Lumosa Therapeutics Co., Ltd

Protocol No: LT5001-101

CP Project ID: LMS19101

Clinical Pharmacology of LT5001 Drug Product in Hemodialysis Patients With Uremic Pruritus to Assess the Safety, Local Tolerance and Pharmacokinetics

Statistical Analysis Plan

Version: 1.0

Date: 13MAY2020

Based on Protocol Version V4.0, 16MAR2020

SIGNATURE PAGE

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Table of Contents

1 Introduction

1.1 Preface

The objective of this document is to detail the statistical methodology to be used for the part A and part B statistical analysis of study LT5001-101.

The statistical analysis plan is based on the following information and documents:

- LT5001-101 Protocol V4.0/ Date: 16 Mar 2020
- LT5001-101 Subject Case Report Forms V3.0/ Date: 20 Mar 2020

1.2 Timing of statistical analyses

The following statistical analyses are planned for this study:

- Analysis for part A
- Analysis for part B

After part A completion, the interim analysis will plan to be done. Final analysis will be completed after Part B completion.

An independent DSMB will be established to review accumulating safety data after part A completion. An ad hoc DSMB meeting may also be requested as necessary to review the safety data in the following situations:

1. In the event of 4 subjects experiencing drug related (at least possible) adverse events with at least moderate intensity after the 1st dose of study drug or any ICDRG grade of ROAT $\geq$ 1+ found during the first 7 days of study treatment, ad hoc DSMB meeting will be held to review the safety data.
2. In the event of $\geq$ 2 subjects experiencing drug related (at least possible) adverse events with at least moderate intensity in the first 6 subjects receiving study drug after the 1st dose or any ICDRG grade of ROAT $\geq$ 1+ found during the first 7 days of study treatment, ad hoc DSMB meeting will also be convened to discuss the safety events

2 Modification History

2.1 Changes to the study protocol

The statistical analysis as specified in this SAP is consistent with the statistical analysis as specified in the study protocol.

2.2 Changes to previous SAP versions

This is the first version of the SAP.

3 Study Design

This study contains 2 parts. Both study parts will include hemodialysis patients with moderate to severe UP. Part A will assess the safety, tolerability, and PK of LT5001drug product with 4-week of daily BID topical dosing. Part B will assess safety and efficacy with 8-week of daily topical dosing.

3.1 General description

Indication	Hemodialysis patients with moderate-to-severe pruritus
Design	This is a randomized, double-blind, placebo-controlled study containing two parts: part A will assess the safety, tolerability and PK with 4-week treatment, part B will assess safety and efficacy for 8-week treatment. Both parts will apply investigational drug in hemodialysis patients with moderate to severe of uremic pruritus.
Phase	1 (Part A) and 2 (Part B)
Study Site:	[redacted]
Sample size	Part A: Approximately 20 subjects will be screened to achieve 18 subjects enrolled (LT5001 drug product: Placebo=12:6). Part B: Approximately 66 subjects will be screened to achieve 60 subjects enrolled (LT5001 drug product: Placebo=30:30).

Objectives	**Primary Objective – Part A** To investigate the safety, local tolerability, and PK of 4-week, multiple dermal applications of LT5001 drug product to hemodialysis patients with UP. • **Part A Primary Endpoint** - Nature and severity of AEs and number of patients with AEs. • **Part A Secondary Endpoints** - [redacted] - Change in mean Worst Itching Intensity from baseline to the end of Week 4 using NRS. - Reduction of itch intensity as assessed by the proportion of patients reduced NRS from baseline (≥ 2 points, ≥ 3 points, or ≥ 4 points) with respect to the weekly mean of the daily 24-hour Worst Itching Intensity NRS score from baseline to the end of Week 4. - Improvement in itch-related quality of life as assessed by the change from baseline in 5-D Itch Scale score to the end of Week 4. - Improvement in itch-related quality of life as assessed by the change from baseline in the total Skindex-10 Scale score to the end of Week 4. **Primary Objective – Part B** To investigate the safety and efficacy of 8-week, multiple dermal applications of LT5001 drug product to hemodialysis patients with UP. • **Part B Primary Endpoint** - Change from baseline to end of Week 8 in mean Worst Itching Intensity using NRS. • **Part B Secondary Endpoints** - Reduction of itch intensity as assessed by the proportion of patients reduced NRS from baseline with respect to the weekly mean of the daily 24-hour Worst Itching Intensity NRS score from baseline to end of Week 8. - Improvement in itch-related quality of life as assessed by the change from baseline in 5-D Itch Scale score to the end of Week 8. - Improvement in itch-related quality of life as assessed by the change from baseline in total Skindex-10 Scale score to the end of Week 8. - Nature and severity of AEs and number of patients with AEs.

