Clinical Study Protocol

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

Protocol Number: LT5001-101

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Protocol Approval – Sponsor Signature Page

Study Title	Clinical Pharmacology of LT5001 Drug Product in Hemodialysis Patients With Uremic Pruritus to Assess the Safety, Local Tolerance and Pharmacokinetics
Protocol Number	LT5001-101
Protocol Version	Version 4.3
Protocol Date	04 Sep, 2020

Protocol reviewed and approved by Lumosa Therapeutics Co., Ltd.

[redacted]

Date (DD-Mmm-YYYY)

Protocol Approval –Investigator Signature Page

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Declaration of Current Good Clinical Practice (GCP) Compliance Statement

- I confirmed that I have carefully read and understood this protocol and agree to conduct this clinical study as outlined in this protocol, according to current Good Clinical Practice and local laws and requirements.
- I will ensure that all subinvestigators and other staff members read and understood all aspects of this protocol.
- I have received and read all study-related information provided to me.
- The objectives and content of this protocol as well as the results deriving from it will be treated confidentially, and will not be made available to third parties without prior authorization by Sponsor.
- All rights of publication of the results made by the Sponsor, unless other agreements were made in a separate contract

Signature of Principal Investigator

Date (DD-Mmm-YYYY)

[redacted]

Printed Name of Principal Investigator

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1 STUDY SYNOPSIS

Protocol Number:	LT5001-101
Title:	Clinical Pharmacology of LT5001 Drug Product in Hemodialysis Patients with Uremic Pruritus to Assess the Safety, Local Tolerance and Pharmacokinetics.
Sponsor:	Lumosa Therapeutics Co, Ltd
Study Phase:	1 (Part A) and 2 (Part B)
Condition:	Hemodialysis patients with moderate-to-severe pruritus
Background:	Uremic pruritus (UP) is a common and distressing complication of end-stage renal disease (ESRD). A global cross-sectional study of 18,000 hemodialysis patients reported a 42% prevalence of moderate or extreme UP, which was strongly associated with sleep disturbance, depression, impaired quality of life, and mortality. Despite high prevalence and life-altering comorbidities, UP remains lack of effective treatment. Treatments currently used for uremic pruritus such as antihistamines, steroids, emollients, and phototherapy (UVB) have not been investigated rigorously, and no drugs have been approved for this indication by the FDA.
Rationale:	[redacted] This study is to evaluate the safety, local tolerance and pharmacokinetics of LT5001 drug product in patients with uremic pruritus.
Objectives:	**Part A:** To investigate the safety, local tolerance and pharmacokinetics of 4-week, multiple dermal applications of LT5001 drug product to the hemodialysis patients with uremic pruritus. **Part B:** To investigate the safety, and efficacy of 8-week, multiple dermal applications of LT5001 drug product to the hemodialysis patients with uremic pruritus.

Endpoints:	**Part A:** **Primary Endpoints** • Nature and severity of adverse events (AEs) and number of patients with AEs **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 at the end of Week 4. • Improvement in itch-related quality of life as assessed by the change from baseline in total Skindex-10 Scale score at the end of Week 4. **Part B:** **Primary Endpoints** • Change from baseline to end of Week 8 in mean Worst Itching Intensity using NRS. **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 at the end of Week 8. • Nature and severity of adverse events (AEs) and number of patients with AEs.

Subject Population	**Inclusion Criteria** 1. Male or female 20 to 75 years of age, inclusive, at the time of signing informed consent. 2. Patient must have been receiving in-center hemodialysis for ≥ 3 months and currently on a schedule of 3 times per week. 3. Patient must have had at least 2 urea reduction ratio (URR) measurements ≥ 65%, at least 2 single-pool Kt/V measurements ≥ 1.2, or 1 single-pool Kt/V measurement ≥ 1.2 and 1 URR measurement ≥ 65% on different dialysis days within the last 3 month period prior to randomization. 4. Body weight ≥ 40 kg (not to exceed 115 kg) and BMI ≥ 18.0 and ≤ 31.0 kg/m^2 at screening (after hemodialysis). 5. History of pruritus > 4 weeks of duration 6. Females with childbearing potential (defined as women ≤50 years of age with a history of amenorrhea for <12 months prior to study entry) must agree to use effective methods of contraception from screening through the last dose of study drug. 7. Males who are sexually active and whose partners are females of childbearing potential must agree to use condoms from screening through 90 days, whichever is longer, after administration of the last dose of study drug, and their partners must be willing to use a highly effective method of contraception from screening through 90 days after administration of the last dose of study drug. 8. Males must agree to not donate sperm from screening through 90 days, whichever is longer, after administration of the last dose of study drug. 9. Patient must have completed at least 6 days of Worst Itching Intensity NRS worksheets in the 7-day Diary run-in period and have a mean Worst Itching Intensity NRS score > 4 prior to randomization. 10. Patients must be able to complete questionnaires, understand the study procedures, and communicate effectively with the study personnel. **Exclusion Criteria** 1. [redacted]. 2. History of major surgery or trauma within 12 weeks of screening in the judgement of the investigator, or surgery planned during the study. 3. [redacted]

	[redacted] 4. Has had a significant alteration in dialysis regimen within 2 weeks of the Screening Visit or anticipated to be receiving nocturnal dialysis, home hemodialysis treatment, or kidney transplant during the study. 5. Has any known history of allergic reaction to opioids. 6. History of latest positive serology test for HBV (HBsAg) or HCV (anti-HCV) within 1 year prior randomization consistent with current infection. Confirmatory tests will be allowed at the discretion of the investigator to rule out false positives. 7. Has any known history of HIV. 8. Positive pregnancy test or is lactating. 9. Has required peritoneal dialysis. 10. Alanine aminotransferase and/or aspartate aminotransferase concentration > 2 x the ULN, or total bilirubin > 1.8 x ULN, or hemoglobin concentration < 9 g/dL at the Screening Visit. 11. Has taken other investigational drugs or participated in any clinical study within 30 days or 5 half-lives (if known) of the investigational drug's PK, PD, or biological activity (if known), whichever is longer, prior to first dose of study drug in this study or is currently participating in another clinical study. 12. Has received a vaccination within 3 days prior to administration of the first dose of study drug. 13. Has pruritus probably or definitely attributed to a cause other than renal disease or its complications such as atopic dermatitis, chronic urticarial, or hepatic pruritus caused by chronic liver disease. 14. Presence of skin infection (as defined by the investigator) on the area to be treated. 15. Any other condition or prior therapy that, in the investigator's opinion, would make the patient unsuitable for the study, or unable or unwilling to comply with the study procedures 16. Involved in the planning or conduct of this study. 17. Unwilling or unlikely to comply with the requirements of the study.

Study Design:	The study contains 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. **Part A:** This study will be a randomized, double-blind, placebo-controlled trial to enroll 18 hemodialysis patients (LT5001: Placebo =2:1) with moderate to severe pruritus between the ages of 20 to 75 years old. The study will assess safety, tolerability and the pharmacokinetic profile of LT5001 drug product when applied to skin for 4 weeks with uremic pruritus. After provision of written informed consent, each subject will be evaluated for study eligibility during the screening period, which is within 28 days prior to receiving the study drug (Day 1). During this period, patients need to daily record the worst itch NRS in the patient diary for 7 days (diary run-in). At least 6 of 7 daily Worst Itching Intensity NRS worksheet must be completed and mean NRS score > 4 to qualify. At screening, physical examination of the skin will be conducted as a full-body skin assessment, which will serve as subject's baseline skin condition. Patient's baseline skin condition will be used as reference for comparison in the application site examination from Visit 2 to 8 in Part A. After signing the informed consent, patients may continue but sustain the dosing regimen of all previous antipruritic prescription medication including oral antihistamine agents and/or corticosteroid during the study. However, gabapentin, pregabalin, topical antihistamine/ corticosteroid agents, OTC antihistamine/ corticosteroid agents for anti-pruritus treatment is prohibited throughout the study. Eligible patients will be randomized into LT5001 drug product or placebo treatment groups with 2:1 ratio. [redacted] Patient will be instructed to directly apply the study drug to the itch area. 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 undergo a 7-day repeated open application tests (7-day ROAT). A 0.5 fingertip unit of the study drug is recommended to apply to a 5x5 cm^2 fixed pre-marked zone without any skin lesions near the antecubital fossa twice daily in the morning and evening for 7 days. If skin lesions occurred on the antecubital fossa, accept to choose the volar forearm or ventral inner arm without skin lesion under the judgment of investigator to perform ROAT (avoid the area depicted in the Drug administration section).

