Kiniksa Pharmaceuticals, Ltd.

STATISTICAL ANALYSIS PLAN (SAP)

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

Protocol Number: KPL-716-C202

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DOCUMENT HISTORY

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1.0	New	April 13, 2020

APPROVAL

Electronic approvals are manifested in the final page of this document.

CONTENTS

LIST OF TABLES

LIST OF ABBREVIATIONS

Abbreviation	Full Form
[redacted]	[redacted]
AE	Adverse event
ANCOVA	Analysis of covariance
ATC	Anatomical Therapeutic Chemical
BMI	Body mass index
CI	Confidence interval
CIU	Chronic Idiopathic Urticaria
CIP	Chronic Idiopathic Pruritus
CRO	Clinical Research Organization
CSR	Clinical Study Report
eCRF	Electronic case report form
EDC	Electronic data capture
EOT	End of treatment
EOS	End of study
DLQI	Dermatology Life Quality Index
LS	Least squares
MedDRA	Medical Dictionary for Regulatory Activities
mITT	Modified intent-to-treat
[redacted]	[redacted]
PK	Pharmacokinetic(s)
PP	Per protocol
PT	Preferred term
QoL	Quality of life
QT	Electrocardiographic interval from the beginning of the QRS complex to the end of the T wave
QTcF	QT interval corrected for heart rate using Fridericia's method
SAE	serious adverse experience/event
SAP	Statistical Analysis Plan
SD	Standard deviation

Abbreviation	Full Form
SE	Standard error
SOC	System organ class
TEAE	Treatment-emergent adverse event
UAS7	Urticaria Activity Score/over 7 days
WHO	World Health Organization
WHODRUG	World Health Organization Drug Dictionary
WI-NRS	Worst Itch Numeric Rating Scale

1. INTRODUCTION

The purpose of this Statistical Analysis Plan (SAP) is to describe statistical analysis methods and data reporting specifications for the preparation of the Clinical Study Report (CSR) and the programming outputs in the study.

The SAP is based on the protocol KPL-716-C202 dated 28 January 2019.

Per FDA request, the impact of COVID-19 on protocol deviations, efficacy and safety data should be documented in the statistical analysis plan. At the time of the finalization of this SAP, the overall sponsor assessment of the impact of COVID-19 to the integrity of efficacy and safety results appears to be limited and doesn't warrant specific mitigation measures in the SAP. More specifically:

All patients have completed week 7 visit dosing. This is the last dosing planned in the study. No doses were missed due to COVID-19. The primary efficacy endpoint of this study protocol is weekly average of worst itch NRS (WI-NRS) at week 8. This score can be entered by patients online, while at home, and therefore unlikely to be affected by COVID-19 restrictions on travel to clinical sites. In addition, other questionnaires which per protocol were filled out on-site, now are released to patients online and filled out at home. Taken together, the impact of COVID-19 restrictions on efficacy data (specifically LOCF analysis) is limited and there are no changes to the statistical analysis plan. Due to travel restrictions, some assessment such as physical evaluation etc. when done virtually may limit the ability to detect potential safety risks, however, apparent safety risks are not likely to be missed. The impact on safety remains to be clarified after final database lock, but not likely to affect the overall benefit-risk evaluation. Protocol deviations due to COVID-19 will be summarized in an additional category.

2. STUDY OBJECTIVES AND ENDPOINTS

2.1. Study Objectives

2.1.1. Primary objective(s)

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

2.1.2. Secondary objective(s)

- 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]

2.2. Study Endpoints

2.2.1. Primary endpoints

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

2.2.2. Secondary endpoints

Related to pruritus:

- Change and percent change from baseline in weekly average of WI-NRS over time
- Change and percent change from baseline in Pruritus Visual Analog Scale (VAS) over time
- Change and percent change from baseline in 5-D Pruritus total score over time
- Proportion of subjects achieving ≥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]

[redacted]

2.2.4. 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)
- Clinical laboratory test results

[redacted]

2.3. Overall Study Design

Study Design:

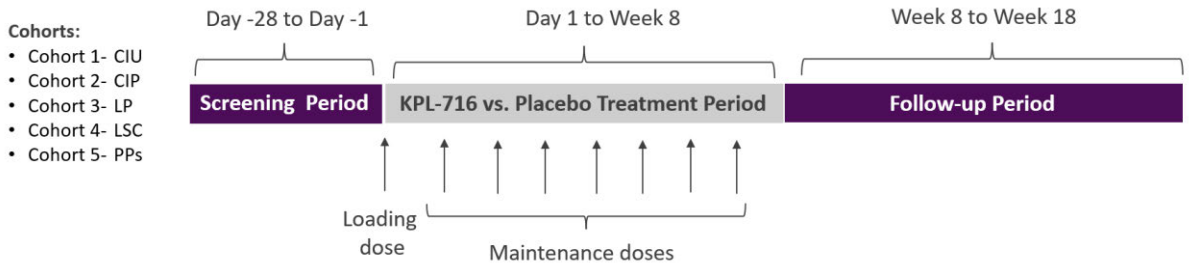
This Phase 2 pilot study is comprised of multiple cohorts each for a different study population. Each cohort is an independent randomized, double-blind, placebo-controlled sub-study to investigate the efficacy, safety, tolerability, PK and immunogenicity of KPL-716 administered SC in reducing pruritus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

