosinophils, neutrophils, basophils, mast cells (also increased in non-lesional skin), and activated macrophages.[13] In patients with CIP, lymphocytic infiltrates are seen in the absence of inflammatory skin lesions.[3] LP lesional biopsies show lysis of basal keratinocytes by $CD8^+$ lymphocytes and IL-31 expression.[14, 15] Epidermal hyperplasia, orthokeratosis, and hypergranulosis with lymphocytic perivascular infiltrates are common features of LSC.[5] Psoriatic skin biopsies characteristically show perivascular and dermal inflammatory cell infiltration, parakeratosis, suprapapillary thinning, spongiform pustules, microabscess, and edema of the dermal papillae.[16]

Chronic pruritus is treated with H1 non-sedating antihistamines as first line therapy. In non-responsive patients, sedating antihistamines such as hydroxyzine or doxepin, topical corticosteroid, and leukotriene receptor antagonists and topical calcineurin inhibitors may be tried. In refractory disease, immunomodulatory agents such as cyclosporin and phototherapy are used. Neuroactive medications such as gabapentin, anti-depressants, capsaicin, opioid agonists and antagonists are used in CIP with limited success. [17, 18, 19] Biologic therapy is available for the most severe patients with CIU (omalizumab) and psoriasis (adalimumab, etanercept, and infliximab,).[7, 20] Despite the availability of a large range of medications with variety of mechanisms of action, chronic pruritus remains a significant unmet medical need due to poor response to treatment or unacceptable side effects. Many patients with CIU, for example, remain symptomatic or are unwilling to tolerate or risk the adverse effects of cyclosporine (renal toxicity) and omalizumab (black box warning for omalizumab: anaphylaxis).

The primary objective of this study is to investigate the efficacy of KPL-716 in reducing pruritus in patients with chronic pruritic diseases experiencing moderate to severe pruritus. The secondary objectives are to investigate the impact of KPL-716 on sleep loss and quality of life. Clinical response [redacted] will be used to understand whether KPL-716 responsiveness is limited to a specific subset of patients with chronic pruritus.

1.2 Summary of Nonclinical Pharmacology

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

1.2.1 In Vivo

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

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

1.3 Study Rationale

KPL-716 is a first-in-class, fully-human monoclonal antibody against Oncostatin M Receptor beta (OSMRβ). OSMRβ is a cell surface receptor that heterodimerizes with IL-31 receptor alpha (IL-31Rα) to mediate signaling of IL-31. It also heterodimerizes with gp130 to mediate signaling of oncostatin (OSM). By targeting a single epitope [redacted], KPL-716 simultaneously inhibits signaling of IL-31 and OSM, two (2) cytokine pathways important in pruritus, inflammation, hyperkeratosis and fibrosis. KPL-716 does not inhibit signaling of OSM down the Leukemia Inhibitory Factor Receptor (LIFR) pathway, a pathway implicated in hematopoiesis and platelet synthesis.[21]

KPL-716 via its dual pathway mechanism is predicted to reduce pruritus in chronic pruritic diseases and potentially modulate many aspects of disease pathology related to inflammation, hyperkeratosis and fibrosis. A clinical effect on pruritus intensity is anticipated at therapeutic doses based on the Phase 1b study results (Protocol KPL-716-C001). The targeted nature of the KPL-716 mechanism of action is expected to offer safety advantages compared to immunosuppressive therapies as well as systemic and topical corticosteroids.

The role of IL-31 in pruritus is well established, as IL-31 receptor inhibition has been shown to decrease pruritus in subjects with atopic dermatitis.[22, 23] The published literature suggests that IL-31 plays a role in many chronic pruritic diseases. Serum IL-31 levels are elevated in CIU patients compared to healthy controls and IL-31 levels decrease upon successful treatment of CIU.[24] Similarly, serum IL-31 levels are increased in patients with psoriasis and levels decrease after UVB irradiation with treatment response.[25] IL-31 levels are also elevated in patients with LP although pruritus intensity does not appear to correlate with IL-31 levels in this disease.[15] Despite absence of a primary dermatologic process in CIP, histologic analysis of CIP skin demonstrates lymphocytic and, in many cases, eosinophilic infiltration, accompanied by increased IgE and peripheral blood eosinophilia pointing to T_H2 polarization as a potential source of IL-31.[3] Chronic scratching, disruption of epidermal barrier function, staphylococcal colonization and subsequent staphylococcal enterotoxin B production promote IL-31 production[26] and may ultimately contribute to the itch-scratch cycle that underlies many chronic pruritic diseases such as atopic dermatitis and LSC.

OSM, the other cytokine pathway inhibited by KPL-716, has been shown to play a role in inflammation, epidermal integrity and fibrosis, three (3) pathways important in many pruritic dermatologic disorders. OSM increases the production of IL-4Rα and IL-13Rα.[27, 28, 29, 30, 31, 32] OSM also increases IL-4 production and synergizes with IL-4 and IL-13 to upregulate downstream signaling events such as eotaxin production.[27, 29, 30, 31, 32, 33] Similarly, OSM synergizes with IL-17 and increases CCL2 and IL-6 production.[32] OSM impacts epidermal barrier function by modulating genes important in keratinocyte activation and differentiation.[27, 28] Finally, OSM levels are increased in fibrotic diseases and OSM over expression in animal models has been shown to result in fibrotic changes.[30, 34]

In a Phase 1b study (KPL-716-C001), KPL-716 demonstrated OSMRβ target engagement and an early signal of efficacy by reducing pruritus in subjects with atopic dermatitis. Please see IB. KPL-716 is therefore being investigated in this Phase 2 study for its efficacy in reducing pruritus in patients with a variety of chronic pruritic conditions (primary endpoint). The reduction in pruritus is anticipated to improve sleep and quality of life. Therefore, this study will investigate the impact of KPL-716 on sleep and quality of life (secondary endpoints).

This double-blind Phase 2 pilot study will utilize a washout design and enroll subjects with a physician-documented diagnosis of diseases characterized by chronic pruritus, including at this time CIU, CIP, LP, LSC, or PPs, of at least 6 months duration. The study will enroll subjects with moderate to severe pruritus, defined as WI-NRS ≥ 7 at the Screening Visit and a mean weekly WI-NRS ≥ 5 for the 2 consecutive weeks immediately prior to randomization. Given the early stage of KPL-716 development, subjects will be excluded if they have co-morbidities that would complicate interpretation of safety data such as infections, malignancies, and rheumatologic diseases.

Ultimately, the data from this pilot study will help establish the range of chronic pruritic diseases responsive to KPL-716, so that future larger studies may then be conducted for further assessment of the impact of KPL-716 on pruritus and other disease manifestations.

1.4 Benefit-risk Assessment

KPL-716 is anticipated to offer a therapeutic benefit to patients with chronic pruritic inflammatory skin diseases through its dual inhibition of IL-31 and OSM, two (2) cytokine pathways important in pruritus, inflammation, hyperkeratosis and fibrosis. In Part 1 of the first-in-human study of KPL-716 (KPL-716-C001), KPL-716 demonstrated OSMRß target engagement and an early signal of efficacy by reducing pruritus in subjects with atopic dermatitis. For a summary of clinical pharmacodynamic(s) (PD) data from Part 1 of KPL-716-C001, please see IB.
Intractable moderate to severe pruritus, as can be seen with CIU, CIP, LP, LSC and PPs, is debilitating and can have a significant impact on quality of life. KPL-716 is being tested in this pilot Phase 2 study for its potential efficacy in reducing pruritus in CIU, CIP, LP LSC, and PPs patients through inhibition of IL-31 signaling. A reduction in pruritus is anticipated to improve sleep and quality of life, as was seen in subjects with atopic dermatitis in the Phase 1b study. Given the potential impact of OSM on pathologic processes important in many of the diseases under study, the inhibition of OSM signaling by KPL-716 may also provide benefit in reducing disease severity. At a minimum, it is anticipated that subjects in this study would benefit from the assessment of their medical status and routine interactions with investigative dermatologists.

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

In Part 4 of KPL-716-C001 (repeated single-dose study), subjects with moderate to severe atopic dermatitis experiencing moderate to severe pruritus are being randomized 1:1 and administered KPL-716 360 mg or placebo SC once weekly for a total of 12 doses. To date, 30 subjects have been randomized in Part 4, 28 subjects have received at least 1 dose of study drug, 25 have received at least 5 doses, and 16 have completed the 12-dose treatment regimen. In this blinded study, KPL-716 continues to be well tolerated to date.