	Patients will need to daily record the itch condition in the patient diary by themselves including the daily 24-hour worst itch NRS, application time/ site of the study drug, time and intensity of the itch between the morning and evening dose and return the diary at every visit. Patient need to return the study drug and the actual dosing in each patient will be determined by subtract the weight of each returned study drug subtract from the initial weight (T_0). Clinical laboratory tests will be obtained at Day 1, 15, 29. Blood sample for pharmacokinetics will be collected at pre-dose, 48, 120, 168, 336, 504, and 672 hrs post dosing. Subjects will return for a follow-up visit to complete safety evaluations for approximately 35 days after study drug administration. **Interim analysis and DSMB:** After Part A completion, the interim analysis will plan to be done. DSMB will review interim analysis and give comments on safety or any medical concern to determine whether the study continued or not. Also, DSMB will give comments for LT5001 drug product daily dose and regimen. **Part B:** This part of study will recruit 90 hemodialysis patients (LT5001: Placebo=1:1) with moderate to severe pruritus. The study will assess safety, and efficacy of LT5001 drug product when applied to skin for 8 weeks with uremic pruritus. Eligible patients will be randomized into LT5001 drug product and placebo treatment groups with 1:1 ratio. [redacted] The daily dose and recommended regimen may be adjusted based on DSMB recommendation. Patients will need to daily record the itch condition in the patient diary by themselves including the daily 24-hour worst itch NRS, application site of the study drug, time and intensity of the itch between the morning and evening dose and return the diary at every visit. They will visit at Day1, 8, 15, 22, 29, 36, 43, 50, and 57 after drug administration. If a subject is withdrawn from the treatment period of the study for reasons not associated with safety considerations, additional subjects may be enrolled if additional data are necessary to establish safety and tolerability.
Estimated Study Duration:	**Part A:** Approximately 6 weeks, includes 1 weeks of screening (Diary Run-in), 4 weeks of treatment and 1 week follow up. **Part B:**

	Approximately 9 weeks, includes 1 weeks of screening (Diary Run-in), 8 weeks of treatment.
Blood Sampling Schedule	**Pharmacokinetic Assessments** Blood Pharmacokinetic Assessments [redacted] • Pre-dose, 48, 120, 168, 336, 504, and 672 hrs post dosing
Safety Assessments:	The safety and tolerability of LT5001 drug product will be assessed via the following: • Adverse events • Vital signs (temperature, respiratory rate, systolic and diastolic blood pressure, and pulse rate) • Clinical laboratory tests • Physical examination • Application site examination (dermatitis, pruritus, paresthesia, erythema, dryness, vesicles, irritation, papules, burning)
Test Drug	LT5001 drug product [redacted]

Drug Administration	Topical administration The study medication will be applied directly to the itching area as instructed by the study staff. Avoid apply LT5001 drug product around the eyes, mouth, nose, mucous membrane, genital, anal region, vascular access for hemodialysis and its surrounding region (1 cm in both sides). Do not apply the study medication on to the vesicles, open wound, or on the area of erythema, rash, swelling, paresthesia, pain, desquamation, discoloration.
Sample Size:	**Part A:** Approximately 20 subjects will be screened to achieve 18 subjects enrolled (LT5001: Placebo=12:6). **Part B:** Approximately 100 subjects will be screened to achieve 90 subjects enrolled (LT5001: Placebo=45:45).
Statistical Methods:	**Safety Analyses** All safety analyses will be performed on the safety analysis set (SAS). Adverse events will be coded by System Organ Class and Preferred Term using the current version of MedDRA. Incidences of treatment-emergent AEs (TEAEs), ie, events that started after exposure to study drug or worsened in severity after dosing, will be presented by dose group. Incidences of TEAEs will also be presented by maximum severity and relationship to study medication. Safety data will be summarized through appropriate data tabulations, standard descriptive statistics, and graphical presentations. For each continuous laboratory parameter, results will be categorized as low, normal, or high based on the laboratory normal ranges. Frequencies and percentages will be presented by dose group for subjects who had a shift to low and for subjects who had a shift to high from baseline to any post-dosing assessment. The association of AEs, clinical laboratory tests, vital sign measurements with the actual dosing of study drug or systemic exposure of LT5001 drug product may also be explored. If appropriate, statistical modeling will be performed to further characterize the associations mentioned above. All out-of-range and clinically significant laboratory results will be identified in subject data listings. The number and percentage of subjects in each dose group with normal and abnormal physical examination results will be presented for evaluations at baseline and final visit. For each body system, changes in the subjects' findings from baseline to final visit (no change, normal to abnormal, or abnormal to normal) will be tabulated for each dose group. **Pharmacokinetics Analyses**

	Pharmacokinetics Parameters From the concentration-time data, the following blood PK parameters will be determined, as data permit: C_{trough} Lowest observed blood concentration prior to next application 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 Adjusted PK parameter= C_{trough}/ Actual Dose In addition, the original blood PK parameter (without dose adjustment) versus time will also be analyzed. 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. Pharmacokinetic parameters will be listed by subject and treatment using the SAS, and summarized by treatment using the using the pharmacokinetic analysis set (PKAS) and the following summary statistics: n, arithmetic mean, standard deviation (SD), CV%, minimum, median, and maximum. Geometric mean and geometric CV% will also be presented for all PK parameters. 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.

2 SCHEDULE OF ASSESSMENTS AND PROCEDURES

[redacted]