Drug Administration	In [redacted]. The study medication will be applied directly to the itching area as instructed by the study staff. A fingertip unit of study drug is recommended to treat an area of skin twice the size of an adult palm. In the first 7 days of study treatment, patient will also need to apply 0.5 fingertip unit of the study drug to a 5x5 cm^2 fixed pre-marked zone without any skin lesions near the antecubital fossa BID in the morning and evening for 7 days. For part B, the maximum daily dose and recommended regimen will depend on DSMB comments.
Estimated Study Duration:	Part A: Patient participation is expected to last up to 63 days, including a 28-day screening period (consisting of a 7-day diary run-in to build baseline itch NRS) and a 36-day on study period (consisting of 56 total doses from Day 1 to Day 29, and a 7 day follow up/EOS visit at Day 36). Part B: Patient participation is expected to last up to 85 days, including a 28-day screening period (consisting of a 7-day diary run-in to build baseline itch NRS) and a 57-day on study treatment period. Procedures for the scheduled visits and contacts are described in Appendix I.

3.2 Sample size estimation

It is planned to complete 18 subjects in Part A and 60 subjects in Part B in this study. This sample size is chosen on clinical rather than statistical rationale. No formal sample size calculations were performed. The sample size is considered adequate to address the study goals.

3.3 Randomisation, blinding and unblinding procedures

Subjects will be randomized into the study once they have completed screening and the Day -1 pre-dosing assessments and have satisfied all eligibility criteria.

Hemodialysis subjects with moderate-to-severe pruritus will be assigned random allocation number as the following ratio in each study part.

For Part A, patients will be randomized into a 2:1 ratio to receive LT5001 drug product or placebo. Thus, LT5001 group, the resulting allocated subjects will be 12 subjects. The placebo group will contain 6 subjects.

For Part B, patients will be randomized into a 1:1 ratio to receive LT5001 drug product or placebo. Thus, LT5001 group, the resulting allocated subjects will be 30 subjects.

The CRO will maintain the randomization code in a secure location with controls to prevent unauthorized access, including the computer program written to generate the randomization, randomization codes, program log, seed number used by the program, copy of the randomization plan along with approval documentation as appropriate, and the write protected electronic storage medium.

The site and CRO will name an unblinded statistician to provide the randomization code. Investigators, pharmacists, site staff, patients, CRO, and the Sponsor will remain blinded to individual patients' treatment assignment for the duration of the study until the study unblinding has been authorized.

In order to preserve the blind, study drug will be prepared and administered in a manner that masks the content for both the patient and staff member administering the drug.

4 Analysis Sets

Enrolled Population (ENR)

The enrolled population will include all patients who provided informed consent. Summary of screening failures and randomized patients will be displayed for ENR population.

Safety Analysis Set (SAS)

The SAS will include all patients who receive at least 1 dose of LT5001 drug product or placebo in Parts A and B. Patients will be analyzed according to the treatment they actually received.

The Safety Population will be used for all safety analysis (adverse events, clinical laboratory tests, vital signs, physical examinations and application site examination).

Full Analysis Set (FAS)

The Full Analysis Set will include all randomized patients who received at least 1 dose of LT5001 drug product or placebo. Subjects will be analyzed based on the treatment assigned.

The Full Analysis Set will be used for all efficacy analysis and demographics.

Per Protocol Set (PP)

The per-protocol population will comprise all FAS patients who complete the study procedures without a major protocol deviation that would impact on efficacy and high compliance.

The PP population will also be used for the analysis of efficacy.

The Per Protocol Set is defined as patients who:

- Receive at least 80% of the planned study drug doses
- Did not receive a different treatment than the treatment to which they were randomized
- Had a mean baseline Worst Itching Intensity score > 4.0
- Had a non-missing weekly mean of daily 24-hour Worst Itching NRS score available for at least 75% of study weeks (weeks with >3 missing daily values set to missing)
- Did not receive prohibited medication listed in protocol section 7.7.3

- Did not have other major protocol violations that would impact efficacy outcomes

The assignment of subjects to the different analysis set will be done prior to unblinding during a blind data review meeting. All subjects excluded from the different analysis sets will be listed together with the reason for exclusion.

Pharmacokinetic analysis set (PKAS)

The PKAS will include patients who have received at least 1 dose of LT5001 drug product and have at least 1 measured concentration of LT5001 drug product at a scheduled PK time point after dosing.

Subjects will be analyzed based on the actual treatment received.

The Pharmacokinetic analysis set will be used for all PK analysis of part A.

5 General Statistical Methods and Definitions

5.1 General statistical methods

The statistical analyses will be presented by treatment group for the different analysis sets as defined in section 4 Analysis Sets.

Statistical Consideration

Continuous variables will be summarized using descriptive statistics (Number of subjects, Mean, Standard deviation (SD), Median, Min, Max).

Categorical variables will be summarized with descriptive statistics (number of subjects, frequency counts, and percentage of subjects).

Changes from baseline in categorical data will be summarized using shift tables where appropriate.

Unless otherwise stated, the calculation of proportions will be based on the number of available data and missing data will not be presented separately.

Common Calculations

- 1 week = 7 days
- 1 year = 365.25 days

Duration is calculated as :

- Duration (days) = (End Date – Start Date + 1)
- Duration (weeks) = (End Date – Start Date + 1) / 7
- Duration (months) = (End Date – Start Date + 1) / 30.44
- Duration (years) = (End Date – Start Date + 1) / 365.25

Multicenter Studies

- Part A: 1 site in Taiwan

- Part B: 4 sites in Taiwan

This study will be conducted by multiple investigators at various centres in part B.