- 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 up to 26 subjects and contain three periods:

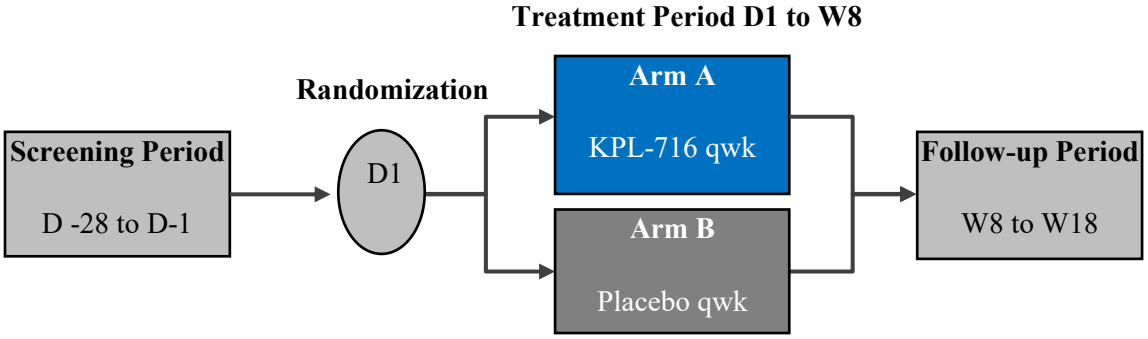
- Screening Period (Day-28 to Day-1, minimum 14 days and maximum 28 days)
- Treatment Period (Day 1 [Baseline] to Week 8)
- Follow-up Period (After Week 8 to Week 18)

Figure 1: Cohort Study Design Diagram



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.

Figure 2: Treatment Assignment Design Diagram



Efficacy assessments:

Efficacy in reduction of pruritus will be assessed via daily recording of WI-NRS as well as on-site assessment of Pruritus VAS and 5-D Pruritus. Improvement in sleep will be assessed via daily recording of two 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. Schedules of these efficacy assessments are specified in Section 17.1.

- WI-NRS score: Subjects will be asked daily 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. The Worst-Itch NRS is provided in the Daily NRS Tool Section 17.2.

- The sleep quality NRS: Subjects will be asked daily to assign a numerical score to the quality of their sleep in the previous night using a scale from 0 to 10, with 0 indicating best possible sleep and 10 indicating worst possible sleep. The sleep quality NRS is provided in the Daily NRS Tool (Section 17.2).

- The difficulty falling asleep NRS: Subjects will be asked daily 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. The difficulty falling asleep NRS is provided in the Daily NRS Tool (Section 17.2).

- 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 indicating the worst imaginable pruritus. Pruritus VAS scale is provided in Section 17.3.

- Sleep Loss VAS: Subjects will be asked to place a line perpendicular to the VAS line at the point that represents the intensity of their average sleeplessness experienced over the previous 3 nights using a scale from 0 to 10, with 0 indicating no sleeplessness and 10 indicating the worst imaginable sleeplessness at every visit. The scale of Sleep Loss VAS can be found in Section 17.3.

- The 5-D Pruritus Scale: This tool 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) (Elman 2010). The 5-D Pruritus Scale is administered every two (2) visits. The score of each of the 5 domains is obtained separately and summed together to get the total 5D-pruritus score.
  - For duration, degree and direction, use the number indicated below the response choice.
  - For disability, take the highest score for any of the 4 items (sleep, leisure/social, housework/errands, work/school).
  - For distribution, use the following scale:

    0-2 areas affected: score 1
    3-5 areas affected: score 2
    6-10 areas affected: score 3
    11-13 areas affected: score 4
    14 to 16 areas affected: score 5

  5-D Pruritus Scale is specified in Section 17.4.

- DLQI: This tool is a 10-question questionnaire that considers symptoms and feelings, daily activities, leisure, school, personal relationships, and treatment. Each question,

except question 7, is answered on a scale of 0 to 3 (0 for not at all, 1 for a little, 2 for a lot, and 3 for very much), taking into account the previous week. For question 7: Subjects will be asked "Over the last week, has your skin prevented you from working or studying?" If answered yes, score=3; If no, a second question will be asked: "Over the last week how much has your skin been a problem at work or studying?" If further answered a lot, score=2; if a little, score=1; if not at all or not relevant, score=0. The DLQI total score is defined as the sum of all 10-quesion scores with minimum of 0 meaning no effect on quality of life and 30 meaning extremely large effect. DLQI questionnaire is provided in Section 17.5.