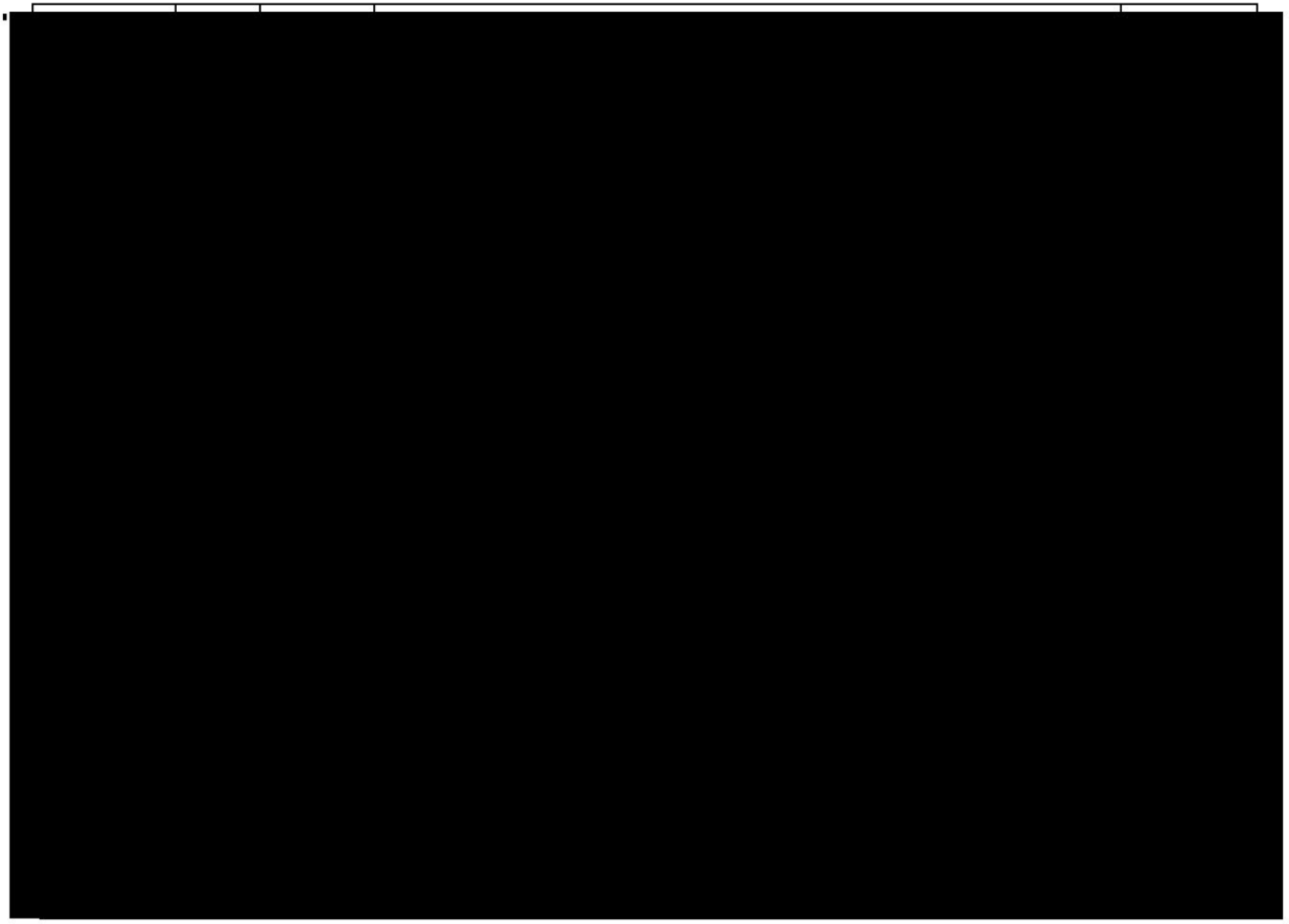


Table 2.2 Schedule of assessments and procedures- Part B

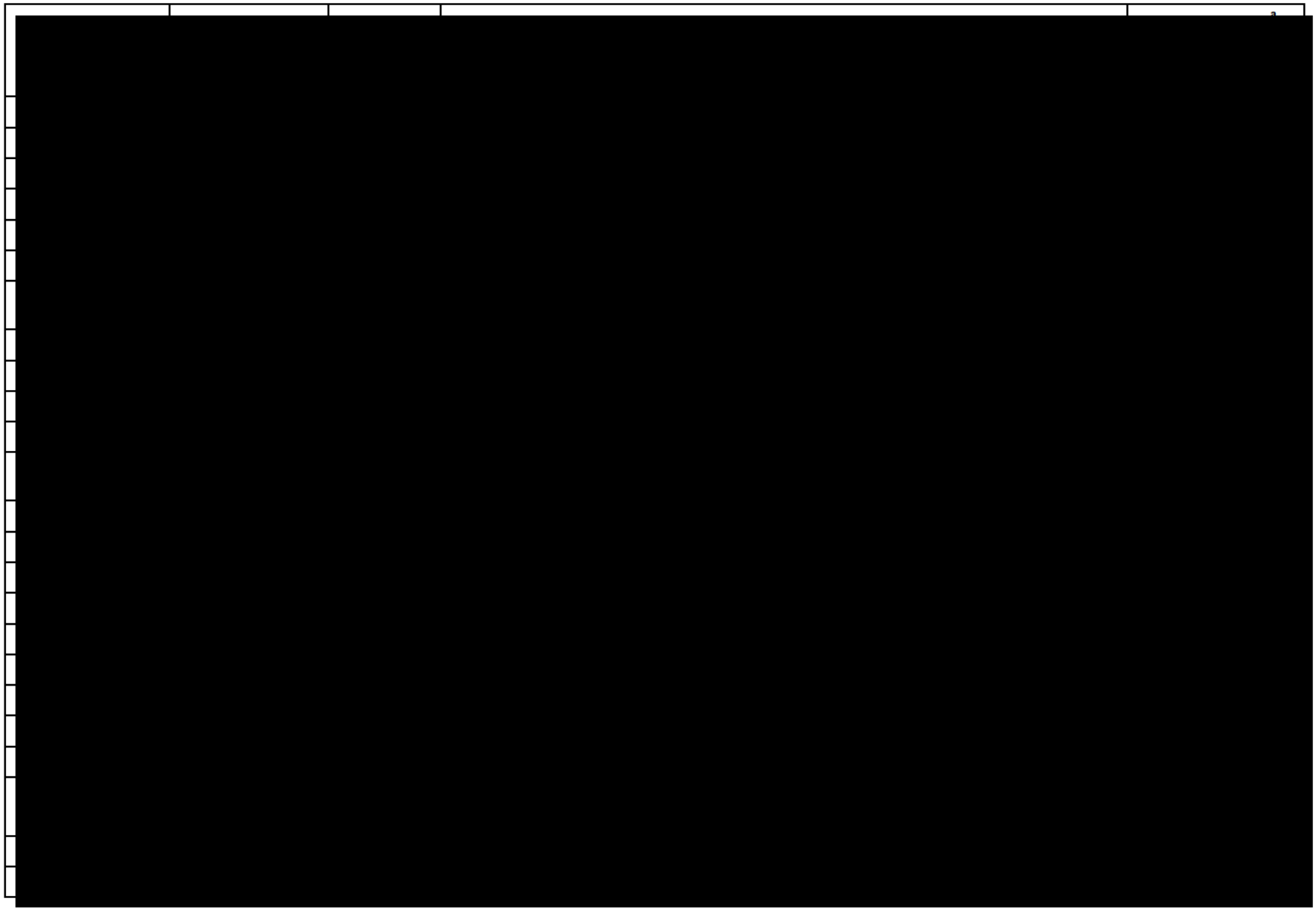


Table 2.3 Pharmacokinetic Sampling Schedule – Part A

Visit	Study Day	Time Relative to 1st Study Drug Administration (Hour)	Pharmacokinetic Blood Sample
0	-28 to -1	Not applicable	Not applicable
1	1	0 (predose)	X
2	3	48 ± 4 (trough)	X
3	6	120 ± 4 (trough)	X
4	8	168 ± 4 (trough)	X
5	15	336 ± 4 (trough)	X
6	22	504 ± 4 (trough)	X
7	29	672 ± 4 (trough)	X
8	36	Not applicable	Not applicable