Data from all centres will be pooled prior to analysis in part B. No data adjustment will be made for multicentre analysis.

Output Presentations

Appendix II details the conventions for presentation of data in outputs.

The mock up templates provided with this SAP describe the presentations for this study and therefore the format and content of the summary tables, figures, and listings to be provided by Clinipace Clinical Research Biostatistics.

5.2 Missing data

Generally, the last-observation-carried-forward procedure will be used to estimate the missing data for efficacy variables.

Note that a subject must report at least 4 values for a week in order for the weekly mean of the 24 hour Worst Itching Intensity NRS to be non-missing.

No imputation will be done for estimating the missing values for safety variables and time to event data.

5.3 Observation and analysis times

Reference Start Date and Study Day

Reference start date is defined as the day of randomization and study day relative to the reference start date will appear in every listing where an assessment date or event date appears.

Study day will be calculated from the reference start date and will be used to show start/stop day of the assessments and events relative to the first administration of study treatment.

- If the date of the event is on or after the reference date, then:
  Study day = (date of event – reference date) + 1.
- If the date of the event is prior to the reference date, then:
  Study day = (date of event – reference date).

In case of that event date is partial or missing, the date will appear partial or missing in the listings, and Study Day, and any corresponding durations will be presented based on the imputations specified in Appendix III; Partial Date Conventions.

Definition of baseline values

The baseline value is defined to be the last value which was assessed before the 1st dose of study medication.

Clinical laboratory data on day 1 (Visit 1) will serve as baseline.

Baseline NRS will use the mean NRS score in the 7-days run-in period.

Baseline of 5D itch and Skindex-10 score will be assessed at Visit 1.

5.4 Multiple Comparison/Multiplicity

No multiplicity adjustment is planned.

5.5 Covariates and Strata

In Mixed-effect model repeated measures analysis, baseline itch and prior anti-itch medication use will be considered as covariates for efficacy endpoints in Part B.

Strata is not applicable in this study.

6 Subject Accounting and Disposition

6.1 Subject accounting

The number and relative frequencies of subjects in each analysis set as defined in section 4 Analysis Sets will be presented overall and by randomised treatment .

Furthermore, the number and percentage of subjects in each analysis set will be presented overall and by treatment group including individual reasons of exclusion from the respective analysis set.

6.2 Disposition and withdrawals

A clear accounting of the disposition of all subjects who enter the study will be provided, from screening to study completion. The subject disposition summaries include a schematic diagram and a table with the registration status including the screening, randomization, discontinuation, and completion will be presented. The table will also include reasons of screen failure and discontinuation.

6.3 Protocol deviations

Protocol deviations will be presented in a listing including the date, severity, protocol deviation type, and the action taken, if any. The protocol deviation which impacts subject safety, ICH-GCP compliance, or efficacy endpoints could be marked as major protocol deviation per study team's approval prior to database lock.

- Any known study medication administration error with continuous 2 times (i.e. subject received incorrect IP dose)
- Any study specific related procedure done before the signature of the informed consent
- New clinical study procedures performed before participant was re-consented
- Missed safety or efficacy assessments related to primary or key secondary endpoints
- SAE(/pregnancy) reporting requirement not followed
- Identification or suspicion of activity which may be fraudulent
- Others will be identified by CP and Lumosa MM influencing Subjects' right and safety
- Source document/data missing
- Violation of inclusion/exclusion criteria

- Subject who developed withdrawal criteria during the study but was not withdrawn
- Any significant non-compliance with persistent non-compliance with persistent non-compliance with persistent non-compliance to adhere to protocol and GCP requirements.

Protocol deviations will be summarized by treatment group. All subjects with protocol deviations including those specified above will be listed.

7 Demographics and Background Characteristics

7.1 Demographics

All demographics data will be performed based on data of Full Analysis Set. Demographics and baseline characteristics will be summarized using appropriate descriptive statistics.

Demographic characteristics will be summarized by overall subjects and treatment group, with corresponding listing as follows:

- Gender : Male, Female
- Age (years) : descriptive statistics
- Race : Asian, American Indian or Alaska Native, Black or African American, Native Hawaiian or Other, Pacific Islander, White, Other
- Weight (kg) at baseline : descriptive statistics
- Height (cm) at baseline : descriptive statistics
- BMI (kg/m^2) at baseline : descriptive statistics

  Body mass index (BMI) will be calculated automatically by the electronic data capture (EDC) system, using the following formula

  BMI (kg/m^2) = weight(kg) / height$(m)^2$

Specifications for computation:

- Age (years): (date of given informed consent – date of birth + 1) / 365.25.

  The integer part of the calculated age will be used for reporting purpose.

A demographic listing will be provided.

7.2 Disease characteristics

- Alcohol abuse history within 6 months: Yes, No
- Drug abuse history within 6 months: Yes, No
- Duration from the start of hemodialysis (months) : descriptive statistics

  Duration from the start of hemodialysis (months) = [date of given informed consent – start date of hemodialysis) + 1] / 30.44
- Duration from the start of pruitus (months) : descriptive statistics

Duration from the start of pruitus (months) = [date of given informed consent – start date of pruitus) + 1] / 30.44

For each of the above, if partial dates are recorded, the first day of the month will be imputed for missing day and January for missing month.