The available toxicology and prior human data support the dose level and duration of treatment in this study. No specific safety concerns are anticipated with inhibition of signaling through OSMRβ in subjects with chronic pruritic diseases as KPL-716 does not inhibit constitutive signaling of OSM down the LIFR pathway, a pathway implicated in hematopoiesis and platelet synthesis.[21] New and unknown adverse events may emerge in a new study as the drug is investigated under chronic use with prolonged exposure in a new disease population.

There may be some discomfort from collection of blood samples, [redacted] or subcutaneous study drug injections. Subcutaneous injections [redacted] can infrequently lead to skin irritation, local inflammation, secondary skin infection, as well as vasovagal reactions. The subjects will undergo supervised study procedures and will be closely monitored for adverse experiences during their participation in the study. Overall, the benefit-risk assessment supports further study in a clinical trial setting.

2 OBJECTIVES

2.1 Primary Objective

- To evaluate the efficacy of subcutaneous (SC) KPL-716 in reducing pruritus in subjects with chronic pruritus experiencing moderate to severe pruritus

2.2 Secondary Objectives

- To evaluate the effect of SC KPL-716 in improving sleep in subjects with chronic pruritus experiencing moderate to severe pruritus
- To evaluate the effect of SC KPL-716 in improving quality of life in subjects with chronic pruritus experiencing moderate to severe pruritus
- To evaluate the safety and tolerability of SC KPL-716 in subjects with chronic pruritus experiencing moderate to severe pruritus
- To evaluate the pharmacokinetics (PK) of SC KPL-716 in subjects with chronic pruritus experiencing moderate to severe pruritus
- To evaluate the immunogenicity of SC KPL-716 in subjects with chronic pruritus experiencing moderate to severe pruritus

3 ENDPOINTS

3.1 Primary Efficacy Endpoints

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

3.2 Secondary Efficacy Endpoints

Related to pruritus:

- Change and percent change from baseline in weekly average of WI-NRS over time
- Change and percent change from baseline in Pruritus Visual Analog Scale (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
- Change and percent change from baseline in weekly itch severity score, a component of Urticaria Activity Score 7 (UAS7) (CIU only)

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 Numerical Rating Scale (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

[redacted]

3.4 Safety Parameters

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

4 INVESTIGATIONAL PLAN

4.1 Study Design

This Phase 2 pilot study is comprised of multiple cohorts each for a different study population. Each cohort is an independent randomized, double-blind, placebo-controlled sub-study to investigate the efficacy, safety, tolerability, PK and immunogenicity of KPL-716 administered SC in reducing pruritus in diseases characterized by chronic pruritus. The following chronic pruritic diseases will be studied.

- Cohort 1: Chronic Idiopathic Urticaria (CIU)
- Cohort 2: Chronic Idiopathic Pruritus (CIP)
- Cohort 3: Lichen Planus (LP)
- Cohort 4: Lichen Simplex Chronicus (LSC)
- Cohort 5: Plaque Psoriasis (PPs)

Each cohort will be enrolled and analyzed independently.

Each cohort will enroll up to 26 subjects and contain three periods:

- Screening Period (Day-28 to Day-1, minimum 14 days and maximum 28 days)
- Treatment Period (Day 1 [Baseline] to Week 8)
- Follow-up Period (After week 8 to Week 18)

Allowable window for Week 1 is ± 1 day and from Week 2 to Week 18 visits is ±2 days.

In every cohort, a loading dose of KPL-716 at 720 mg SC (or matching placebo) will be followed by maintenance doses of 360 mg SC (or matching placebo) administered every week for 7 additional weekly doses in order to detect an early signal of efficacy on pruritus once exposures approach an expected steady state. In addition, the impact of KPL-716 on sleep and quality of life will be assessed. Furthermore, the impact of KPL-716 on urticaria in CIU (Cohort 1) will be investigated.

Each cohort will utilize a washout design in which concomitant therapies that could impact pruritus will be prohibited from a designated timepoint prior to dosing through the End of Study (EOS) Visit, thus removing the confounding effect of these therapies on the assessment of KPL-716 efficacy. Subjects who use a moisturizer cream/emollient will be instructed to use the same moisturizer cream/emollient at the same frequency throughout the study. Only subjects with CIU (Cohort 1) will be allowed to use H1 antihistamines at approved stable doses from 14 days prior to dosing to EOS Visit. The permitted H1 antihistamines for CIU will be outlined in the Pharmacy Manual. Should subjects in any cohort experience an exacerbation of symptoms that is significant enough to warrant intervention, they will be provided with H1 antihistamines and/or topical corticosteroids (TCS) as rescue medication. The permitted rescue medications for each cohort will be outlined in the Pharmacy Manual.

Accountability for rescue medications will be maintained by the sites. The date, time, and the number of antihistamine tablets will be recorded and the weight of TCS tubes will be measured at dispensation, at every visit, and upon return.

4.1.1 Screening Period

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

During the Screening Visit, subject's medical and surgical history will be reviewed including allergic history. Review of medical history will include the specific cohort disease history and history of co-morbidities. Prior and concomitant medications, therapies and procedures will be recorded. Subjects will be instructed on the required washout for specific excluded medications.

Vital signs and body weight will be measured, and subjects will undergo a full physical examination. Clinical laboratory tests and an ECG will be performed. Urine drug screen and pregnancy test (if applicable) will also be performed.

To be eligible for study participation, subjects must have moderate to severe pruritus, defined as WI-NRS ≥ 7 at the Screening Visit and a mean weekly WI-NRS ≥ 5 for each of the two consecutive weeks immediately prior to randomization. A minimum of 85% compliance with daily WI-NRS recording during the last 14 days of Screening Period prior to randomization is required for eligibility unless approved by the Sponsor.

At the Screening Visit, subjects will be asked to rate their pruritus severity (WI-NRS) in the previous 24 hours on a numerical rating scale. Subjects also will be instructed to record their daily rating of WI-NRS and two sleep parameters, difficulty falling asleep NRS and sleep quality NRS, from the beginning of screening to Day 1. The daily recordings (WI-NRS, difficulty falling asleep NRS, and sleep quality NRS) will continue throughout the study for eligible subjects that proceed to dosing.

Furthermore, subjects with CIU will also be instructed to complete on a daily basis the UAS7 questionnaire (on itch and hives severity) from the beginning of screening to Day 1. Daily completion of the UAS7 questionnaire will continue throughout the study for eligible CIU subjects that proceed to dosing.

Additional assessments at the Screening Visit include those related to pruritus (Pruritus VAS, and 5-D Pruritus), sleep (Sleep Loss VAS), dermatology life quality index (DLQI) and Itchy quality of life (ItchyQoL).

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

4.1.2 Treatment Period

The treatment period will last 8 weeks.

4.1.2.1 Pre-dose

Eligibility must be confirmed prior to dosing on Day 1.

Subjects will have the following procedures performed prior to dosing on Day 1:

- Review of medical and surgical history
- Review of prior and concomitant medications

- Review of adverse events
- Review of compliance with recording of daily WI-NRS
- Review of clinical laboratory results from the Screening Visit
- Full physical examination
- Vital Signs and weight
- ECG (if more than 30 days since screening ECG)
- Subjects will record their Pruritus VAS, Sleep Loss VAS and complete the 5-D Pruritus, DLQI and ItchyQoL questionnaires
- Collection of laboratory blood tests
- Collection of urine for urinalysis
- Pregnancy test (if applicable)
- [redacted]
- [redacted]

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

4.1.2.2 Randomization and Dosing

A loading dose of KPL-716 720 mg (2x maintenance dose) or matching placebo will be administered via two (2) SC injections within 30 minutes on Day 1 by the Investigator or qualified designee at the study sites.

All subsequent doses of KPL-716 (360 mg maintenance dose) or matching placebo will be administered by the Investigator or qualified designee at the study sites via a single SC injection.

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

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

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

- Physical examination
- Collection of safety blood and urine samples

- Urine pregnancy test (if applicable); a serum pregnancy test will be performed if the urine pregnancy test is positive
- [redacted]
- Completion of 5-D pruritus questionnaire
- Completion of quality of life questionnaire (DLQI and ItchyQoL)
- [redacted]

Subjects will be observed for 3 hours after completion of the loading dose, for 2 hours after the first 2 maintenance doses and for 1 hour after all subsequent doses. Vital signs will be measured every hour during the observation period. The post-dose observation period duration may be modified based on emerging safety and tolerability data.