- ItchyQoL: This tool focuses on impact of pruritus on daily activities and on the level of psychological stress. It contains 22 items. The frequency items are scored using a 5-point Likert scale ranging from "never" to "all the time". The bother items are scored from 1 (not bothered) to 5 (severely bothered). The recall period in ItchyQoL is the past week. The ItchyQoL total score is defined as the sum of all 22-items scores. The ItchyQoL symptom subscale score is calculated as the sum of question 1-6. The ItchyQoL functional subscale score is calculated as the sum of question 7-13. The ItchyQoL emotional subscale score is calculated as the sum of question 14-22. If there is only 1 item skipped in a subscale, the missing item value in the subscale will be imputed as the average of other non-missing item values. If 2 or more items are skipped in any given subscale, the subscale and total scores are set to missing. For other subscales that have less than 2 items skipped, those subscale scores need to be calculated. Total scores can be classified as little (0-30), mild (31-50), moderate (51-80), severe (81-110). ItchyQoL questionnaire is provided in Section 17.6 .

- The UAS7: Subjects will be asked daily to self-assess the number of wheals and the intensity of the subject's pruritus. It is graded from 0 to 3 for each parameter and is averaged over seven consecutive days to obtain the UAS7 Score with a maximum score of 6. The greater the severity of the disease the higher the score. The total score will be calculated from weekly average of subcomponents. The UAS7 tool will be completed only by subjects in the CIU Cohort. UAS7 questions are can found in Section 17.7 .

Safety Assessments:

Safety will be assessed by monitoring of AEs, measurements of vital signs, physical examination, ECG evaluation, and clinical laboratory tests specified in Section 0. Assessments are specified in Section 17.1 .

PK Assessment:

PK blood samples will be collected according to Section 17.1.

[redacted]

3. 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.

4. STUDY ANALYSIS SETS

4.1. Randomized Subjects

Randomized subjects will include all subjects whose date of randomization is not missing.

4.2. Modified Intent-to-Treat (mITT) 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. All mITT analyses will be based on each subject's randomized treatment assignment.

4.3. Per Protocol (PP) Analysis Set

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

4.4. 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.

4.5. PK Analysis Set

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

5. GENERAL ASPECTS FOR STATISTICAL ANALYSIS

5.1. General Methods

- All analyses and summaries will be produced using SAS® version 9.4 (or higher).

- Descriptive statistics in each cohort will be presented for all endpoints and will include number of subjects (n), mean, standard error (SE) and standard deviation (SD), first quartile (Q1), median, third quartile (Q3), minimum and maximum for continuous variables. Where specified, 80% and 95% Confidence Intervals (CI) of the mean will be calculated.
- For categorical variables (including binary variables), counts and percentages will be presented. Where specified, 95% 2-sided CI for proportions and 80% and 95% for odds ratios will be presented. CI for proportions will be calculated based on exact binomial distribution.
- For inferential statistical analyses in each cohort, the efficacy data will be analyzed and displayed by treatment group (KPL-716 and placebo) and visits. Unless otherwise specified, all tests will be two-tailed using pre-specified levels of significance.
- Subject listings in all randomized subjects, except the listing for screen failures will be provided for all efficacy and safety data. In general, the subject listings will be sorted by treatment group, subject number and assessment date (and time, if applicable).
- In general, 1 year will be defined as 365.25 days and 1 month will be defined as 30.4375 days (365.25 days/12 months).

5.2. Baseline Value and Change from Baseline

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

For daily collected efficacy endpoints (WI-NRS, difficulty falling asleep NRS, sleep quality NRS, UAS7), baseline is calculated as weekly average of non-missing scores from 7 days prior to Day 1, which is the day when the first SC injection is administered. For those daily collected efficacy endpoints, weekly average will be calculated based on every 7 days starting on the day after the start of injection (Day 1). Change and percent change from baseline in weekly averages will be summarized and compared between KPL-716 and placebo.

5.3. Study Day

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

It is calculated as follows:

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

Study Day = Event or Visit Date – 1st Treatment Date + 1

If the event date falls before the date of 1st treatment,

Study Day = Event or Visit Date – 1st Treatment Date

5.4. Analysis Visits

All data will be organized and analyzed according to the scheduled times as outlined in the protocol and by the visit denoted on the electronic case report form (eCRF), except for unscheduled and early termination (ET) visits. For unscheduled and early termination visits,

analysis visits will be assigned to closest visits based on event schedule table in Appendix 1. For multiple records on the same visit, CRF collected records will be used for the analysis. Summary by analysis visits will not include unscheduled analysis visits (after reassignment). However, unscheduled analysis visits will be included to define baseline, worst post baseline, or minimum, maximum post baseline and listings.