- Baseline anti-itch medications
- Baseline Worst Itching Intensity NRS
- Baseline 5D-itch scale total score
- Baseline Skindex-10 scale total score

7.3 Medical history

Medical history still ongoing at enrolment or ended prior to enrolment will be listed together for the Full Analysis Set. Medical history will be coded according to Medical Dictionary for Regulatory Activities (MedDRA® version 22.0 (or later)) and will be classified as follows

- Previous medical conditions: medical conditions that stopped prior to start of treatment
- Ongoing (concomitant) medical conditions: medical conditions still present after start of treatment

The frequency of diseases recorded from medical history will be presented after classification into previous and concomitant conditions by system organ class (SOCs) as well as the frequencies of preferred terms (PT) within each SOC. If subjects have more than one disease within an SOC or PT they will be counted only once for the respective SOC or PT.

8 Exposure and Compliance

Exposure and compliance data will be summarized and listed by subject based on Full Analysis Set. A listing of drug administration will be created and will include the date and time of administration.

8.1 Treatment groups

Treatments will be labelled as follows:

- LT5001 drug product
- Placebo

For the FAS, subjects will be assigned to the treatment groups they were randomised to and for the SAS, PP and PKAS to the treatment they actually received.

In case that a subject received different treatments due to mix-up the subject will be assigned as follows in the SAS:

- In case of mixture of placebo and active treatment the subject will be assigned to the respective active treatment.

Deviations from the randomised treatment will be presented in the protocol deviation listing, see section 6.3 Protocol deviations.

8.2 Dosage

Descriptive statistics for the actual total dose will be presented overall and by treatment group for the FAS.

8.3 Treatment duration

The treatment duration will be calculated in days as:

Treatment duration (days) = (date of last application – date of first application) + 1

If the date of first application of study medication is missing, it will be assumed to be identical to the date of randomisation.

Descriptive statistics for the treatment duration will be presented.

8.4 Compliance

Details regarding dosing, including the dose administered and the date and time of dosing, will be recorded.

Formulation of study drug is ointment and it will be applied to the skin to treatment.

The number of tubes applied will be the sum of the number of "Drug Used (AM)" and "Drug Used (PM)" from the eCRF "Treatment of Study Medication" form when "Yes" are selected.

Percent compliance will be derived as the number of tubes actually applied divided by the number of tubes expected to be applied, expressed as a percent.

- Treatment compliance:

  (The actual number of tubes applied in each treatment group / Expect total tubes applied in each treatment group)*100%

  If the subjects do not feel itchy, drug used will be recorded as "not applicable" in CRF. In this case, it will be excluded from calculating of the compliance.

- Treatment compliance by categories (<80%, 80%-100%)

9 Previous and Concomitant Therapies/ Anti-itch medications

Prior and concomitant medications are coded according to the World Health Organization drug dictionary (WHO-Drug latest version) and stored with ATC codes and generic names.

Prior and concomitant medication will be recorded on the eCRF (Form: Concomitant Medications). Prior medication is defined as any medication or device other than the study drug within 30 days prior to the Screening Visit. Concomitant medication is any medication other than the study drug that is taken from the time of study entry (date of informed consent signed) to the end of study. Upon entering the study, each subject will be instructed to report the use of any medication to the investigator.

The summary tables by treatment groups and overall for prior and concomitant medication will be provided detailing the number and percentage of subjects by anatomical main group (ATC Level 2) and preferred term using World Health Organization Drug Dictionary (WHO-DD) Enhanced latest version

Anti-itch medications are identified as medications where "Yes" is checked on the Previous or Concomitant Medications CRF page to the question "Is the medication anti-itch?" The prior and concomitant medication summaries described above will be repeated for the anti-itch medications, presented by generic name.

10 Efficacy

The FAS will be used for efficacy endpoint evaluation. Efficacy analysis will be repeated on the PP Population.

The following efficacy endpoints will be assessed by Part of study.

Part A:

- Change in mean Worst Itching Intensity using NRS from baseline to the end of Week 4.
- Proportion of patients reduced NRS from baseline with respect to weekly mean of the daily 24-hour Worst Itching Intensity NRS score from baseline to the end of Week 4.
- Change from baseline in 5-D Itch Scale score at the end of Week 4.
- Change from baseline in total Skindex-10 Scale score at the end of Week 4.

Part B:

- Change from baseline to the end of Week 8 in mean Worst Itching Intensity using NRS (Primary endpoint in Part B)
- Proportion of patients reduced NRS from baseline with respect to the weekly mean of the daily 24-hour Worst Itching Intensity NRS score from baseline to the end of Week 8.
- Change from baseline in 5-D Itch Scale score at the end of Week 8.
- Change from baseline in total Skindex-10 score at the end of Week 8.

The efficacy analysis will be based on a linear mixed effect model for repeated measurements (MMRM) using all the longitudinal observations at each post-baseline visit through the last visit.