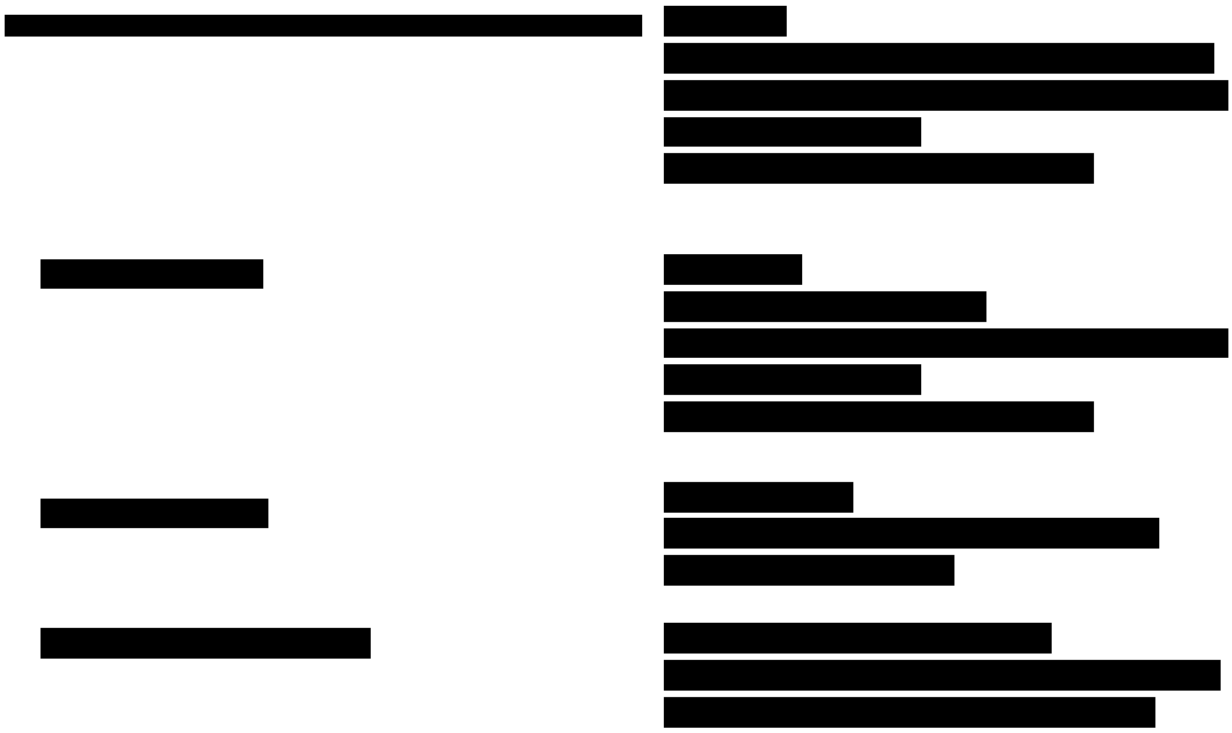
Pharmacokinetic samples will be collected as close to the nominal time point as possible. Allowable windows for PK collection will be ± 4 hours for all trough samples.

LIST OF ABBREVIATIONS

Abbreviation	Definition
UP	uremic pruritus
AE	adverse event
BLQ	below the limit of quantification
BMI	body mass index
BUN	blood urea nitrogen
CFR	Code of Federal Regulations
CNS	central nervous system
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
FDA	Food and Drug Administration
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
IEC	independent ethics committee
IRB	institutional review board
Itch NRS	itch numerical rating scale
NOAEL	no observed adverse effect limit
NRS	numerical rating scale
MedDRA	Medical Dictionary for Regulatory Activities
OTC	over-the-counter
PK	pharmacokinetic(s)
SAE	serious adverse event
SAS	safety analysis set
SD	standard deviation
SOP	standard operating procedure
SRM	study reference manual
ULN	upper limit of normal

STUDY ADMINISTRATIVE STRUCTURE

Sponsor: Lumosa Therapeutics Co., Ltd.



[redacted].

3.5 Hypotheses

The study is to determine the safety, local tolerance, PK, and explore the potential efficacy of 4-week (Part A) and the safety and efficacy of 8-week (Part B) multiple dermal applications of LT5001 drug product in the hemodialysis patients with moderate to severe UP.

4 OBJECTIVES

4.1 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.

4.2 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.

5 STUDY DESIGN

5.1 Study Design and Overview

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. The maximum daily dose and recommended regimen for Part B will depend on DSMB comments.

Part A:

Part A will be a randomized, double-blind, and placebo-controlled. It will enroll 18 patients between 20 to 75 years of age, inclusive.

After providing written informed consent, each patient will be evaluated for study eligibility within 28 days of Day 1. During this period, patient need to daily record the worst itch NRS in the patient diary for 7 days (diary run-in). At least 6 of 7 daily Worst Itching Intensity NRS worksheet must be completed and mean NRS score > 4 to qualify. At screening, physical examination of the skin will be conducted as a full-body skin assessment, which will serve as subject's baseline skin condition. Photographs of the treatment area may be considered under the investigator's judgment (optional). Patient's baseline skin condition will be used as reference for comparison in the application site examination from Visit 2 to 8 in Part A. After signing the informed consent, patients may continue previous antipruritic therapy throughout the study prescribed by the physician (unless specified in the prohibited medication Section 7.7.3).The dosing regimen of the previous antipruritic therapy cannot be changed. Gabapentin, pregabalin, topical antihistamine/ corticosteroid agents, OTC antihistamine/ corticosteroid agents are prohibited throughout the study. Eligible patients will be randomized into 2 groups (LT5001 drug product and Placebo) at a ratio of 2:1. [redacted]

Topical dosing will occur for 4 weeks, consisting of 56 total doses throughout the treatment period. Patient will be instructed to directly apply the study drug to the itch area. 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 undergo a 7-day repeated open application tests (ROAT). A 0.5 fingertip unit of the study drug is recommended to apply to a 5x5 cm^2 fixed pre-marked zone without any skin lesions near the antecubital fossa twice daily in the morning and evening for 7 days. If skin lesion is occurred in the antecubital fossa, it is acceptable to choose the volar forearm or ventral inner arm without skin lesion under the judgment of investigator to perform ROAT (avoid the area depicted in the Section 7.2 Treatments Administered). Patients will need to daily assess the itch condition at a fixed period by themselves and record in the patient diary including the daily 24-hour worst itch NRS,

application time/ site of the study drug, time and intensity of the itch between the morning and evening dose and return the diary at every visit.

Patients will visit the CRU for dosing on Day 1, and for procedures including clinical laboratory test samplings, physical examinations, vital sign assessments, itch assessment (Skindex-10 and 5D-itch scale), and application site assessments by ICDRG scale (dermatitis, pruritus, paresthesia, erythema, dryness, vesicles, irritation, papules, burning) according to Table 8.2, and PK blood samples will be performed according to Table 2.3. Application site evaluation will be conducted in each visit (Visit 2 to 8) in Part A. Photographs of the application site may be considered under the investigator's judgment (optional). Baseline skin condition performed at screening will be used as reference for comparison.

Patient will need to return the study drug during 3 times per week following his/her dialysis schedule. The actual dosing in each patient will be determined by subtract the weight of each returned study drug from the initial weight (T_0).

Patients will return for a follow-up visit to complete safety evaluations according to Table 2.1. Application site assessments (dermatitis, pruritus, paresthesia, erythema, dryness, vesicles, irritation, papules, burning) by ICDRG scale according to Table 8.2, AEs, and concomitant medications and procedures will be recorded.

Part B:

Part B will be randomized, double-blind, and placebo-controlled. It will enroll 90 patients between 20 to 75 years of age, inclusive.

After providing written informed consent, each patient will be evaluated for study eligibility during screening (within 28 days of Day 1). During this period, patient need to daily record the worst itch NRS in the patient diary for 7 days (diary run-in). At least 6 of 7 daily Worst Itching Intensity NRS worksheet must be completed and mean NRS score > 4 to qualify. At screening, physical examination of the skin will be conducted as a full-body skin assessment, which will serve as subject's baseline skin condition. Photographs of the treatment area may be considered under the investigator's judgment (optional). Patient's baseline skin condition will be used as reference for comparison in the application site examination from Visit 2 to 9 in Part B.