5.5. Time on study

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

5.6. Missing Data Handling

No imputations will be performed for missing data for safety endpoints, unless otherwise specified. Missing data handling for efficacy endpoints is specified in Section 8 .

5.7. Multiple Comparisons/Multiplicity

No Multiplicity adjustment is planned.

6. STUDY SUBJECTS

6.1. Subject Disposition

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

- Screened subjects
- Randomized subjects
- Safety analysis set
- mITT analysis set
    - Subjects who completed treatment and the primary reasons for treatment discontinuation
- Subjects who complete study and the primary reasons for study discontinuation

6.2. Protocol Deviations

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

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

Current ICH GCP guidelines list the important protocol deviations that must be listed in the clinical report. Important protocol deviations are a subset of protocol deviations that may significantly impact the completeness, accuracy, and/or reliability of key study data or that may significantly affect a subject's rights, safety, or well-being. These may include:

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

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

7. DEMOGRAPHICS AND BASELINE CHARACTERISTICS

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

7.1. Demographics

The following demographic variables will be summarized.

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

- Age (years)
- Sex (Male or Female)
- Race (White, Black or African American, Asian, American Indian or Alaska Native, Native Hawaiian or Other Pacific Islander, Other)
- Ethnicity (Hispanic or Latino, Not Hispanic or Latino)
- Height (cm)
- Weight (kg)
- BMI (kg/m^2) = Weight(kg)/[Height$(m)^2$]

7.2. Screening and Baseline Disease Characteristics

The following screening and baseline characteristics will be summarized.

- Years since diagnosis (calculated relative to randomization date)
- Screening visits and baseline efficacy endpoints

7.3. Medical History

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

7.4. Prior and Concomitant Medications

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

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

For analysis purpose, topical corticosteroids [TCS], oral antihistamines [OH], and/or systemic corticosteroids which were used to treat pruritus or study skin conditions on or after first dose date, are defined as rescue medications. Transient use of TCS and systemic corticosteroids for non-study indications, are not considered as rescue medications. For example, transient use of TCS for injection site reactions, transient intranasal, or inhaled systemic corticosteroids for non-study indications are not considered as rescue medications. Identification of rescue medications will be based on medical review. Number and percentage of subjects who used rescue medication will be summarized. Time to 1st use of any rescue medication, such as time to 1st use of TCS, or time to 1st use of oral antihistamine will be summarized descriptively as well.

Prior TCS use regardless of indications, systemic corticosteroid, OH will be summarized as well, of which identification will be based on medical review.

Prohibited medications include, but not limited to, Systemic corticosteroids (IV/IM/oral) , Intralesional corticosteroids and intra-articular corticosteroids, Topical treatments including but not limited to corticosteroids, calcineurin inhibitors, phosphodiesterase inhibitors, retinoids, calcipotriol, capsaicin, camphor, polidocanol or tars, Antihistamines, Immunomodulators (for example, cyclosporine, methotrexate, retinoids, azathioprine, mycophenolate, and thalidomide) , Neuroactive drugs such as gabapentin and pregabalin, Cannabinoids, Opioid antagonists or agonists, Janus Kinase (JAK) inhibitors, Dupilumab and ustekinumab, Any other marketed biologic, Any investigational biologic drug, Any investigational non-biologic drug, Phototherapy involving UVA, UVB, or excimer, Tanning salon use which are used after first dose date. 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. Subjects with CIU (Cohort 1) may use H1 antihistamine at approved and stable doses. For further details refer to the Pharmacy Manual. Identification of prohibited medications will be based on medical review. Number and percentage of subjects who used prohibited medications will be summarized as well if any data available.

7.5. Prior and concomitant procedures

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

8. EFFICACY ANALYSES

All efficacy analyses will be performed in the mITT analysis set. The analysis of primary efficacy endpoint will be repeated in the PP population. Analysis based on the mITT set will be the primary analysis and the analyses based on other analysis sets will be considered as the supportive analyses.

Line plots of LS Mean (SE) in percent change from baseline based on ANCOVA overtime will be presented and bar charts for responder analysis will be provided as well if needed for selected endpoints.

8.1. Analysis of primary efficacy endpoint

To minimize confounding impact on efficacy endpoints by rescue medications, efficacy assessments will be set to missing if collected in intervals:

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

Then, all missing post baseline values including those due to early discontinuation are imputed with last observation carried forward (LOCF) method up to the end of the period with last non-missing CRF collected data or cutoff date whichever is first. Then weekly average will be calculated and Analysis of Covariance (ANCOVA) model will be fitted with treatment as factor and corresponding baseline value as covariate. Least square (LS) mean and standard error (SE) with 80% and 95% confidence intervals (CI), and p-value for difference of the between-treatment comparison of treatment with placebo will be provided. LS means (SE) and 80% and 95% CIs will be reported for each treatment as well.