To select an appropriate covariance model, covariates of baseline itch and status of prior anti-itch medication use

Proportion of patients improved NRS from baseline (2-points, 3-points, or 4-points) was evaluated at each time point compared between treatment group using logistic regression analysis.

10.1 Primary efficacy analysis

Numerical Rating Scale (NRS)

Numerical Rating Scale (NRS), an unidimensional scale, which may be the most widely used is a validated measurement of UP intensity in HD patients. Patients can be asked to rate their itch intensity from 0 ("no itch") to 10 ("worst imaginable itch") with the NRS.

Patients will be recorded the daily Worst Itching Intensity in the patient diary and review will be conducted in each visit.

The weekly mean of the 24-hour Worst Itching Intensity NRS score will be defined as the sum of the daily Worst Itching Intensity NRS scores reported during a specific week during the Treatment Period (e.g., Days 1 to 7, Days 8 to 14, Days 15 to 21) divided by the number of days with non-missing scores for that week. If the daily worst itching score is missing for >3 days during a specific week, the corresponding weekly mean worst itching score will be set to missing. Additionally, subjects who discontinue treatment but continue on study and report NRS scores will have their NRS scores censored following discontinuation of treatment; missing data rules will apply to these censored values as though they had missing values/ dropped out from the study entirely.

The baseline score was defined as the average of the daily 24-hour Worst Itching Intensity NRS scores reported over the 7-day Run-in Period. As defined in the protocol, to be randomized, subjects had to report at least 6 non-missing Worst Itching Intensity scores from the start of the 7-day Run-in Period and mean NRS score>4 to qualify.

As a continuous variable, the data value of NRS on the each visit will be derived based on the average value of the values that each subjects had recorded from the previous visit day to next visit day. Change from baseline in NRS will be summarized as descriptive statistics by overall subjects and treatment group for Part A and Part B. For Part B, it will further be analyzed using mixed-effect model repeated measure analysis of covariance to compare the treatment group considering covariates (baseline itch and prior anti-itch medication use). Additionally, treatment group, time, an interaction term for treatment group and time will be included into the model as factors. The model will be used to estimate the NRS at end of treatment. Least square means and their standard errors, along with their 95% confidence interval (CI) of treatment difference will be calculated.

To perform MMRM, SAS programming will be used as follows.

```
proc mixed data= dataset  ;
    class treatment time subject prior_med;
    model NRS=treatment time treatment*time baseline_itch prior_med /solution ddfm=kr;
    lsmeans treatment*time/cl pdiff;
    repeated time/type=un subject=subject;
run;
```

By using derived NRS at the timepoint, the subjects reduced NRS from baseline (≥2-points, ≥3-points, ≥4-points) to each time point will be categorized. It will be summarized by frequency and percentage of subjects. For Part A and B, logistic regression analysis will be further performed to compare treatment group differences at each time-point, providing with odds ratio and 95% CI.

10.2 Secondary efficacy analyses

In Part A, the secondary efficacy endpoints will be summarized using descriptive statistics. Statistical comparisons will only be performed in park B using a two-sided test at a significance level of 5%, and 95% CI and a P-value will be reported in case of efficacy analysis.

5-D Itch Scale

The 5-D itch scale was developed as a brief but multidimensional questionnaire designed to be useful as an outcome measure in clinical trials. The five dimensions are degree, duration, direction,

disability and distribution. The duration, degree and direction domains each included one item, while the disability domain had four items. All items of the first four domains were measured on a five-point Likert scale.

The five-point Likert scale are rated from 1 to 5 points. For disability domain, the highest score on any of the four items will be used. For the distribution domain, the number of affected body parts is tallied (potential sum 0–16) and the sum is sorted into five scoring bins: sum of 0–2 = score of 1, sum of 3–5 = score of 2, sum of 6–10 = score of 3, sum of 11–13 = score of 4, and sum of 14–16 = score of 5. The total score of 5-D itch will be the sum of the 5 domains, ranging from 5 to 25 points.

5-D itch scale will be assessed at Visit 1, Visit 5, Visit 7 in Part A and Visit 1, Visit 3, Visit 5, Visit 7, Visit 9 (End of study) in Part B. Baseline of 5D itch score will be assessed at Visit 1.

Change from baseline in 5-D Itch Scale score at week 4 in Part A and Week 8 in Part B (total score and score for each domain) will be summarized by treatment group and visit.

In Part A and B, mixed-effect model repeated measure analysis of covariance will be performed to compare the treatment group considering covariates (baseline itch and prior anti-itch medication use).

Skindex-10 scale

Skindex-10 consists of 10 questions used to evaluate how the patient's itch affects three important domains of quality of life.

The total score of skindex-10 scale is the sum of the numeric value of each answered question. The domain scores are sums of the following: disease domain (questions 1 to 3), mood/emotional distress domain (question 4 to 6), and social functioning domain (questions 7 to 10)

Skindex-10 scale will be assessed at Visit 1, Visit 5, Visit 7 in Part A and Visit 1, Visit 3, Visit 5, Visit 7, Visit 9 (End of study) in Part B. Baseline of Skindex-10 score will be assessed at Visit 1.