Adverse events and concomitant medications will be collected throughout the study. Subjects will continue to complete their daily questionnaire on pruritus (WI-NRS) and sleep until the EOS Visit. CIU subjects will continue to complete their daily UAS7 questionnaire (on itch and hives severity) until the EOS Visit.

In case of study drug discontinuation, subjects will continue to follow the schedule of activities for each visit minus study drug administration. [redacted] In case of study drug interruption or missed dosing visits, subjects will resume the schedule of activities in accordance with their study day. Study drug will be discontinued if more than three consecutive doses are withheld or missed.

In case of early withdrawal from the entire study, subjects will complete an EOS Visit.

4.1.3 Follow-up Period

During the Follow-up Period, subjects will undergo vital signs measurement, review of concomitant medications, therapies and procedure, review of adverse events, and monitoring of compliance at every visit. Pruritus VAS, 5-D Pruritus, and Sleep Loss VAS will also be completed at every visit during the Follow Up Period. Physical examination, clinical laboratory blood tests, urinalysis, and quality of life assessment (DLQI and ItchyQoL), will be performed at designated visits. Subjects will continue to complete their daily questionnaire on pruritus and sleep throughout the Follow-up Period. CIU subjects will continue to complete their daily UAS7 questionnaire (on itch and hives severity) throughout the Follow-up Period.

The EOS Visit includes vital signs and weight, full physical examination, ECG, clinical laboratory blood tests, urinalysis, and urine pregnancy test (if applicable) as well as all efficacy assessments for pruritus, sleep, and quality of life. All subjects will complete an EOS Visit.

4.2 Duration of Study

The planned study duration per subject is approximately 20 to 22 weeks. This includes a maximum of 4 weeks for the Screening Period, 8 weeks for the Treatment Period, and a 10-week Follow-up Period. The minimum duration for the Screening Period will be 14 days.

4.3 Study Drug and Treatment

Study Drug: KPL-716 or matching placebo

Active Substance: Fully-human monoclonal antibody against OSMRβ

Strength and Route of Administration: KPL-716: 180 mg/mL solution [redacted]

A loading dose of KPL-716 (2x maintenance dose) or matching placebo will be administered via up to two (2) SC injections within 30 minutes on Day 1. Maintenance doses of KPL-716 or matching placebo will be administered via a single SC injection for the remainder of the Treatment Period. The planned loading and maintenance dose levels are currently 720 mg and 360 mg weekly, respectively.

4.4 Selection of Doses in the Study

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

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

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

The weekly SC dosing regimen is proposed to ensure subsequent doses are administered before a significant decline in blood concentrations has occurred so as to reach initial KPL-716 exposure levels similar to those achieved with 7.5 mg/kg IV as a single dose. A loading dose of 720 mg is administered in this Phase 2 pilot study in order to achieve blood concentrations that are likely to provide clinical benefit sooner in particular given the short treatment duration of this exploratory study. 720 mg was chosen for the loading dose since the peak concentration levels from this dose are anticipated to be less than those achieved by 7.5 mg/kg IV, which showed acceptable safety and tolerability in the single dose study. A loading dose that is twice maintenance is typical, in particular to minimize risk of dosing errors. Based on PK modeling, the expected C_{max} and C_{trough} from a loading dose of 720 mg SC followed by 7 weekly SC doses at 360 mg, the proposed regimen in this Phase 2 pilot study, are expected to be similar to those anticipated with 12 weekly doses of 360 mg SC, which has shown acceptable safety and tolerability to date in KPL-716-C001 Part 4.

The available pre-clinical toxicology data support the selection of the above doses. The multi-dose, 7-week, preclinical toxicology study in cynomolgus monkeys revealed no specific toxicities, and the highest administered dose (500 mg/kg IV) was identified as the NOAEL. In a chronic toxicology study, weekly administration of KPL-716 by IV bolus injection or SC at doses up to 200 mg/kg for 26 weeks (27 total doses) was well tolerated in cynomolgus monkeys. Based on these results under the conditions and duration of the study provided in the study report, the NOAEL was considered to be 200 mg/kg IV/SC, the highest dose tested. The number of doses (total of 8) and the dose levels (720 mg loading dose and 360 mg maintenance dose or 10 mg/kg and 5 mg/kg in a 72 kg adult, respectively) in this Phase 2a study fall well under the number of doses (total of 27) and the NOAEL (200 mg/kg) in the chronic toxicology study.

The available safety data support the selection of above dose levels. In the first-in-human study (KPL-716-C001), 50 healthy volunteers (Part 3) and 32 subjects with atopic dermatitis (Part 1) were exposed to single doses of KPL-716 or placebo IV or SC. There were no deaths, SAEs, or discontinuations due to AEs. There were no infusion reactions or injection site reactions. Drug-related or possibly related treatment-emergent AEs were infrequent. In Part 4 of KPL-716-C001 (repeated-single-dose study), subjects with moderate to severe atopic dermatitis experiencing moderate to severe pruritus are being randomized 1:1 and administered KPL-716 360 mg or placebo SC once weekly for a total of 12 doses. Based on PK modeling, steady state exposures should be achieved after approximately 5 doses of 360 mg SC. To date, 30 subjects have been randomized in Part 4, 28 have received at least 1 dose

of study drug, 25 have received 5 doses and 16 have completed the 12-dose treatment regimen. In this blinded Part 4 study, safety and tolerability have been acceptable to date. For summary of safety data from KPL-716-C001 Part 1 and Part 3, please see the IB. The 720 mg SC loading dose represents a modest incremental increase from the SC 360 mg dose. The anticipated C_{max} from a 720 mg SC loading dose is anticipated to be lower than that seen with 7.5 mg/kg in the Phase 1 study, which showed acceptable safety and tolerability in healthy volunteers when administered as a single IV dose.

4.5 Study Assessments

4.5.1 Efficacy Assessment

Efficacy in reduction of pruritus will be assessed via daily recording of WI-NRS as well as on-site assessment of Pruritus VAS and 5-D Pruritus. Improvement in sleep will be assessed via daily recording of two (2) NRS scales, one for difficulty falling asleep and the other for quality of sleep. Impact on sleep will also be assessed via on-site Sleep Loss VAS. Impact on quality of life will be assessed via on-site PROs: DLQI and ItchyQoL. Impact on pruritus and disease severity for subjects with CIU will be assessed via daily completion of UAS7 questionnaire. Efficacy assessments will be performed as per Schedule of Activities (Appendix 1).

[redacted]

4.5.2 Safety Assessments

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

4.5.3 PK Assessments

PK blood samples will be collected from all subjects at every visit from the baseline visit to EOS. PK samples will be collected pre-dose on dosing days.

[redacted]

4.6 Selection of Study Population

4.6.1 Inclusion Criteria

1. Male or female, aged 18 to 75 years, inclusive, at the time of consent.

2. Has a physician-documented diagnosis of the specified chronic pruritic disease. Duration of disease must be at least 6 months. The study dermatologist or the study allergist/immunologist confirms the diagnosis of the specified chronic pruritic disease. The duration of disease (at least 6 months) can be documented as affirmed by the subject.