As sensitivity analysis of primary endpoint, observed data will be used for ANCOVA model as well. If 50% or more data are missing for weekly average calculation at post baseline, the week will be set to missing.

In addition, randomization ratio and sex may be considered for exploratory purpose.

8.2. Analyses of other continuous efficacy endpoints

Other continuous efficacy endpoints will be analyzed with ANCOVA models based on data with LOCF imputation and observed data as primary efficacy endpoints described above. The detailed statistical analyses are specified and marked as 'X' in Table 1.

Table 1: Statistical Analyses for Change and Percent Change Endpoints

		ANCOVA	
		LOCF	**as Observed**
Primary efficacy endpoint: • Percent change from baseline in weekly average WI-NRS score at Week 8		X	X
other continuous efficacy endpoints: Change and percent change from baseline endpoints			
Related to pruritus:	- in weekly average of WI-NRS Pruritus over time	X	X
	-in Visual Analog Scale (VAS) over time	X	X
	- in 5-D Pruritus total score and subscales over time	X	X
	- in weekly itch severity score (a component of UAS7 (CIU only)) over time	X	X
Related to sleep	- in Sleep Loss VAS over time	X	X
	- in weekly average of difficulty falling asleep NRS over time	X	X
	- in weekly average of sleep quality NRS over time	X	X
Related to quality of life	- in DLQI total score over time	X	X
	- in ItchyQoL total score over time	X	X
	- in ItchyQoL symptom subscale score over time	X	X
	- in ItchyQoL functional subscale score over time	X	X
	-in ItchyQoL emotional subscale score over time	X	X

8.3. Responder Analysis

For primary efficacy endpoint and other selected efficacy endpoints, binary responder analyses will be conducted based on data with LOCF imputation or observed data described above. Proportions of responders will be summarized, and 95% confidence intervals will be calculated based on binomial exact distribution. For statistical inference, odds ratios and corresponding 80% and 95% CIs will be calculated with Fisher exact tests.

Selected endpoints with responder analyses are listed in Table 2.

Table 2: Statistical Analyses for Responders

	Fisher exact test	
Responder endpoints by visits	LOCF	As observed
Related to pruritus: • Weekly average WI-NRS with a ≥4-point reduction	X	X
Related to sleep: • Difficulty falling asleep NRS with a ≥4-point reduction • Sleep quality NRS with a ≥4-point reduction	X X	X X
Related to quality of life: • DLQI total score with a ≥4-point reduction	X	X
[redacted]	[redacted]	[redacted]

8.4. Shift table for selected efficacy endpoints

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

[redacted]

9. SAFETY ANALYSES

Safety analyses will consist of data summaries for clinical and laboratory parameters, vital signs, and for adverse events (AEs). Adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA v21.1). Laboratory parameters will be summarized using descriptive statistics, by post-treatment shifts relative to baseline. Vital signs and ECG data will be summarized using descriptive statistics.

9.1. Treatment Exposure

Descriptive statistics will be provided for the following.

- Duration of treatment calculated as [min(last dose date+6, end of study date)-first dose date +1]/7
- Number and percentage of subjects will be tabulated by number of doses (1, 2, 3… and 8). The loading dose is comprised of two injections of maintenance dose.
- Treatment compliance calculated as (100 * number of study doses received/ total planned number of doses on treatment. For early discontinued subjects, total planned doses on treatment will be counted from first dose date to last dose date.

9.2. Adverse Events

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

9.2.1. Overall Summary of Adverse Events

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

- Overview of AEs, summarizing number (%) of subjects with any:
  - Any AEs
  - Any TEAEs
  - Drug-related TEAEs
  - Serious TEAEs
  - Drug related serious TEAEs
  - TEAEs leading to dose interruption
  - Drug-related TEAEs leading to dose interruption
  - TEAEs leading to treatment discontinuation
  - Drug-related TEAEs leading to treatment discontinuation
  - TEAEs leading to study discontinuation
  - Drug-related TEAEs leading to study discontinuation
  - Death

9.2.2. TEAEs

- Summary of TEAEs by primary SOC, PT
- Summary of TEAEs by primary SOC, PT, and maximum severity (mild, moderate, or severe)
- Summary of drug related TEAEs by primary SOC, PT

- Summaries of TEAEs presented by PT

9.2.3. Serious TEAEs

The following serious TEAE summaries will be generated:

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

9.2.4. TEAEs Leading to Dose Interruption

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

9.2.5. TEAEs Leading to Treatment Discontinuation

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

9.2.6. TEAEs Leading to Study Discontinuation

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

9.3. Laboratory Parameters

Blood and urine samples will be collected for clinical laboratory evaluations (including clinical chemistry, hematology, urinalysis, and serology) at the time points specified in Section 0. The data collected in different units will be converted in SI units (the International System of Units) for summary. The following summaries will be provided by laboratory category of chemistry, hematology, urinalysis, and serology.