Change from baseline in Skindex-10 Scale at week 4 in Part A and Week 8 in Part B (total score and score for each domain) will be summarized by treatment group and visit. In part A and B, mixed-effect model repeated measure analysis of covariance will be performed to compare the treatment group considering covariates (baseline itch and prior anti-itch medication use)

11 Safety

11.1 Adverse events

All AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) Version 22.0 (or later).

Adverse events will be grouped by system organ class (SOC) and PT and summarised by treatment. The summary tables will present the number and percentage of subjects with AEs and number of events, by SOC and by PT for each treatment group.

All AE summaries will be restricted to Treatment-emergent adverse events (TEAEs) only.

A treatment emergent adverse events (TEAE) is defined as any AE with an onset date on or after the first dose of study treatment if the AE was absent before the first dose of study treatment, or pre-existing medical condition worsens after the first dose of study treatment.

For the summaries of AEs, subjects who experience the same AE (in terms of the MedDRA SOC and

PT) more than once will only be counted once for that event in the number of subjects but all occurrences of the same event will be counted in the number of events.

For analysis, at AE level, the worst severity and the strongest relationship to trial treatment will be assigned to the AE if the severity and relationship changes overtime for the AE with the same AE ID. At subject level, a subject with the same AE term being reported multiple times, the maximum severity and the strongest relationship to trial treatment will be tabulated.

Study drug related TEAEs are defined as TEAEs with definitely, probably, or possibly relationship with study drug

Nature and severity of adverse event (AEs) and number of patients with AEs will be analysed as primary endpoint in part A and secondary endpoints of Part B.

An overview table of TEAEs will be provided detailing the number and percentage of subjects along with the number of reported events with

- Any TEAE
- TEAEs by severity (Mild, Moderate, Severe)
- Any TEAE related to study drug
- Any serious TEAE
- Any serious TEAE, related to study drug
- Any TEAE leading to discontinuation of study drug
- Any TEAE leading to death

Summary tables will also be provided for TEAEs, TEAE by severity, study drug related TEAEs, TEAEs leading to discontinuation of study drug, and TEAEs leading to death, detailing the number and percentage of subjects and number of events by MedDRA SOC (ordered by frequency) and PT (ordered by frequency).

Separate patient listings will be provided for AEs, SAEs, AEs leading to study drug discontinuation, and AEs leading to death. The listings will also include subjects enrolled but not randomised.

11.2 Deaths

Deaths will be presented as listing in detail by using death report form of CRF.

11.3 Vital signs

The following vital signs will be measured at every study visit and reported for this study.

- Temperature(°C)
- Respiratory rate (breaths/min)
- Systolic blood pressure/SBP (mmHg)
- Diastolic blood pressure/DBP (mmHg)

- Pulse Rate (mmHg)

Observed value and absolute change from baseline to each visit will be summarized by descriptive statistics (number of subjects with data, number of subjects with missing values, mean, SD, median, minimum, and maximum) by treatment group.

11.4 Clinical laboratory tests

[redacted]

The following statistical analyses will be presented:

Observed value and absolute change from baseline to each visit will be summarized by descriptive statistics (number of subjects with data, number of subjects with missing values, mean, SD, median, minimum, and maximum) by treatment group.

Shift in evaluation for laboratory assessment results (Normal, Abnormal Not Clinically Significant [NCS], Abnormal Clinically Significant [CS]) from baseline to each visit will be summarized by treatment group, using frequency tabulations. Also laboratory assessment results will be classified low, normal, high value based on LNR (Laboratory Normal Range) and it will be summarized by treatment group, using frequency tabulations. For the shift tables that present changes from baseline to each post-baseline visit, the number and percentage (%) of subjects in each category will be calculated relative to the total number of subjects in the relevant analysis set with assessments available at Baseline and the relevant post-baseline visit.

Pregnancy test: It will be done at Screening and presented as number and percentage (%) of subjects in the result (negative, positive).

[redacted]

[redacted]

11.5 Physical examination

The following physical examinations will be evaluated by the investigator as Normal, abnormal NCS, Abnormal CS at every study visit and reported for this study.

- General appearance
- Skin
- Head and neck (eyes, ears, nose, mouth, and throat)
- Chest and Lung
- Heart
- Abdomen
- Extremities
- Neurologic System
- Other

The following summaries will be provided:

A summary of the number and percentage of subjects with normal, abnormal but not clinically significant, and abnormal clinically significant physical examination findings, by body system, treatment group, and visit.

For each physical examination, shift from baseline to each post-baseline protocol scheduled time point's evaluation, will be summarised by treatment group, using frequency tabulations.

A by-subject listing of physical examination results will be provided.

11.6 Application site examination

The application site evaluation will include dermatitis, pruritus, paresthesia, erythema, dryness, vesicles, irritation, papules, burning assessed by ICDRG scale. ICDRG scale consist of negative(-), doubtful reaction(+/?), weak positive reaction(+), strong positive reaction(++), extreme positive reactions(+++), irritant reaction (IR). Application site examination (observed and change from baseline) will be summarized as number and percentage of subjects by each treatment group.