After signing the informed consent, patients may continue all previous antipruritic therapy prescribed by the physician throughout the study (unless specified in the prohibited medication Section 7.7.3). The dosing regimen of the previous antipruritic therapy cannot be changed. Gabapentin, pregabalin, topical antihistamine/ corticosteroid agents, OTC antihistamine/ corticosteroid agents are prohibited throughout the study. Eligible patients will be randomized into 2 groups (LT5001 drug product and Placebo) at a ratio of 1:1. Topical dosing will occur for 8 weeks. [redacted] Topical dosing will occur for 8 weeks. Patients will need to daily assess the

itch condition at a fixed period by themselves and record in the patient diary including the daily 24-hour worst itch NRS, application site/ time of the study drug, time and intensity of the itch between the morning and evening dose, and return the diary every visit.

Patients will visit the CRU for dosing on Day 1 and procedures including clinical laboratory test sampling, physical examinations, vital sign assessments, and itch assessment (Skindex-10 and 5D-itch scale), and application site assessments (dermatitis, pruritus, paresthesia, erythema, dryness, vesicles, irritation, papules, burning) by ICDRG scale according to Table 8.2, AEs, and concomitant medications and procedures will be performed according to Table 2.2. Application site evaluation will be conducted in each visit (Visit 2 to 9) in Part B. Photographs of the application site may be considered under the investigator's judgment (optional). Baseline skin condition performed at screening will be used as reference for comparison.

Patient will need to return the study drug during 3 times per week following his/her dialysis schedule. The actual dosing in each patient will be determined by subtract the weight of each returned study drug and subtract from the initial weight (T_0).

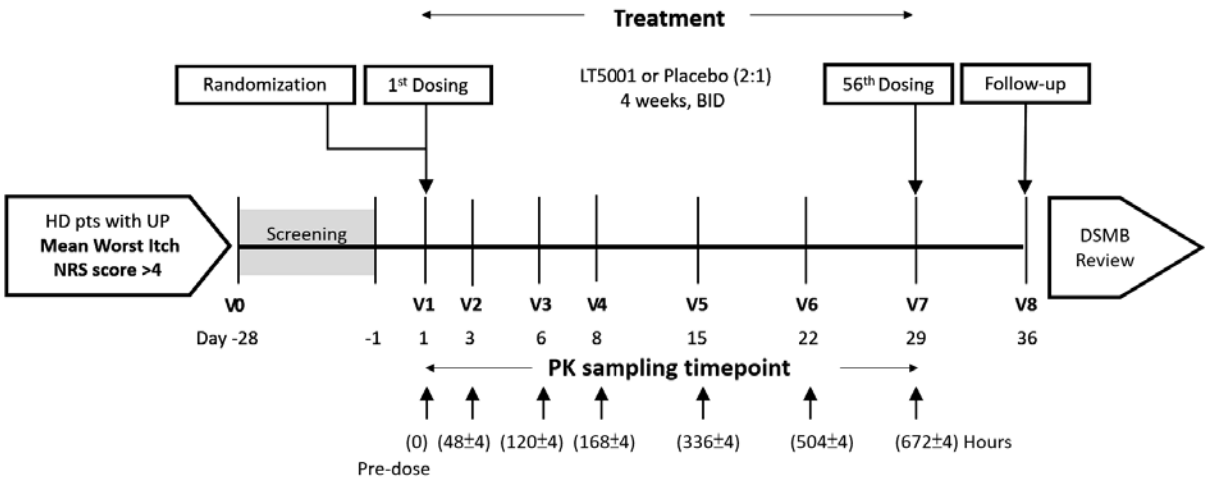


Figure 5.1 Study Design Schematic (Part A)

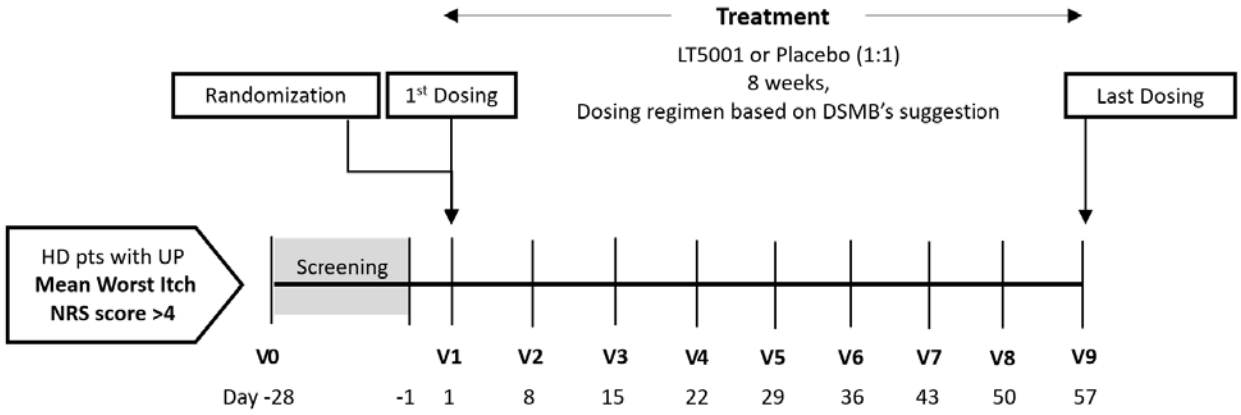


Figure 5.2 Study Design Schematic (Part B)

5.1.1 Interim Safety/ Pharmacokinetic Data Review

Subject will receive application site examination at each visit (Part A: Visit 2 to 8; Part B: Visit 2 to 9) assessed by the trained study team, using ICDRG scale. If subject experience a new or worsening localized skin reaction in the treatment area, the subject should report to the study coordinator and/or investigator during the visit. Baseline skin condition conducted at screening in the physical examination should be used as a reference for comparison. All AEs should be recorded in the eCRF

If a subject experience 1 newly arise acute inflammation of the skin (e.g. pain, transient erythema, vesiculation, severe swelling with bullae, ulceration, or even both) at the application site, and is related (at least possible) with study drug, study treatment is recommended to be interrupted. Upon resolution of the acute inflammation, subject may resume study treatment upon investigator's judgment.

After completion of 18 subjects in Part A, the DSMB will convene to review all safety and PK data. Part B will only occur if the DSMB determines that the current dose was safe and well-tolerated. Doses for Part B will be decided by the DSMB after their review of the cumulative safety data targeted for review (AEs, vital signs, clinical laboratory results, physical examination results, itch results, and application site examination results) and available PK data from Part A. Sponsor will make the final decision in an unblinded fashion.

An ad hoc DSMB meeting will be convened 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 ≥ 1+ found during the first 7 days of study treatment, ad hoc DSMB meeting will be held to review the safety data and recommend in writing to Sponsor whether to continue, modify, or stop the clinical study on the basis of safety considerations.

2. In the event of ≥ 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 ≥ 1+ found during the first 7 days of study treatment, ad hoc DSMB meeting will also be convened to discuss the safety events to recommend Sponsor whether to continue, modify, or suspension the enrollment of the study.

DSMB members will include experts in the disease under study and biostatistics who are not participating in this study and do not have affiliation with the Investigators or the Sponsor. Full details of the role, remit and membership of the DSMB will be detailed in a separate DSMB Charter

5.1.2 Duration of Study

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.

5.1.3 Definition of Study Completion

End-of-study procedures will be performed as specified in the schedules of assessments (Table 2.1 and Table 2.2); patients who withdraw from the study early will have EOS procedures performed at the time or within 7 days of discontinuation. Patients with ongoing clinically significant clinical or laboratory findings will be followed until the finding is resolved or medically stable; reasonable attempts will be made to follow-up with patients. The patient's participation in the study will end once all study assessments and follow-up have been completed.