Laboratory values will be summarized as descriptive statistic for both actual value and change from baseline (post baseline minus baseline) by week. If lab values are recorded as <xx, the limits of xx will be used for summary. If lab values are recorded as TNTC (too many to count), correspondingly maximum values per confirmation by vendors will be used for summary.

Shift table summarizing subject incidence of laboratory normal range (Low, Normal, High) at baseline contrasted with individual visits and minimum or maximum post baseline.

For parameters with bidirectional abnormality (low and high) will be presented by post baseline minimum and maximum.

9.4. Vital Signs and Weight

Vital signs (systolic and diastolic blood pressure, pulse, respiration, temperature) and weight will be summarized in descriptive manner by visit for both actual values and changes from baseline (post baseline minus baseline) for each visit. At any visit and timepoint, if the test is repeated, the average will be used for the analysis at this visit.

All vital signs including weight, pulse rate, body temperature, respiration rate, and systolic and diastolic blood pressure will be summarized. Descriptive statistics will be presented for the observed value and the change from baseline at each scheduled visit, and dose group (active versus pooled placebo). Incidence of clinically relevant vital signs noted post-baseline will also be summarized for each study part and treatment group (active versus pooled placebo). Clinical relevance is based on the following criteria (Table 3).

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

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

9.5. Electrocardiograms

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

For the assessment of QT interval changes from baseline, Fridericia's method was used to correct for heart rate

Below incidence of QTcF shifts from baseline will be summarized by category:

- QTcF interval >450 msec
- QTcF interval >470 msec
- QTcF interval >500 msec

- QTcF change from the baseline (pre-dose) is >30 msec and >60 msec

9.6. 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.

10. PHARMACOKINETIC ANALYSIS

The PK analysis plan and report will be done separately.

[redacted]

13. SUBGROUP ANALYSIS

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

Table 4: Subgroups Defined at Baseline

Subgroup	Values
Age group	<65 years, ≥65 years
Sex	Female, Male
Race	White, Non-white (American Indian or Alaska Native, Asian, Black or African American, Native Hawaiian or Other Pacific Islander, Other)

14. INTERIM ANALYSES

Unblinded efficacy data endpoint review and unblinded interim analyses may be performed 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 will be communicated to selected Sponsor members who are 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).

15. DATA HANDLING CONVENTIONS

15.1. General Conventions

Imputation rules for the missing AE onset date

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

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

Imputation rules for the missing CM or MH onset date

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

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

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

The imputed dates need to be capped by end of study dates, death dates, and cutoff dates when they are applicable.

16. REFERENCES

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

17. APPENDICES

17.1. Study Schema and Schedule of Assessment

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)														

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
Concomitant meds/therapies/procedures monitoring	From the Screening Visit through EOS Visit (Week 18)														
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
UAS7	Completed daily 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
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 judgment.

[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.

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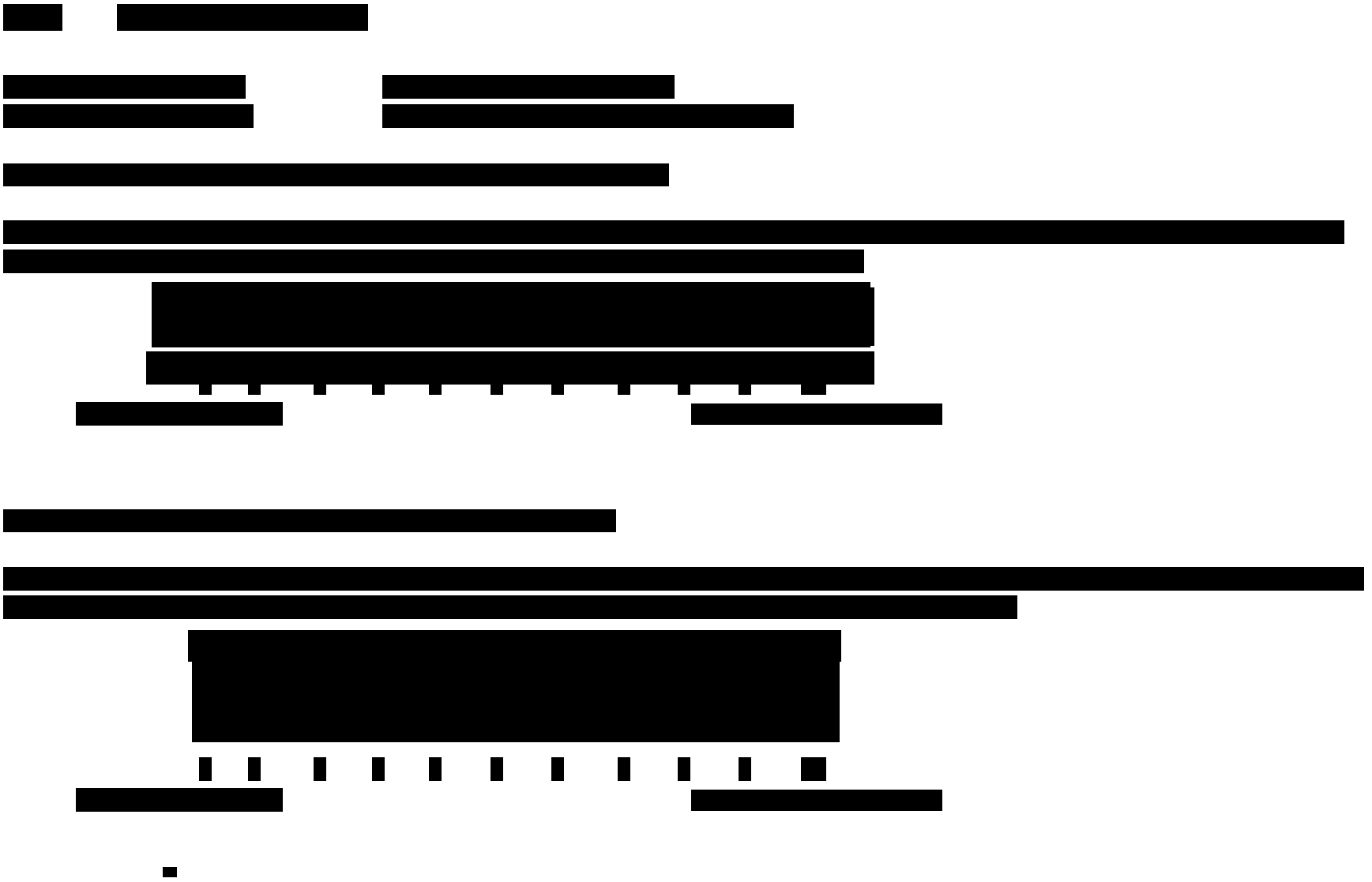