7-days ROAT assessed by ICDRG scale will also be summarized as number and percentage of subjects by each treatment group

12 Pharmacokinetics

Pharmacokinetics analysis will be performed only in Part A.

Pharmacokinetic parameters will be listed by subject and treatment using the pharmacokinetic analysis set (PKAS)

All calculations for PK parameters will be based on actual dosing and sampling times recorded during the study. Considering the actual dose received by each patient may vary, the PK parameter will be adjusted by dividing to the actual dose of each patient.

[redacted]

[redacted]

Blood concentrations that are below the limit of quantification (BLQ) prior to the first measurable concentration will be set to zero, BLQ values that are between measurable concentrations will be set to missing, and BLQ values that occur at the end of the profile (after the last quantifiable concentration) will be set to missing.

All PK parameters will be summarized as descriptive statistics (n, arithmetic mean, standard deviation (SD), CV%, minimum, median, and maximum, geometric mean, and geometric CV%). Missing values will be omitted from the calculation of descriptive statistics

Scatter plots of individual adjusted PK parameters (C_{trough}/ Actual Dose) and non-adjusted PK parameters (C_{trough}) versus time for LT5001 drug product will be produced on log-log scales using the PKAS.

13 Interim Analyses

Interim analysis and DSMB:

After Part A completion, the interim analysis for all data will be done.

Statistical analysis for interim analysis will be performed based on this SAP.

DSMB will review interim analysis and give comments on safety or any medical concern to determine whether the study continues or not. Also, DSMB will give comments for LT5001 drug product daily dose and regimen for Part B. Sponsor will make the final decision in an unblinded fashion.

14 Statistical Analyses for Safety Monitoring

The statistical analysis for safety monitoring is specified in a separate DMC charter.

15 Applicable Software

All analyses will be conducted using SAS® Version 9.4 or higher in a secure and validated environment. Figures may be prepared using the same version of SAS®.

16 Abbreviations

UP	uremic pruritus
AE	adverse event
BMI	body mass index
BUN	blood urea nitrogen
CFR	Code of Federal Regulations
CRU	clinical research unit
CRO	contract research organization
C_{trough}	lowest observed blood concentration prior to next application
DSMB	data and safety monitoring board
eCRF	electronic case report form

EOS	end-of-study
FU	follow-up
GCP	Good Clinical Practice
HBV	hepatitis B virus
HCV	hepatitis C virus
HIV	human immunodeficiency virus
ICF	informed consent form
ICH	International Council for Harmonisation
Itch NRS	itch numerical rating scale
NRS	numerical rating scale
MedDRA	Medical Dictionary for Regulatory Activities
PK	pharmacokinetic(s)
SAE	serious adverse event
SAS	safety analysis set
SD	standard deviation
SOP	standard operating procedure