    - Pruritus associated with these diagnoses must be refractory to treatment with H1 antihistamines and must have been present for at least 6 weeks prior to Day 1
    - Subjects with CIU must have had pruritus and hives for at least 6 consecutive weeks prior to Day 1. In subjects with CIU, urticarial eruptions must typically last less than 24 hours

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

4. Sexually active female subjects must be:

    - postmenopausal, defined as at least 12 consecutive months post cessation of menses (without an alternative medical cause) and confirmed by a follicular stimulating hormone (FSH) test, or
    - surgically sterile following documented hysterectomy, bilateral salpingectomy, bilateral oophorectomy or
    - nonpregnant, nonlactating, and having agreed to use a highly effective method of contraception from the Screening Visit until 16 weeks after final study drug administration
        - Note: highly effective methods of contraception include:
            - hormonal contraceptives associated with inhibition of ovulation (stable dose for at least 4 weeks prior to first dose)
            - intrauterine device (IUD)
            - intrauterine system (IUS)
            - double barrier methods of contraception (barrier methods include male condom, female condom, cervical cap, diaphragm, contraceptive sponge) in conjunction with spermicide
            - tubal ligation
            - vasectomized male partner

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

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

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

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

4.6.2 Exclusion Criteria

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

    a. Systemic corticosteroids (IV/IM/oral): 8 weeks for IV/IM, 4 weeks for oral; Note: Intranasal corticosteroids, eye drops containing corticosteroids, and inhaled corticosteroids for stable medical conditions are allowed.

    b. Intralesional corticosteroids and intra-articular corticosteroids: 8 weeks

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

    d. Antihistamines: 1 week

        - Subjects with CIU (Cohort 1) may use H1 antihistamine at approved and stable doses. The acceptable H1 antihistamines will be defined in the Pharmacy Manual

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

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

    g. Cannabinoids: 2 weeks

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

    i. Janus Kinase (JAK) inhibitors: 3 months

    j. Dupilumab and ustekinumab: 6 months

    k. Any other marketed biologic: 3 months or until cell numbers return to normal in case of depleting antibodies such as rituximab

    l. Any investigational biologic drug: 6 months

m. Any investigational non-biologic drug: 3 months

n. Phototherapy involving Ultraviolet A (UVA), Ultraviolet B (UVB), or excimer: 4 weeks

o. Tanning salon use: 4 weeks

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

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

4. Has diagnosis of LP and is currently using medication known to cause lichenoid reaction (e.g., angiotensin converting enzyme inhibitors and/or beta blockers) unless timing of onset of lichenoid skin changes and initiation of medication do not suggest that lichenoid reaction was caused by the medication.

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

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

7. Has any inflammatory, pruritic, and/or fibrotic skin condition other than the diagnosis that defines the cohort unless approved by the Sponsor.

    a. Has urticarial vasculitis, urticaria pigmentosa, systemic mastocytosis, familial cold urticaria or hereditary or acquired angioedema due to C1 inhibitor deficiency.

    b. Has a clear cause of urticaria including but not limited to cold, heat, solar, pressure, and delayed pressure. Has contact urticaria, aquagenic urticaria or cholinergic urticaria.

    c. Has pustular psoriasis, erythrodermic/exfoliative psoriasis, drug-induced psoriasis, or psoriatic arthritis

    d. Has atopic dermatitis

8. Has significant severe xerosis that persists despite the regular use of an emollient unless approved by the Sponsor.

9. Has uncontrolled hyperthyroidism or hypothyroidism. Has insulin dependent diabetes or uncontrolled diabetes defined as hemoglobin A1c >7.5%

10. Has had cancer or lymphoproliferative disease within 5 years prior to Day 1

11. Has had any autoimmune disorder other those under investigation in this study

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

13. Has had systemic amyloidosis

14. Has had immune deficiency, or opportunistic infections

15. Has positive results for hepatitis B surface antigen (HbsAg)

16. Has positive results for hepatitis B anti-core antibody (anti-HBc) but negative results for anti-surface antibody (anti-HBs)

17. Has positive results for hepatitis C antibody

18. Has human immunodeficiency virus (HIV) infection or positive HIV serology

19. Has psychiatric illness other than stable mild to moderate anxiety and/or depression unless approved by the Sponsor

20. Has been hospitalized for a psychiatric illness

21. Has laboratory abnormalities that fall outside the windows below at the Screening Visit:

    a. Alanine aminotransferase > 1.5 x Upper limit of normal (ULN)
    b. Aspartate aminotransferase > 1.5 x ULN
    c. Gamma-glutamyl transferase > 1.5 x ULN
    d. Blood bilirubin > 1.25 x ULN
    e. Hemoglobin more than 1g/dL below the lower limit of normal for sex per the laboratory in which screening lab is performed.
    f. Platelet count <120,000/ µl
    g. Creatinine > 1.25 x ULN

22. Has a body mass index (BMI) of <16 kg/m2 or >38 kg/m2

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

24. Has been hospitalized within 12 weeks prior to Day 1

25. Has had major surgery within 12 weeks prior to Day 1 or has a major surgery planned during the study

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

27. Has any medical (heart, lung, kidney, liver, metabolic) or psychiatric condition which, in the opinion of the Investigator or the Sponsor, may place the subject at increased risk as a result of study participation, interfere with study participation or study

assessments, affect compliance with study requirements, or complicate interpretation of study results.

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

29. Has previously taken part in or withdrawn from this study or has previously received the study drug. Subjects may be rescreened if they have failed the Screening Period.

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

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

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

33. Has received blood products within 8 weeks prior to Day 1

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

4.7 Subject Number and Identification

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

Once a subject qualifies for randomization, a unique treatment code will be obtained from a designated center via the interactive web response system (IWRS), which will assign the treatment for the subject. The randomization number will be kept on-file at the study sites and included in the electronic Case Report Form (e-CRF).

4.8 Subject Withdrawal and Replacement

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

- Adverse event
- Life threatening or other unacceptable toxicity
- Subject requires use of a prohibited concomitant medication or therapy
- General or specific changes in the subject's condition unacceptable for further treatment within the study parameters, in the Investigator's opinion

- Severe noncompliance
- Lost to follow-up (Subjects will be defined as lost to follow up if they have not responded to 3 phone calls and one certified letter)
- A decision to modify or discontinue development of the drug

In case of study drug discontinuation, subjects will continue to follow the schedule of activities for each visit minus dosing. [redacted] In case of study drug interruption or missed dosing visits, subjects will resume the schedule of activities in accordance with their study day. Study drug will be permanently discontinued if more than three consecutive doses are withheld or missed.

If a subject withdraws from the entire study, the subject must complete the EOS Visit.

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

4.9 Study Termination or Temporary Suspension

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

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

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

5 STUDY TREATMENTS

5.1 Description, Storage, Packaging, and Labeling

The study drug will be supplied by the Sponsor. Study drug labeling will contain a batch/lot number and unique med ID number and be in compliance with applicable, local and national regulations. Study drug refers to KPL-716 and the matching placebo.

- Active Ingredient: KPL-716
- Strength [redacted] and Route of Administration: 180 mg/mL solution [redacted]

[redacted]

[redacted]

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

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

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

5.2 Study Treatment Administration

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

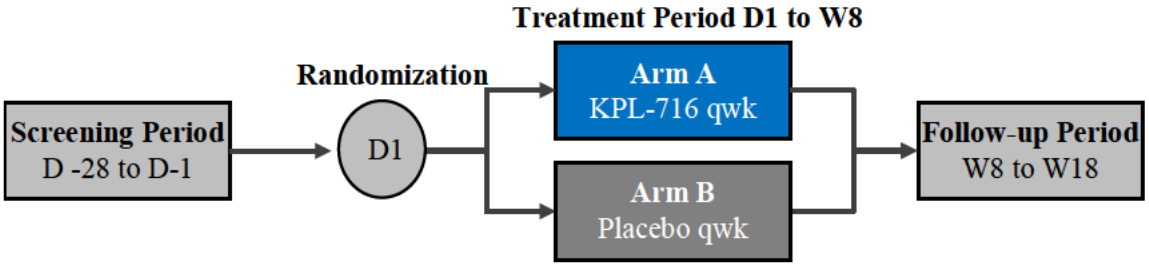
A loading dose of KPL-716 (2x maintenance dose) or matching placebo will be administered via up to two (2) SC injections within 30 minutes on Day 1 by the Investigator or designee at the study sites. All subsequent doses of KPL-716 (maintenance dose) or matching placebo will be administered by the Investigator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

5.3 Randomization

All subjects who are eligible for study participation will be randomized prior to study drug administration. Eligible subjects will be randomized to receive KPL-716 or placebo (Figure 2). The first 12 subjects of each cohort will be randomized to the KPL-716 and placebo arms in a 3:1 randomization ratio. The rest of the 14 subjects will be randomized in a 1:1 ratio. The randomization will be based on a computer-generated treatment randomization schedule prepared before the study by the Sponsor or designee.

An Interactive Web Response System (IWRS) will issue a unique treatment code to each subject, which will assign the treatment for the subject. Prior to each dosing, medical ID number of the vial to be administered will be obtained from (IWRS) based on the computer-generated treatment randomization schedule. The study drug will be prepared and administered according to instructions in the Pharmacy Manual.

Figure 2 Treatment Assignment Design Diagram



5.4 Blinding

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

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

5.5 Study Treatment Compliance

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

- All doses will be administered under the supervision of the Investigator or an authorized designee.
- At each dosing occasion, accountability of study drug will be performed.