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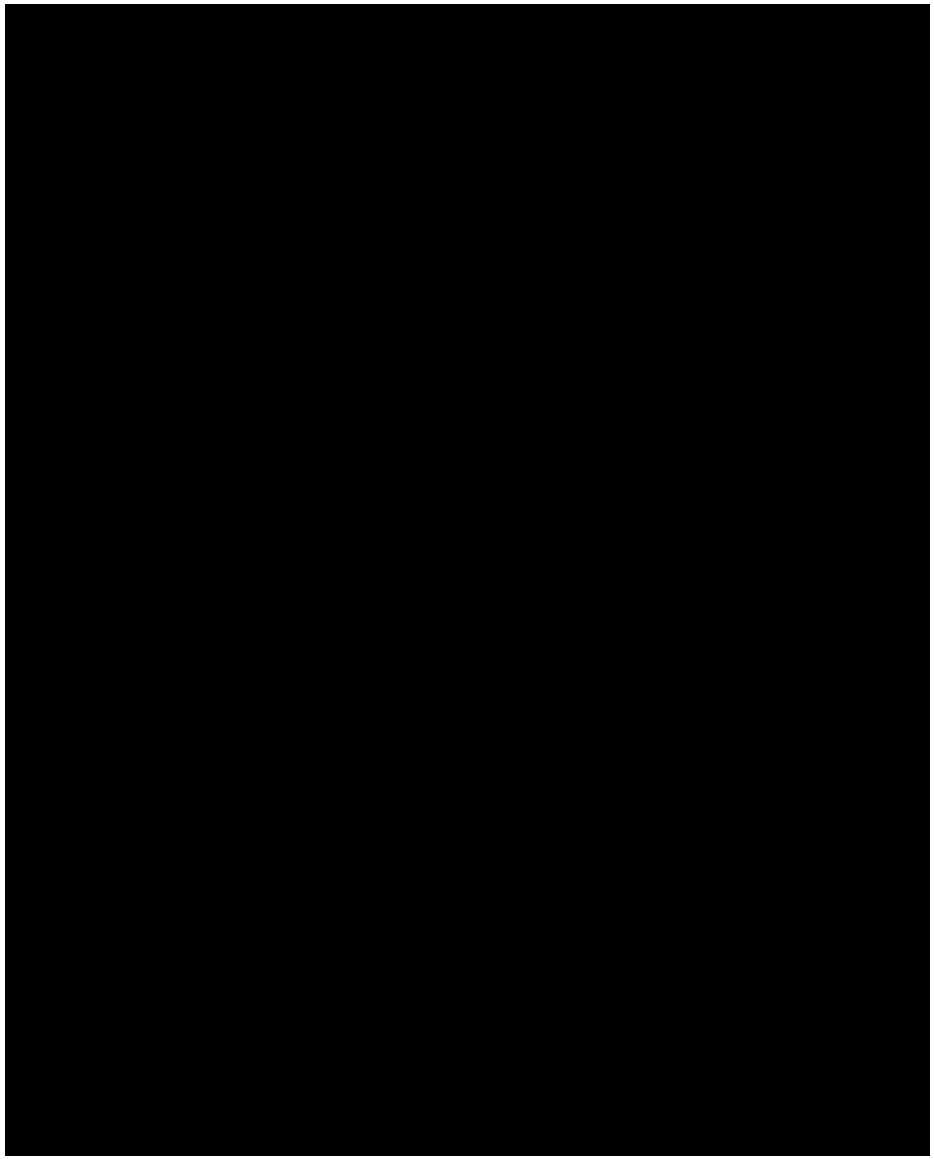