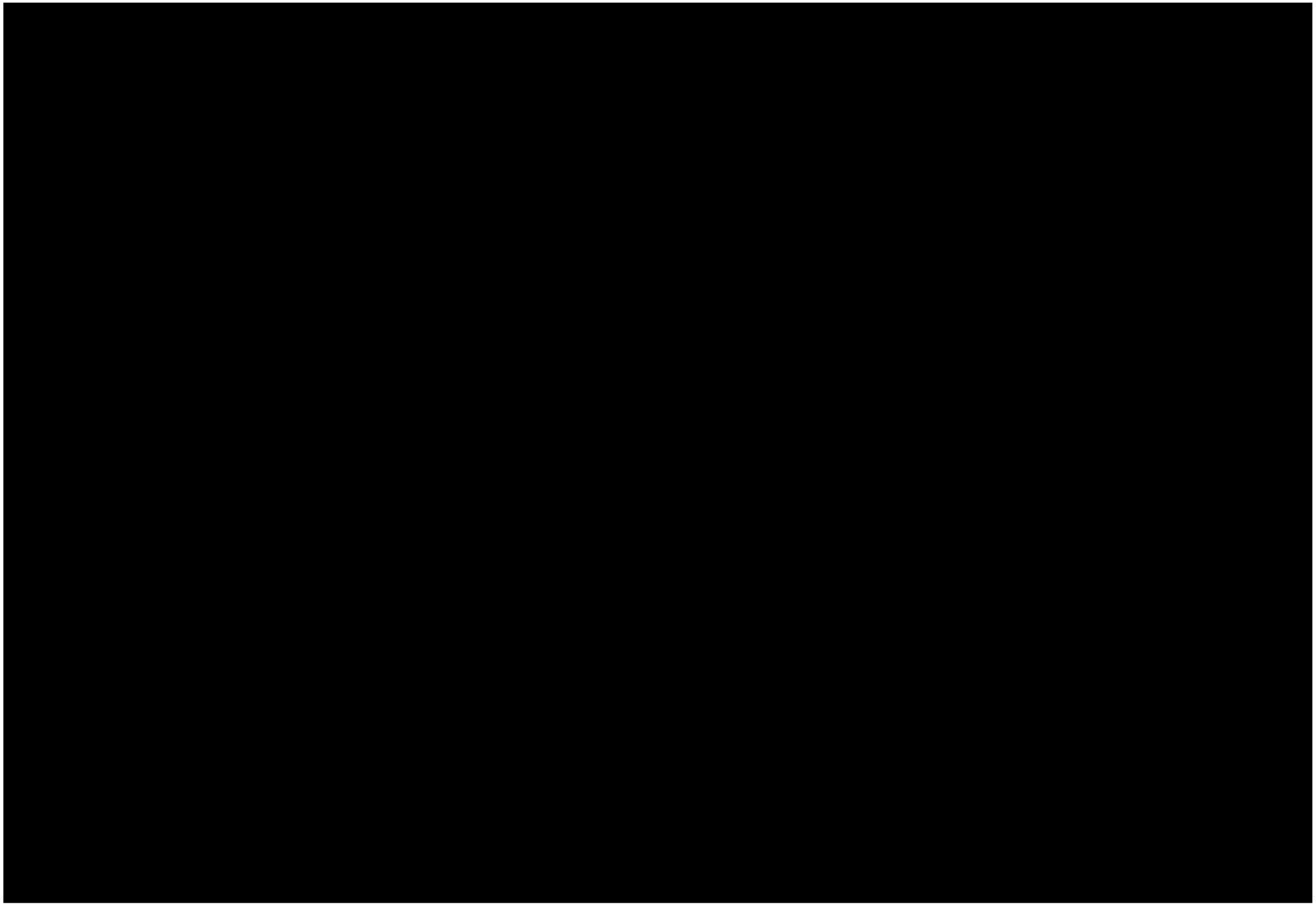
17 References

1. LT5001-101 Protocol V3.0/ Date: 17 Jan 2020
2. LT5001-101 Subject Case Report Forms V2.0/ Date: 20 Feb 2020
3. Elman S, Hynan LS, Gabriel V, Mayo MJ. The 5-D itch scale: a new measure of pruritus. Br J Dermatol. 2010 Mar;162(3):587-93. doi: 10.1111/j.1365-2133.2009.09586.x. Epub 2009 Dec 1.
4. Statistical Principles for Clinical Trials E9. ICH Harmonised Tripartite Guideline
5. Good Clinical Practice: Consolidated Guideline E6. ICH Harmonised Tripartite Guideline

18 Appendices

Appendix I: Schedule of assessments and Procedures

[redacted]



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Appendix II: Programming Conventions for Outputs

❖ Clinipace Output Conventions

Outputs will be presented according to the Clinipace general guidelines and template for outputs conventions.

❖ General Rules

The following conventions will be applied for reporting descriptive statistics of all continuous data.

Mean, Median, Q1, Q3, Minimum, and Maximum will have the same precision as Raw data (number of digits) for non-derived data (*e.g.* weight).

SD will be presented with one digit more than mean.

Statistics on derived data (*e.g.* treatment exposure time in days) will be rounded to reasonable number of digits.

Qualitative variables will be summarized by counts and percentages. Unless otherwise stated, the calculation of proportions will be based on the number of available subjects. Therefore, counts of missing observations will be included in the denominator and presented as a separate category.

Total of missing and non-missing observations at each time-point will reflect the population still in the trial at that time. For example, if a subject is still in the trial at the time-point but with missing data, it should be counted in the number of missing observations.

❖ Dates & Times

Depending on data available, dates and times will take the form DDMMMYYYY and HH:MM.

❖ Spelling Format

English US

❖ Presentation of Treatment Groups

All listings will be ordered by the following (unless otherwise indicated in the template):

- Treatment group
- Center-subject ID
- Date (where applicable)

All tables containing coded terms (CM, MH, AE), coded records will be sorted in frequency order.

Appendix III: Partial Date Conventions

- **Algorithm for Treatment Emergence of Adverse Events:**

START DATE	STOP DATE	ACTION
Known	Known	If start date < study med start date, then not TEAE. If start date ≥ study med start date, then TEAE.
	Partial	If start date < study med start date, then not TEAE. If start date ≥ study med start date, then TEAE.
	Missing	If start date < study med start date, then not TEAE. If start date ≥ study med start date, then TEAE.
Partial, but known components show that it cannot be on or after study med start date	Known	Not TEAE
	Partial	Not TEAE
	Missing	Not TEAE
Partial, could be on or after study med start date	Known	If stop date < study med start date, then not TEAE. If stop date ≥ study med start date, then TEAE.
	Partial	Impute stop date as latest possible date (*i.e.* last day of month if day unknown or 31st December if day and month are unknown), then: If stop date < study med start date, then not TEAE. If stop date ≥ study med start date, then TEAE.
	Missing	Assumed TEAE
Missing	Known	If stop date < study med start date, then not TEAE. If stop date ≥ study med start date, then TEAE.
	Partial	Impute stop date as latest possible date (*i.e.* last day of month if day unknown or 31st December if day and month are unknown), then: If stop date < study med start date, then not TEAE. If stop date ≥ study med start date, then TEAE.

START DATE	STOP DATE	ACTION
	Missing	Assumed TEAE.