5.6 Study Drug Accountability

The accurate record of the medical ID number of the study drug administered will be maintained including the exact volume and the date and time of dispensing. This study drug accountability record will be available for inspection at any time by an unblinded study monitor. At the completion of the study, the original drug accountability record will be available for review by the Sponsor upon request.

Used vials and containers will be destroyed upon satisfactory completion of the treatment compliance and study drug accountability procedures. Any unused unit doses will be retained until completion of the study or until permission to destroy has been received by the Sponsor.

At the completion of the study, unused study drug remaining at the sites (if applicable) will be returned to the Sponsor or designee or disposed of by study sites with drug destruction standard operating procedures and written Sponsor approval.

For further details refer to the Pharmacy Manual.

6 CONCOMITANT THERAPIES AND OTHER RESTRICTIONS

6.1 Concomitant Medications

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

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

b. Intralesional corticosteroids and intra-articular corticosteroids

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

d. Antihistamines

- Subjects with CIU (Cohort 1) may use H1 antihistamine at approved and stable doses. The acceptable H1 antihistamines will be defined in the Pharmacy Manual

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

f. Neuroactive drugs such as gabapentin and pregabalin

g. Cannabinoids

h. Opioid antagonists or agonists

i. Janus Kinase (JAK) inhibitors

j. Dupilumab and ustekinumab

k. Any other marketed biologic

l. Any investigational biologic drug

m. Any investigational non-biologic drug

n. Phototherapy involving UVA, UVB, or excimer

o. Tanning salon use

Topical corticosteroids and antihistamines may be provided in consultation with the Sponsor as rescue medications for an exacerbation of symptoms that is significant enough to warrant intervention.

For further details refer to the Pharmacy Manual.

6.2 Blood Donation

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

6.3 Contraception

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

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

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

7 STUDY ASSESSMENTS AND PROCEDURES

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

7.1 Pharmacokinetic Assessments

7.1.1 Pharmacokinetic Blood Sample Collection and Processing

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

[redacted]

7.3 Clinical Response Assessments

Clinical response assessments will be conducted at times specified in Appendix 1. Pruritus will be assessed using daily recording of WI-NRS as well as on-site recording of Pruritus VAS and 5-D Pruritus. Sleep will be assessed using daily recording of difficulty falling asleep NRS and sleep quality NRS as well as on-site recording of Sleep Loss VAS. Quality of life will be followed via DLQI and ItchyQoL. For CIU patients only, disease severity will be evaluated using the UAS7. Biomarkers will be assessed in the blood and the skin to understand the mechanism of clinical response to KPL-716.

7.3.1 Daily NRS Tool

The Daily NRS Tool provided in Appendix 4 contains three numerical rating scales to assess subjects' pruritus and sleep on a daily basis. The Daily NRS tool will be used from the Screening Visit through the EOS Visit (Week 18). Please see sections 7.3.1.1, 7.3.1.2 and 7.3.1.3.

7.3.1.1 Worst Itch Numerical Rating Scale

Subjects will be asked to assign a numerical score to the intensity of their most severe (worst) pruritus in the past 24 hours 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 the Screening Visit through the EOS Visit (Week 18). The Worst-Itch NRS is provided in the Daily NRS Tool Appendix 4.

7.3.1.2 Difficulty falling asleep Numerical Rating Scale

Subjects will be asked to assign a numerical score to the intensity of their difficulty falling asleep last night due to itch using a scale from 0 to 10, with 0 indicating not difficult at all

and 10 indicating extremely difficult. This NRS will be used to assess subjects' level of difficulty falling asleep from the Screening Visit through EOS Visit (Week 18). The difficulty falling asleep NRS is provided in the Daily NRS Tool Appendix 4.

7.3.1.3 Quality of Sleep Numerical Rating Scale

Subjects will be asked to assign a numerical score to the quality of their sleep in the previous night using a scale from 0 to 10, with 0 indicating best possible sleep and 10 indicating worst possible sleep. This NRS tool will be used to assess subjects' quality of sleep from the Screening Visit through the EOS Visit (Week 18). The sleep quality NRS is provided in the Daily NRS Tool Appendix 4.

7.3.2 Pruritus Visual Analog Scale (Pruritus VAS)

Subjects will be asked to place a line perpendicular to the VAS line at the point that represents the intensity of their average pruritus experienced over the previous three days using a scale from 0 to 10, with 0 indicating no pruritus and 10 indication the worst imaginable pruritus.[35] The Pruritus VAS is administered at every visit.

7.3.3 Sleep loss Visual Analog Scale (Sleep Loss VAS)

Subjects will be asked to place a line perpendicular to the VAS line at the point that represents the intensity of their average sleeplessness experienced over the previous three nights using a scale from 0 to 10, with 0 indicating no sleeplessness and 10 indicating the worst imaginable sleeplessness .[35] The Sleep Loss VAS is administered at every visit.

7.3.4 Weekly Urticaria Activity Score (UAS7)

The UAS is a daily self-assessment tool that evaluates the number of wheals and the intensity of subject's pruritus. It is graded from 0 to 3 for each parameter and is summed over seven consecutive days to obtain the UAS7 Score with a maximum score of 42. The greater the severity of the disease the higher the score. The UAS7 tool will be completed only by subjects in the CIU Cohort. The tool will be used from the Screening Visit through the EOS Visit (Week 18).[36]

7.3.5 5-D Pruritus Scale

The 5-D Pruritus Scale evaluates pruritus in five domains: duration, degree, direction, disability and distribution. Duration, degree and direction each consist of one item. The disability domain contains four items and the distribution domain includes 16 items. The first four domains are measured on a five-point Likert scale. The scores from each domain are added together to obtain a total 5-D score ranging from 5 (no pruritus) and 25 (most severe pruritus).[37] The 5-D Pruritus Scale is administered every two (2) visits.

7.3.6 Dermatology Life Quality Index

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

meaning no effect on quality of life and 30 meaning extremely large effect.[38] DLQI will be administered at designated visits.

7.3.7 ItchyQoL questionnaire

The ItchyQoL tool focuses on impact of pruritus on daily activities and on the level of psychological stress. It contains 22 items. The frequency items are scored using a 5-point Likert scale ranging from "never" to "all the time". The bother items are scored from 1 (not bothered) to 5 (severely bothered). The recall period in ItchyQoL is the past week. There is a total score and three subscale scores: Symptom subscale, Functional subscale and Emotional subscale.[39] ItchyQoL will be administered at designated visits.

[redacted]

7.5 Safety and Tolerability Assessments

7.5.1 Adverse Events

The investigator is responsible for collecting all AEs that are observed or reported during the study from the time the subject signs the ICF through the EOS Visit (Week 18), regardless of their relationship to study drug or their clinical significance.

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

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

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

The condition of subjects will be monitored from time of signing the ICF through the EOS Visit (Week 18). In addition, subjects will be observed for any signs or symptoms and asked about their condition by open questioning, such as "How have you been feeling since you were last asked?", at every study visit from the Screening Visit through the EOS Visit (Week 18).

All non-serious AEs, whether volunteered, elicited, or noted on the physical examination, and serious adverse events (SAEs) will be recorded from the Screening Visit (signing the ICF) through the EOS Visit (Week 18). The AE information collected during the period from the Screening Visit until study drug administration on Day 1 is intended only for establishing a baseline status for subjects and for recording any screening procedure-related AEs. The nature, time of onset, duration, and severity of all AEs, both serious and non-serious, will be documented, together with an Investigator's opinion of the relationship to study drug administration.

Identification and reporting of injection site reactions (ISRs) will be performed in the context of safety surveillance for Adverse Events as outlined above. Instructions on recording and reporting of ISRs will be provided to study sites through the Study Manual.