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17.8. Clinical Laboratory Tests

Urinalysis	Hematology	Chemistry
APPEARANCE	ABS.BASOPHIL COUNT	IGE
BACTERIA	ABS.EOSINOPHIL COUNT	ALBUMIN
BILIRUBIN	ABS.LYMPHOCYTE COUNT	ALKALINE PHOSPHATASE
BLOOD	ABS.MONOCYTE COUNT	ALT
CA OXALATE CRYSTALS	ABS.NEUTROPHIL COUNT	AST
COLOR	APTT	BICARBONATE
EPITHELIAL RENAL	ATYPICAL LYMPHS	BILIRUBIN, TOTAL
EPITHELIAL SQUAMOUS	BANDS	BUN
EPITHELIAL TRANSITIONAL	BASOPHILS	CALCIUM
GLUCOSE	BASOS	CHLORIDE
GRANULAR CAST	BIZARRE PLATELETS	CHOLESTEROL, TOTAL
HYALINE CAST	BLASTS	CREATININE
KETONE	CALC.ABS.BASOPHIL COUNT	GGT
LEUKOCYTE ESTERASE	CALC.ABS.EOSINOPHIL COUNT	GLUCOSE, RANDOM
NITRITE	CALC.ABS.LYMPHOCYTE COUNT	HDL-CHOLESTEROL
PH	CALC.ABS.MONOCYTE COUNT	LDH
PROTEIN	CALC.ABS.NEUTROPHIL COUNT	LDL-CHOLESTEROL
RBC CAST	DIFF COMMENT	POTASSIUM
RBCS	EOS	PROTEIN, TOTAL
SPECIFIC GRAVITY	EOSINOPHILS	SODIUM
TRI PHOSPHATE CRYSTALS	FIBRINOGEN	TRIGLYCERIDES
URIC ACID CRYSTALS	GIANT PLATELETS	URIC ACID
UROBILINOGEN	HCT	
WAXY CAST	HGB	
WBC CAST	HYPERSEG.NEUTROPHILS	**Serology**
WBCS	I.N.R.	HEP B SURFACE AB
YEAST	LYMPHOCYTES	HEP B SURFACE AG
APPEARANCE	LYMPHS	HEP. C ANTIBODY
BACTERIA	MCH	HEPATITIS B CORE AB
	MCHC	HIV-1&2 AB SCREEN
	MCV	
Urine Drug Screen	METAMYELOCYTES	
AMPHETAMINE	MONOCYTES	
AMPHETAMINES	MONOS	
COCAINE METAB CONF.	MYELOCYTES	
COCAINE METABOLITES	NEUTROPHILS	
METHADONE	NUCLEATED RBCS	
METHAMPHETAMINE	PLATELET COUNT	**Others**
OPIATES	PLATELET ESTIMATE	Hemoglobin A1c
OXYCODONE	PROMYELOCYTES	FSH
PHENCYCLIDINE	PROTIME	PREGNANCY, QUALITATIVE
	RBC	

RDW
REACTIVE LYMPHS
SEGS
SMUDGE CELLS
TOXIC GRANULATION
UNCLASSIFIED
WBC

17.9. Statistical Methods and SAS Codes

- **Analysis of Covariance (ANCOVA)**

The primary and secondary endpoints of change and percent change from baseline value by week will be analyzed using ANCOVA. The ANCOVA model includes factors of treatment, sex, and baseline value as a covariate. The following is an example of the SAS codes used to perform the analysis.

```
**************************************************************************
* SAS Codes: ANCOVA model
* Variables in the model:
* chg = change from baseline in
* trt = treatment group code
* base = baseline value
* week = visit
**************************************************************************;
proc mixed data=eff;
    by week;
    class trt;
    model chg = trt base;
    lsmeans trt /pdiff cl;
run;
```

- **Fisher's Exact Test**

```
**************************************************************************
* SAS Codes: Fisher's Exact Test
* Variables in the model:
* resp = response variable (Y/N or 1/0)
* trt = treatment group code
* week = visit number
**************************************************************************;
proc freq data=dset order=data;
    by week;
```

```
    table trt*resp / alpha=0.05;
    exact relrisk fisher;
    output out=outname exact;
run;
```

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Approval	Aaron Young Legal 01-Oct-2021 12:48:07 GMT+0000

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