5.1.4 End of Study

The end of the study is defined as the date when the last patient has completed all study procedures up to and including the EOS/early termination visit as specified in the schedules of assessments (Table 2.1 and Table 2.2).

6 SELECTION AND WITHDRAWAL OF PATIENTS

Patients must meet all the following inclusion criteria and none of the exclusion criteria in order to be enrolled in this study. Prospective approval of protocol deviations to recruitment and enrollment criteria, also known as protocol waivers or exemptions, is not permitted.

6.1 Inclusion Criteria

Patients must meet all inclusion criteria to be eligible for study participation.

1. Male or female 20 to 75 years of age, inclusive, at the time of signing informed consent.
2. Patient must have been receiving in-center hemodialysis for ≥ 3 months and currently on a schedule of 3 times per week.
3. Patient must have had at least 2 urea reduction ratio (URR) measurements ≥ 65%, at least 2 single-pool Kt/V measurements ≥ 1.2, or 1 single-pool Kt/V measurement ≥ 1.2 and 1 URR measurement ≥ 65% on different dialysis days within the last 3 month period prior to randomization.
4. Body weight ≥ 40 kg (not to exceed 115 kg) and BMI ≥ 18.0 and ≤ 31.0 kg/m^2 at screening (after hemodialysis).
5. History of pruritus > 4 weeks of duration
6. Females with childbearing potential (defined as women ≤50 years of age with a history of amenorrhea for <12 months prior to study entry) must agree to use effective methods of contraception from screening through the last dose of study drug.
7. Males who are sexually active and whose partners are females of childbearing potential must agree to use condoms from screening through 90 days, whichever is longer, after administration of the last dose of study drug, and their partners must be willing to use a highly effective method of contraception from screening through 90 days after administration of the last dose of study drug.
8. Males must agree to not donate sperm from screening through 90 days, whichever is longer, after administration of the last dose of study drug.
9. Patient must have completed at least 6 days of Worst Itching Intensity NRS worksheets in the 7-day Diary run-in Period and have a mean Worst Itching Intensity NRS score > 4 prior to randomization.
10. Patients must be able to complete questionnaires, understand the study procedures, and communicate effectively with the study personnel.

6.2 Exclusion Criteria

Patients will not be eligible for study participation if they meet any of the exclusion criteria, or will be discontinued at the discretion of the investigator in consultation with the medical monitor if they develop any of the exclusion criteria during the study.

[redacted]

2. History of major surgery or trauma within 12 weeks of screening in the judgement of the investigator, or surgery planned during the study.
3. [redacted].
4. Has had a significant alteration in dialysis regimen within 2 weeks of the Screening Visit or anticipated to be receiving nocturnal dialysis, home hemodialysis treatment, or kidney transplant during the study.
5. Has any known history of allergic reaction to opioids.
6. History of a latest positive serology test for HBV (HBsAg) or HCV (anti-HCV) within 1 year prior randomization consistent with current infection. Confirmatory tests will be allowed at the discretion of the investigator to rule out false positives.
7. Has any known history of HIV.
8. Positive pregnancy test or is lactating.
9. Has required peritoneal dialysis.
10. Alanine aminotransferase and/or aspartate aminotransferase concentration > 2 x the ULN, or total bilirubin > 1.8 x ULN, or hemoglobin concentration < 9 g/dL at the Screening Visit.
11. Has taken other investigational drugs or participated in any clinical study within 30 days or 5 half-lives (if known) of the investigational drug's PK, PD, or biological activity (if known), whichever is longer, prior to first dose of study drug in this study or is currently participating in another clinical study.
12. Has received a vaccination within 3 days prior to administration of the first dose of study drug.
13. Has pruritus probably or definitely attributed to a cause other than renal disease or its complications such as atopic dermatitis, chronic urticarial, or hepatic pruritus caused by chronic liver disease.
14. Presence of skin infection (as defined by the investigator) on the area to be treated.

15. Any other condition or prior therapy that, in the investigator's opinion, would make the patient unsuitable for the study, or unable or unwilling to comply with the study procedures
16. Involved in the planning or conduct of this study.
17. Unwilling or unlikely to comply with the requirements of the study.

6.3 Screen Failures

Patients who are discontinued from the study prior to study drug administration will be considered screen failures. The patient may be re-screened if the patient was not discontinued from the study due to noncompliance with the protocol, and also the investigator considers the patient suitable to participate in the study. If the patient is re-screened, the patient must be re-consented.

Screen failure data will be recorded in the eCRF.

6.4 Patient Withdrawal

Patients are free to withdraw from the study at any time, for any reason, and without prejudice to further treatment. The investigator may withdraw a patient if, in the investigator's judgment, continued participation would pose unacceptable risk to the patient or to the integrity of the study data. All procedures for early withdrawal must be completed. Reasons for withdrawal may include:

- AE
- Lost to follow-up
- Physician decision
- Pregnancy
- Protocol deviation
- Study terminated by Sponsor
- Withdrawal by patient
- Death
- Noncompliance with study drug or procedure
- Other

If patients who are withdrawn for reasons other than AEs, additional patients may be enrolled if additional data are necessary to establish safety and tolerability.

In the event of a patient's withdrawal, the investigator will promptly notify the medical monitor and will make every effort to complete the follow-up/EOS assessments. All withdrawn patients with ongoing clinically significant clinical or laboratory findings will be followed until the

finding is resolved or medically stable; reasonable attempts will be made to follow-up with patients.

6.5 Early Termination of Study

The study may be terminated at any time by the Sponsor if serious side effects occur, if potential risks to study participants are identified, if the investigator does not adhere to the protocol, or if, in the Sponsor's judgment, there are no further benefits to be achieved from the study. In the event that the clinical development of the study drug is discontinued, the Sponsor shall inform all investigators/institutions and regulatory authorities.

7 TREATMENT OF PATIENTS

7.1 Identity of Study Drugs

A description of the study drugs is presented in Table 7.1.

Table 7.1 Study Drugs

[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]

[redacted]

7.2 Treatments Administered

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. If skin lesion is occurred in the antecubital fossa, it is acceptable to choose the volar forearm or ventral inner arm without skin lesion under the judgment of investigator to perform ROAT (avoid the area depicted below).

Avoid apply LT5001 drug product around the eyes, mouth, nose, mucous membrane, genital, anal region, vascular access for hemodialysis and its surrounding region (1 cm in both sides). Do not apply the study medication on to the vesicles, open wound, or on the area of erythema, rash, swelling, paresthesia, pain, desquamation, discoloration.

Part A:

LT5001 drug product will be applied BID in the morning and evening per the schedule of assessment in Table [redacted].

Part B:

The dosing regimen will adjust according to DSMB suggestion after Part A completion. If DSMB has no comment for frequency of treatment administration, the dosing regimen will be kept the same as Part A. [redacted].

7.3 Method of Assigning Patients to Treatment Groups

The CROs will prepare the randomization scheme in accordance with its SOPs and the randomization plan, which reflect GCP standards. Refer to Section 10.3 for a description of

randomization methods. Eligible patients will be assigned to a treatment group according to the list of patient randomization assignments.

7.4 Measurements of Treatment Compliance

Study drugs will be administered by delegated and trained staff at the CRUs. Details regarding dosing, including the dose administered and the date and time of dosing, will be recorded.

7.5 Study Drug Storage, Accountability, and Retention

7.5.1 Storage Conditions

The investigator will ensure that all the study drugs are stored and dispensed in accordance with the regulations from the regulatory authority concerning the storage and administration of investigational drugs.