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

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

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

- Not Related: when the AE is definitely caused by the subject's underlying clinical state, or the study procedure/conditions
- Unlikely Related: when the temporal association between the AE and the drug is such that the drug is not likely to have any reasonable association with the AE

- Possibly Related: when the AE follows a reasonable temporal sequence from the time of drug administration but could have been produced by the subject's clinical state or the study procedures/conditions
- Related: when the AE follows a reasonable temporal sequence from administration of the drug, abates upon discontinuation of the drug, follows a known or hypothesized cause-effect relationship, and (if appropriate) reappears when the drug is reintroduced

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

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

Adverse Drug Reactions

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

Serious Adverse Events

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

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

- results in persistent or significant disability/incapacity. Disability is defined as a substantial disruption of a person's ability to conduct normal life functions. An AE is incapacitating or disabling if it results in a substantial and/or permanent disruption of the subject's ability to carry out normal life functions
- is a congenital anomaly/birth defect
- is an important medical event

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

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

Serious Adverse Event Reporting

Investigator Reporting Responsibilities to the Sponsor

SAEs due to any cause, whether or not related to the study drug, must be reported to the Sponsor or designee within 24 hours of occurrence or when the Investigator becomes aware of the event. Report SAEs by fax, email, or telephone call to:

Zamaneh Mikhak, MD
Senior Director, Clinical Research and Development
Kiniksa Pharmaceuticals Corp.
100 Hayden Avenue
Lexington, MA. 02421
Tel: 781-430-8549
Tel (after hours): 781-690-7633
Email: zmikhak@kiniksa.com

If the Investigator reports a SAE by telephone, then a completed SAE report form must follow within 1 business day and is to include a full description of the event and sequelae in the format detailed in the SAE reporting form.

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

Pregnancy

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

Female subjects of childbearing potential must therefore agree to use a highly effective and protocol approved contraceptive method (Section 6.3) for the duration of the study and until

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

Male subjects who have a female partner of childbearing potential must agree to use a highly effective and protocol approved contraceptive method (Section 6.3) for the duration of the study and until 16 weeks after last study drug administration under this protocol.

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

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

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

Investigator Reporting Responsibilities to IRB

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

Sponsor Reporting Responsibilities to Participating Investigators

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

7.5.2 Clinical Laboratory Evaluations

Blood and urine samples will be collected for clinical laboratory evaluations (including clinical chemistry, hematology, urinalysis, and serology) at the time points specified in Appendix 2.

At the Screening Visit and at any time during the study at the discretion of the Investigator and in consultation with the Sponsor, if needed, subjects will be asked to provide urine samples for a drugs abuse screening.

For all female subjects of childbearing potential, the serum pregnancy test will be performed at the Screening Visit and the urine pregnancy test will be performed at the designated

timepoints in Appendix 1. A serum pregnancy test will be performed if urine pregnancy is positive.

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

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

7.5.3 Vital Signs

Supine blood pressure (systolic and diastolic), pulse rate, respiratory rate, and body temperature will be assessed at every visit from the Screening Visit through the EOS Visit (Week 18) as outlined in Appendix 1. Subjects must be supine for at least 5 minutes before blood pressure and pulse rate measurements.

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

7.5.4 12-Lead Electrocardiogram

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

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

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

- QT interval corrected for heart rate using Fridericia's method (QTcF) interval >450 ms in men and >470 ms in women
- QTcF change from the baseline (pre-dose) is > 60 msec

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

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

7.5.5 Physical Examination

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

A full physical examination includes head/neck/thyroid, eyes/ears/nose/throat (HEENT), lymph nodes, skin, respiratory, cardiovascular, gastrointestinal, musculoskeletal, and

neurological exams. Breast, anorectal, and genital examinations will be performed only if medically indicated.

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

7.6 Committees

7.6.1 Safety Review Committee (SRC)

During KPL-716-C202, periodic reviews of safety and tolerability data will be conducted by a safety data review committee consisting of Investigators from active sites and a Sponsor physician representative. In addition, the Sponsor will review internally emerging safety and tolerability data periodically.

8 SAMPLE SIZE AND DATA ANALYSES

8.1 Statistical Methods

All statistical analyses will be performed using Statistical Analysis Software (SAS®) Version 9.4 or later. All clinical study data will be presented in subject data listings. Descriptive statistics will be presented for all endpoints and will include number of subjects (n), mean, standard deviation (SD), first quartile (Q1), median, third quartile (Q3), minimum and maximum for continuous variables, and frequency and percentage for categorical and ordinal variables. Unless otherwise specified, all tests will be two-tailed using pre-specified levels of significance. Statistical analyses of efficacy endpoints will be conducted separately for each cohort. Details will be specified in the Statistical Analysis Plan (SAP).

8.2 Handling of Dropouts and Missing Data

Criteria for removal of subjects from therapy or assessments are explained in Section 4.8. To the extent possible, attempts will be made to minimize the amount of missing data through measures planned in the study conduct. Details for handling missing values will be specified in the SAP.

8.3 Multiple Comparisons/Multiplicity

No Multiplicity adjustment is planned.

8.4 Determination of Sample Size

This is a double-blind study. Each cohort will be independently analyzed. A total of approximately 26 subjects will be randomized in each cohort. The first 12 subjects will be randomized to the KPL-716 and the placebo arms in a 3:1 randomization ratio. The rest of the 14 subjects will be randomized in a 1:1 randomization ratio. There will be approximately 16 subjects and 10 subjects randomized to the KPL-716 arm and the placebo arm respectively. Based on a two-sample t-test for the primary efficacy endpoint, change from baseline in weekly average of WI-NRS at Week 8, assumed mean changes of 4 for the KPL-716 arm and 1.5 for the placebo arm, a total sample size of 26 subjects per cohort will provide about 80% power to detect a 2.5-point mean difference with a standard deviation of 2.8, given a two-sided alpha of 0.2. Given the exploratory nature of this pilot study, the precision attained with the above cohort samples size is acceptable for early signal of efficacy assessments.

8.5 Analysis Populations

8.5.1 Modified Intent-to-Treat Analysis Set

All randomized subjects who receive at least one (1) dose of KPL-716 or placebo and have at least one (1) post-baseline efficacy assessment in the double-blind Treatment Period will be included in the modified intent-to-treat (mITT) analysis set. Efficacy analyses will be based on the mITT analysis sets. All mITT analyses will be based on each subject's randomized treatment assignment.

8.5.2 Safety Analysis Set

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

8.5.3 Per Protocol Analysis Set

All mITT subjects who have no protocol deviations that may potentially bias statistical analyses of the study will be included in the PP set. Protocol deviations that may potentially bias statistical analyses will be defined in the SAP before database lock.

8.5.4 Pharmacokinetic Analysis Sets

Subjects who received KPL-716 and who had at least one (1) PK sample will be included in the PK population.

8.6 Efficacy Analyses

Efficacy endpoints are defined in Section 3. All efficacy analyses for each disease cohort will be done separately based on the mITT analysis set. The analyses of primary and selected secondary efficacy endpoints will be repeated using the PP set to assess the sensitivity of the results to deviations of the protocol that could potentially bias the analysis. All efficacy data will be listed by subject. Missing data will be imputed using the last observation carried forward (LOCF) method. The corresponding p-value and 80% CI for the treatment mean difference will be displayed. Sensitivity analyses will be conducted. Details for the analysis will be provided in the SAP.

8.6.1 Primary Efficacy Endpoint Analyses

The primary efficacy endpoint, the change from baseline in weekly average WI-NRS score at Week 8, will be analyzed using ANCOVA. The model will include treatment as the independent variable and baseline WI-NRS as the covariate. In addition, randomization ratio, and gender might be considered as covariates. Details for the modeling will be specified in the SAP.

8.6.2 Key Secondary Endpoint Analyses

For continuous secondary endpoints, the same ANCOVA models as primary endpoint will be used.

For categorical endpoints, frequency and percentage will be presented. Proportions of responders with 80% CI will be summarized and fisher exact tests will be conducted.

[redacted]

8.7 Safety Analyses

All safety analyses will be conducted based on the Safety Analysis Set. All safety data will be listed by subject. Details for the analysis of safety data will be provided in the SAP.

8.7.1 Extent of Exposure

Statistical quantity of study drug administered will be summarized for each cohort. Number of subjects requiring dose interruption and treatment discontinuation with corresponding reasons will be summarized as well.

8.7.2 Adverse Events

All AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) dictionary. Any AEs not present before exposure to study drug or any event already present that worsens in either intensity or frequency after exposure to study drug are considered TEAEs. The number and percentage of subjects reporting TEAEs will be summarized by MedDRA System Organ Class (SOC) and preferred term (PT), by severity, and by relationship to study treatment. The number and percentage of subjects with SAEs, and the number and percentage of subjects with AEs leading to treatment discontinuation will also be summarized by MedDRA system organ class and preferred term.

8.7.3 Clinical and Laboratory Events and Analyses

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

8.7.4 ECG Analyses

For repeated performance of 12-lead ECG, average values will be taken. Descriptive statistics of actual values and changes from baseline over time will be summarized by ECG parameter. For ECG overall interpretation of normal and abnormal, shift tables from baseline to each post baseline time points and worst post baseline will be presented.