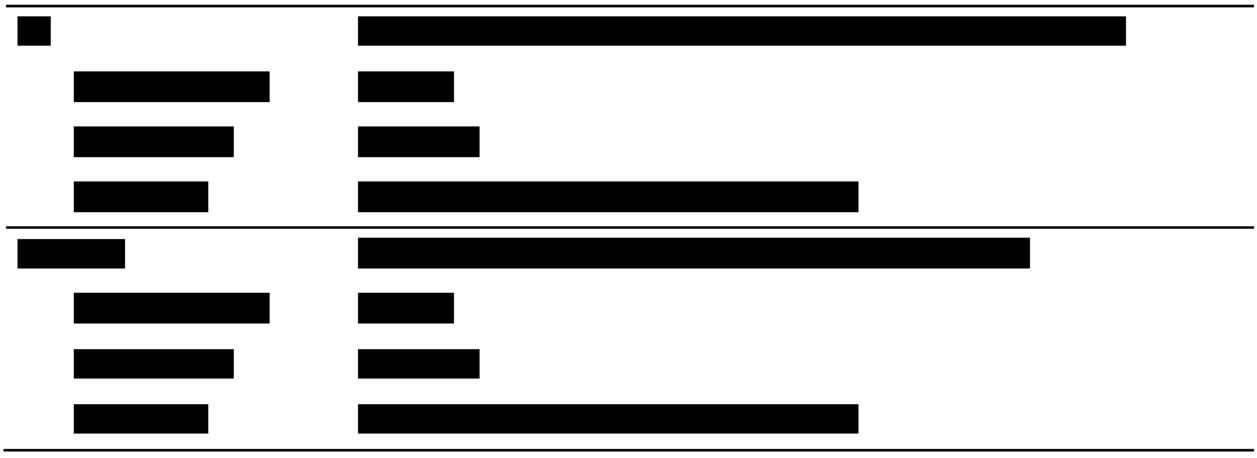
LT5001 drug product will be stored at controlled room temperature (≤ 25°C) in the original packaging.

7.5.2 Drug Accountability and Retention

The investigators must ensure that all study drug supplies are kept in a secure locked area with access limited to those authorized by the investigator. The investigator must maintain accurate records of the receipt of all study drug shipped by Lumosa Therapeutics Co., Ltd. or their representative, including but not limited to the date received, lot number, expiration date, amount received, and the disposition of all study drug. Current dispensing records will also be maintained including the date and amount of study drug dispensed and the patient receiving the drug. All remaining study drug not required by regulations to be held by the CRU must be returned to Lumosa Therapeutics Co., Ltd. or their representative immediately after the study is completed.

7.6 Packaging and Labeling

7.6.1 Study Drug



7.6.2 Blinding of Treatment Assignment

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.

7.6.3 Unblinding of Treatment Assignment

7.6.3.1 Unblinding for Adverse Event/Safety Reasons

Should an SAE or other circumstance require that the blind be broken to ensure patient safety, the investigator must immediately notify the medical monitor. The medical monitor will notify the Sponsor as soon as possible and will release the treatment assignment of the patient to the appropriate personnel in accordance with the applicable study-specific procedure.

If the treatment assignment is unblinded by the site pharmacist or any party other than CRO, the investigator must notify CRO in writing and document the course of events in the source records. Any patient for whom the treatment code is prematurely released will be withdrawn from the study.

7.7 Concomitant Medications & Procedures/ Prohibited medication/ Other Restrictions

7.7.1 Concomitant Medications

Concomitant medications during the study will be documented on the concomitant medication eCRF. Information recorded will include: start and stop dates and times, dose and route of administration, and indication.

- <u>Allowed concomitant medication</u>

  Concomitant medications or vaccinations may be administered if they are prescribed or confirmed by the investigator for the treatment of specific clinical events. When possible, the Sponsor will be consulted before administration of concomitant medications. Maintenance medications as prescribed by the patient's physicians are permitted.

- <u>Allowed but need to maintain stable treatment regimen</u>

  After signing informed consent, subjects may continue previous antipruritic therapy prescribed by their physician throughout the study (unless specified in the prohibited

medication Section 7.7.3), including but not limited to oral antihistamine agents and corticosteroids. The antipruritic regimen must maintain stable (defined as no change in prescription) throughout the study.

Medications for the management of serum phosphorus, calcium, or iPTH is recommended to maintain stable unless are permitted by the subject's physician for the treatment of specific clinical events. .

7.7.2 Concomitant procedures

No concomitant procedures other than dialysis will be performed during the study unless approved by the investigator. Medications taken for a procedure will also be included on the concomitant medication eCRF, as well as the procedure itself.

7.7.3 Prohibited medication

Gabapentin, pregabalin, and topical antihistamine/ corticosteroids are prohibited throughout the study. Administration of OTC antihistamine and corticosteroids for antipruritic treatment are also not allowed.

7.7.4 Other Restrictions

Patients will be instructed to adhere to the following restrictions:

- Patients are not permitted to participate in any other clinical trial or donate blood or plasma while participating in this clinical trial.

8 STUDY ASSESSMENTS AND PROCEDURES

Patients will undergo study procedures and assessments at time points specified in the schedule of assessments (Table 2.1, Table 2.2, and Table 2.3)

8.1 Diary run-in (7-days itch NRS)

Subject need to record the daily worst itching intensity NRS for 7 days in the patient diary at screening. At least 6 of 7 itch NRS must be completed and the mean NRS score > 4 to be qualified for participation in the study.

After signing informed consent, a patient diary will be provided to the subject for the Diary run-in procedure at screening. Patient eligibility will be confirmed after completion the study procedures specified in the schedule of assessment. In practice, the order of the procedures should be: (1) obtain informed consent (2) review inclusion and exclusion criteria (3) Diary run-in and all other assessments for screening indicated in the schedule of assessments (Table 2.1, Table 2.2) (4) confirm eligibility (5) randomization.

8.2 7-days Repeated open application tests (7-days ROAT)

In the first 7 days of study treatment, subject will need to undergo a 7-day repeated open application tests (ROAT). A 0.5 fingertip unit of the study drug is recommended to apply to a 5x5 cm^2 fixed pre-marked zone without any skin lesions near the antecubital fossa twice daily in the morning and evening for 7 days. If skin lesion is occurred in the antecubital fossa, it is acceptable to choose the volar forearm or ventral inner arm without skin lesion under the judgment of investigator to perform ROAT (avoid the area depicted in the Section 7.2 Treatments Administered).

During the 7-days ROAT, the pre-marked zone applied with the study drug will be examined and assessed by ICDRG scale in each visit (details in Section 8.8.6 Application Site Examination). In the event of ICDRG ≥ + that is considered clinically significant will be recorded as AE. The investigator may photograph the skin condition if the investigator considered helpful for the safety assessment in the DSMB meeting (optional).

8.3 Medical and Surgical History

The investigator or designee will collect a complete medical and surgical history within 3 months prior signing ICF at screening.

8.4 Demographic Characteristics

Demographic characteristics including sex, age, race will be recorded at screening.

8.5 Physical Measurements

Height (cm) and body weight (kg) (after hemodialysis) without shoes will be recorded. Body mass index will be calculated using the height obtained at screening.

8.6 Itch assessments

8.6.1 Daily Assessment of the itch intensity by the patient

Subjected will be instructed by the study personnel to daily self-record the itch intensity by NRS (Appendix A) in the patient diary in a fixed period. The following information will need to be documented during the study.