8.7.5 Vital Signs

Vital signs will be summarized using descriptive statistics of actual values and changes from baseline over time.

8.7.6 Physical Examination

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

8.7.7 Concomitant Medications

Concomitant medications will be coded using World Health Organization (WHO) Drug Dictionary. Frequencies and percentages of subjects using each concomitant medication will

be presented. All medication use will be listed regardless of the timing of the start of the medication.

8.8 Pharmacokinetic Analyses

Descriptive statistics will be calculated for serum concentrations over time of KPL-716 by visit for each cohort. Individual listings of serum concentrations will be provided. The effect of serum KPL-716 antibodies on PK parameters and KPL-716 concentrations may also be evaluated as appropriate. Pharmacokinetic parameter estimation using PK related approach will be described in a separate PK report.

[redacted]

8.11 Interim Analyses

Unblinded efficacy data endpoint review and unblinded interim analyses may be performed by the Sponsor for individual cohorts while enrollment is ongoing; one possible unblinded interim analysis for a given cohort may be conducted, for example, when approximately 12 subjects have been randomized in the cohort and treated for at least 8 weeks. The purpose of the interim analysis is to assess for potential early signals of efficacy to inform updates of the clinical development plan. The interim analysis will be performed by an unblinded independent biostatistician; unblinded results and anonymized subject data will be communicated to select Sponsor members not involved with the conduct of the study. Investigators and subjects will remain blinded to treatment assignment until after database lock and completion of the clinical study report (CSR) as defined in the SAP. Details of the unblinded interim analysis plan will be specified in the SAP.

9 QUALITY CONTROL AND QUALITY ASSURANCE

9.1 Auditing

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

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

9.2 Monitoring

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

Monitoring to review study drug receipt, inventory, storage, documentation, and handling will be conducted by unblinded monitoring resource.

Specific details will be outlined in the Clinical Monitoring Plan.

10 DATA HANDLING AND RECORD KEEPING

10.1 Data Handling

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

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

10.2 Case Report Form

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

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

10.3 Records

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

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

11 ETHICAL AND REGULATORY CONSIDERATIONS

11.1 Ethics Committee or Institutional Review Board

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

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

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

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

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

11.2 Regulatory Considerations

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

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

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

11.3 Informed Consent

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

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

11.4 Subject Confidentiality

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

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

11.5 Protocol Amendments

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

12 ADMINISTRATIVE ASPECTS

12.1 Disclosure

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

12.2 Reports and Publications

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

12.3 Finances and Insurance

Financing and insurance will be addressed in a separate agreement.

13 REFERENCES

1. Mollanazar NK, Koch S, and Yosipovitch G. Epidemiology of chronic pruritus: where we have been and where are we going? Curr Derm Rep 2015
2. Greaves MW. Chronic urticaria. New England Journal of Medicine. 1995. Jun 29;332(26):1767-72.
3. Xu A, Tripathi S, Kau A, et al. Immune dysregulation underlies a subset of patients with chronic idiopathic pruritus. JAM Acad Dermatol. 2016; 74:1017-1020
4. Welz-Kubiak K, Reich A. Mediators of pruritus in Lichen Planus. Autoimmun Dis. 2013; 2013:1-4.
5. Lotti T, Buggiani G, Prignano F. Prurigo nodularis and lichen simplex chronicus. Derm Therapy 2008; 21:42-46
6. Szepietowski JC, Reich A. Pruritus in psoriasis: an update. Eur. J. Pain 2016; 20 (1): 41-46
7. Kim BW, Jerome D, Yeung J. Diagnosis and management of psoriasis. Canad. Fam. Physic. 2017; 63:278-285
8. Maurer M, Weller K, Bindslev-Jensen C, et al. Unmet clinical needs in chronic spontaneous urticaria. A GA2LEN task force report 1. Allergy. 2011 Mar;66(3):317-30.
9. Gorouhi F, Davari P, Fazel N. Cutaneous and mucosal lichen planus: a comprehensive review of clinical subtypes, risk factors, diagnosis, and prognosis. The Scientific World Journal 2014; 214: 1-22
10. Georgieva F. Current Epidemiology of lichen simplex chronicus. J of IMAB 2016; 22 (3):1221-1225
11. Parisi R, Simmons DP, Griffiths CE, et al. Global epidemiology of psoriasis: a systematic review of incidence and prevalence. J. Investig. Derm. 2013; 133 (2): 377-385
12. Weisshaar E, Dalgard F. Epidemiology of itch: adding to the burden of skin morbidity. Acta dermato-venereol. 2009 Jun 15;89(4):339-50.
13. Ying S, Kikuchi, Y, Meng Q. et al. Th1/Th2 cytokines and inflammatory cells in skin biopsy specimens from patients with chronic idiopathic urticaria: Comparison with the allergen-induced late-phase cutaneous reaction. JACI. 2002; 109:694-700
14. Weston G, Payette M. Update on lichen planus and its clinical variants. Int J Women's Derm. 2015; 140-149
15. Welz-Kubiak K, Kobuszewska A, Reich A. IL-31 is overexpressed in lichen planus but its level does not correlate with pruritus severity. J Immunol Res. 2015:2015
16. Kim BY, Choi JW, and Kim BR, et al. Histopathological findings associated with clinical types of psoriasis but not with corresponding lesional psoriasis severity index. Ann Dermatol. 2015; 27: 26-31.
17. Bernstein JA, Lang DM, Khan DA, et al. The diagnosis and management of acute and chronic urticaria: 2014 update. J All and Clin Immunol. 2014 May 1;133(5):1270-7.

18. Powell R, Leech SC, Till S, et al. BSACI guideline for the management of chronic urticaria and angioedema. Clinical & Experimental Allergy. 2015 Mar; 45(3):547-65

19. Yosipovitch G, Bernhard JD. Chronic pruritus. New England Journal of Medicine. 2013 Apr 25;368(17):1625-34.

20. Casale T. Biologics and biomarkers for asthma, urticaria, and nasal polyposis. JACI. 2017;139(5):1411-1421

21. Qadi AA, Taberlay PC, Phillips JL, et al. The leukemia inhibitory factor receptor gene is a direct target of RUNX1. J of Cellular Biochem. 2016; 117:49-58

22. Nemoto O, Furue M, Nakagawa H, et al. The first trial of CIM331, a humanized antihuman interleukin-31 receptor A antibody, in healthy volunteers and patients with atopic dermatitis to evaluate safety, tolerability and pharmacokinetics of a single dose in a randomized, double-blind, placebo-controlled study. Br J Dermatol. 2016;174(2):296-304.

23. Ruzicka T, Hanifin JM, Furue M, et al; XCIMA Study Group. Anti-Interleukin-31 Receptor A Antibody for Atopic Dermatitis. N Engl J Med. 2017;376(9):826-835.

24. Altricher S, Hawro T, Hanel K, et al. Successful omalizumab treatment in chronic spontaneous urticaria is associated with lowering of serum IL-31 levels. J Eur Acad Dermatol Venereol 2016;30:454-455

25. Narbutt I, Olejncizak D, Sobolewska-Sztychny,et al. Narrow band ultraviolet B irraditatin cause alteration in interleukin-31 serum level in psoriatric patients. Arch Dermatol Res. 2013;305:191-195

26. Sonkoly E, Muller A, Lauerma AI, et al. IL-31: A new link between T cells and pruritus in atopic skin inflammation. J Allergy Clin Immunol. 2006; 117 (2): 411-417

27. Gazel A, Rosdy M, Bertino B, et al. A characteristic subset of psoriasis-associated genes is induced by oncostatin-M in reconstituted epidermis. J Invest Dermatol. 2006;126(12):2647-57.

28. Boniface K, Diveu C, Morel F, et al. Oncostatin M secreted by skin infiltrating T lymphocytes is a potent keratinocyte activator involved in skin inflammation. J Immunol. 2007;178(7):4615-22.

29. Fritz DK, Kerr C, Fattouh R, et al. A mouse model of airway disease: oncostatin M-induced pulmonary eosinophilia, goblet cell hyperplasia, and airway hyperresponsiveness are STAT6 dependent, and interstitial pulmonary fibrosis is STAT6 independent. J Immunol. 2011;186(2):1107-18.

30. Mozaffarian A, Brewer AW, Trueblood ES, et al. Mechanisms of oncostatin M-induced pulmonary inflammation and fibrosis. J Immunol. 2008;181(10):7243-53.

31. Fritz DK, Kerr C, Botelho F, et al. Oncostatin M (OSM) primes IL-13- and IL-4-induced eotaxin responses in fibroblasts: regulation of the type-II IL-4 receptor chains IL-4Ralpha and IL-13Ralpha1. Exp Cell Res. 2009;315(20):3486-99.

32. Kwofie K, Scott M, Rodrigues R, et al. Regulation of IL-17A responses in human airway smooth muscle cells by Oncostatin M. Respir Res. 2015; 16:14.

33. Botelho FM, Rangel-Moreno J, Fritz D, et al. Pulmonary expression of oncostatin M (OSM) promotes inducible BALT formation independently of IL-6, despite a role for IL-6 in OSM-driven pulmonary inflammation. J Immunol. 2013;191(3):1453-64.

34. Wong S, Botelho FM1, Rodrigues RM1, et al. Oncostatin M overexpression induces matrix deposition, STAT3 activation, and SMAD1 Dysregulation in lungs of fibrosis-resistant BALB/c mice. Lab Invest. 2014;94(9):1-14.

35. Kunz B, Oranje AP, Labrèze L, et al. Clinical validation and guidelines for the SCORAD index: consensus report of the European Task Force on Atopic Dermatitis. Dermatology. 1997;195(1):10-9

36. Hollis K, Proctor C, McBride D, et al. Comparison of Urticaria Activity Score Over 7 Days (UAS7) Values Obtained from Once-Daily and Twice-Daily Versions; Results from the ASSURE-CSU Study. AM J Clin Dermatol. 2018 19:267-274.

37. Elman S, Hynan LS, Gabriel V, et al. The 5-D itch scale: a new measure of pruritus. The British Journal of Dermatology. 2010;162(3):587-593.

38. Finlay AY, Khan GK. Dermatology Life Quality Index (DLQI): a simple practical measure for routine clinical use. Clin Exp Dermatol. 1994; 19: 210-216.

39. Desai NS, Poindexter GB, Monthrope YM, et al. A pilot quality-of-life instrument for pruritus. J Am Acad Dermatol. 2008; 59(2):234-44.

14 APPENDICES

14.1 Appendix 1: Schedule of Activities

Table A Schedule of Activities

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**	**W14**	**W16**	**W18 (EOS)**
Day (D)	**D -28 to -1**	**D1**	**D8**	**D15**	**D22**	**D29**	**D36**	**D43**	**D50**	**D57**	**D71**	**D85**	**D99**	**D113**	**D127**
Study Procedures	Windows (D)	0	±1	±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
Vital signs[3]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Body weight, height, BMI[2]	X	X								X					X
ECG (12-lead)[3]	X	X								X					X
Adverse Events Monitoring	From the Screening Visit through EOS Visit (Week 18)														
Concomitant meds/therapies/procedures monitoring	From the Screening Visit through EOS Visit (Week 18)														

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**	**W14**	**W16**	**W18 (EOS)**
Day (D)	**D -28 to -1**	**D1**	**D8**	**D15**	**D22**	**D29**	**D36**	**D43**	**D50**	**D57**	**D71**	**D85**	**D99**	**D113**	**D127**
Study Procedures	Windows (D)	0	±1	±2	±2	±2	±2	±2	±2	±2	±2	±2	±2	±2	±2
Subject Compliance assessment	From the Screening Visit through EOS Visit (Week 18)														
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
Serology (HIV, HBV, HCV)	X														
Urine Drug Screen[5]	X														
Dosing															
Randomization		X													
Study drug administration[6]		X	X	X	X	X	X	X	X						
Study drug accountability		X	X	X	X	X	X	X	X						
Efficacy Measures															
Daily NRS Tool for assessment of pruritus and sleep	Completed daily from the Screening Visit through EOS Visit (Week 18)														
Pruritus VAS	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
5-D Itch Scale	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**	**W10**	**W12**	**W14**	**W16**	**W18 (EOS)**
Day (D)	**D -28 to -1**	**D1**	**D8**	**D15**	**D22**	**D29**	**D36**	**D43**	**D50**	**D57**	**D71**	**D85**	**D99**	**D113**	**D127**
Study Procedures	Windows (D)	0	±1	±2	±2	±2	±2	±2	±2	±2	±2	±2	±2	±2	±2
UAS7	Completed daily from the Screening Visit through EOS Visit (Week 18)														
ItchyQoL	X	X				X				X		X		X	X
DLQI	X	X				X				X		X		X	X
[redacted]		[redacted]		[redacted]		[redacted]		[redacted]		[redacted]		[redacted]		[redacted]	[redacted]
[redacted]		[redacted]								[redacted]					
PK		X	X	X	X	X	X	X	X	X	X	X	X	X	X
[redacted]		[redacted]		[redacted]		[redacted]				[redacted]		[redacted]		[redacted]	[redacted]

[redacted] BMI=body mass index; DLQI=Dermatology Life Quality Index; ECG=electrocardiogram; HBV=hepatitis B virus; HCV=hepatitis C virus; HIV=human immunodeficiency virus; ItchyQoL=Itchy Quality of Life; [redacted] PK=pharmacokinetic; UAS7=Urticaria Activity Score/over 7 days; VAS=Visual Analog Scale; WI-NRS=Worst itch numeric rating scale.

[1] At the Screening Visit and prior to dosing on Day 1, Week 8 and Week 18, a full physical examination will be performed including head/neck/thyroid, eyes/ears/nose/throat (EENT), skin, lymph nodes, respiratory, cardiovascular, gastrointestinal, musculoskeletal, and neurological exams. Breast, anorectal, and genital examinations will be performed only if medically indicated. At all other designated visits, an abbreviated physical examination will be performed including skin, cardiovascular, respiratory, and abdominal exams and as indicated based on subject's symptoms. A physical examination may be performed at any time if medically indicated per the Investigator's medical judgement.

[2] Height will be measured, and BMI will be calculated only at the Screening Visit.

[3] ECG and vital signs will be performed prior to blood draws, drug injections [redacted] ECG at Day 1 will be performed if it has been more than 30 days since screening ECG. Vital signs will be measured every hour during the observation period on dosing days.

[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 procedures will be performed prior to dosing.

14.2 Appendix 2: Clinical Laboratory Tests

Clinical chemistry:	**Hematology:**	**Urinalysis:**
Alanine aminotransferase	Hematocrit	Bilirubin
Albumin	Hemoglobin	Blood
Alkaline phosphatase	Mean corpuscular hemoglobin	Color and appearance
Aspartate aminotransferase	Mean corpuscular hemoglobin concentration	Glucose
Blood urea nitrogen	Mean cell volume	Ketones
Calcium	Platelet count	Leukocyte esterase
Carbon dioxide	Red blood cell (RBC) count	Nitrite
Chloride	RBC distribution width	pH
Cholesterol	White blood cell (WBC) count	Protein
Creatinine	WBC differential (total and percentage):	Specific gravity
Gamma-glutamyl transferase	Basophils	Urobilinogen
Glucose	Eosinophils	Microscopic examination (for cells, cellular debris, crystals and bacteria, completed only if abnormal findings upon macroscopic examination)
High-density lipoprotein	Lymphocytes	
Lactate dehydrogenase	Monocytes	
Low-density lipoprotein	Neutrophils	
Potassium	Prothrombin time	
Sodium	Partial thromboplastin time	
Total bilirubin	International normalized ratio	
Total protein	Fibrinogen	
Triglycerides	D-dimer (if abnormal fibrinogen levels)	
Uric acid		
Serology[a]:	**Drug screen[b]:**	**Other:**
Hepatitis B surface antigen	Must include at least the following:	Serum βhCG test[c]
Hepatitis B core antibody	Amphetamines/methamphetamines	Urine βhCG test[c]
Hepatitis B surface antibody	Cocaine (metabolite)	FSH
Hepatitis C virus antibody	Methadone	Total IgE
Human immunodeficiency antibodies (type 1 and 2)	Phencyclidine	
	Opiates	
	Opioids	

[a] Analyzed only at the Screening Visit

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

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

14.3 Appendix 3: Total Blood Volume

The following approximate blood volumes will be obtained from each subject.

	Volume per blood sample (mL)	Maximum number of blood samples	Approximate total amount of blood (mL)
Safety laboratory tests	15	9	135
Pregnancy test[a]	3	4	12
Serology	10	1	10
Pharmacokinetics	3	14	42
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
Total:		43	354

[a]Females only