Diary run-in (7 days itch NRS):

- The daily worst itch NRS

From Day 1 to the end of study:

- The time of the drug administration
- The application site of the drug
- The daily worst itch NRS
- The time of the itch before the next dose administration
- The intensity of the itch before the next dose administration assessed by NRS

8.6.2 Questionnaire interviewed by investigator or designee

The Skindex-10 Scale and 5-D Itch scale are both multidimensional scales not only access pruritus intensity but measure the impact of pruritus on patients. The Skindex-10 evaluate how the patient's itch affects three important domains of quality of life including 3 domains (disease, mood/emotional distress, and social functioning) as noted in in Appendix B. Subjects filled one of seven bubbles ("0 [never bothered], 1, 2, 3, 4, 5, and 6 [always bothered]") for each of the questions. The total score was the sum of the numeric value of each answered question ranging from 0 to 60, with higher scores indicating worse itch-related quality of life. The 5-D itch scale include 5 domains (the duration, degree, direction, disability, and distribution) as noted in Appendix C, with a total score ranging from 5 (no itching) to 25 (maximum severity).

The Skindex-10 and 5-D Itch scale will be performed when patients were in the dialysis unit. The investigator or designee will conduct a face-to-face interview to assist the subject complete the Skindex-10 Scale and 5-D Itch scale. Before the interview, the investigator or designee will be trained by the medical monitor to ensure the accuracy and maintain the consistency of the interview across individuals. Subjects will complete the questionnaire without input on the answers from the study team.

The questionnaire interview will be conducted every 2 weeks at day 1 (Visit 1), day 15 (Visit 5), and day 29 (Visit 7) in Part A, and day 1 (Visit 1), day 15 (Visit 3), day 29 (Visit 5), day 43 (Visit 7), day 57 (Visit 9) in Part B as noted in the schedule of assessments (Table 2.1, Table 2.2).

In practice, the order of the procedures is recommended as follows but may be adjusted upon investigator's judgement: (1) Before dialysis: vital signs, blood sampling for the PK and

laboratory tests (2) During dialysis: Skindex-10 Scale and 5-D Itch scale (3) After dialysis: body weight, physical examination, and other safety assessment procedures.

8.7 Pharmacokinetic Assessments

8.7.1 Drug Concentration Measurements

Blood PK samples will be collected in Part A only; at time points specified in the PK sampling schedule (Table 2.3). Blood sample collection, processing, and shipping details will be outlined in a separate SRM.

[redacted]

8.7.2 Pharmacokinetic Parameters

The following PK parameter will be determined:

C_{trough}	The lowest observed blood concentration prior to next application

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:

Adjusted PK parameter = C_{trough}/ Actual Dose

The actual dosing in each patient will be determined by subtract the weight of each returned study drug and subtract from the initial weight (T_0). In addition, the original blood PK parameter without dose adjustment (C_{trough}) versus time will also be analyzed.

8.8 Safety Assessments

8.8.1 Adverse Events

Patients will be monitored for AEs according to Section 9.

8.8.2 Clinical Laboratory Tests

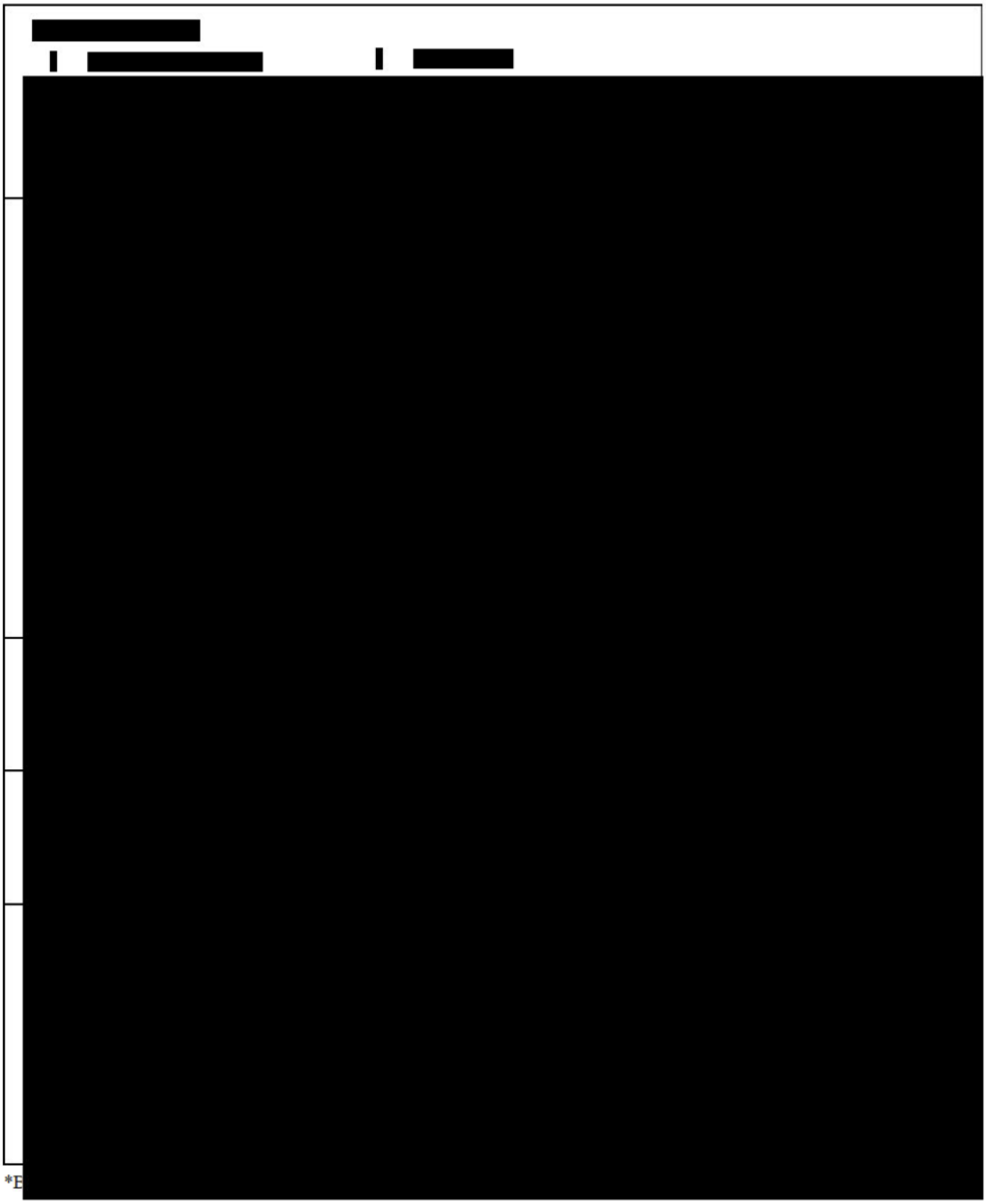
A certified laboratory will be utilized to process and provide results for the clinical laboratory tests listed in Table 8.1. Clinical laboratory test will be conducted every 2 weeks as indicated in the schedule of assessments (Table 2.1, Table 2.2). The assessment time for specific tests such as BUN, intact PTH, serum or urine β-hCG, URR, Kt/V is listed in Table 8.1.

The baseline laboratory test results for clinical assessment for a particular test will be defined as the last measurement prior to the first dose of study drug. Blood collection for clinical laboratory tests will be performed before dialysis unless specified in the BUN test in Table 8.1.

During the screening period, if a patient has an out-of-range value for a clinical laboratory parameter that the investigator believes is not clinically significant or the investigator does not believe is correct (eg, lab or specimen processing error), but the investigator wants to confirm with a repeat laboratory test, a single repeat is allowed to confirm the initial result. However, only the final verified data confirmed by the investigator need be recorded in the eCRF.

Additional safety laboratory tests may be conducted as needed by the investigator to evaluate patient safety.

Table 8.1 Clinical Laboratory Tests *



*E

For any laboratory test value outside the reference range that the investigator considers clinically significant during the on-study period (ie, following dose administration), the investigator will:

- Repeat the test to verify the out-of-range value and clinical significance but only the final verified data confirmed by the investigator need be recorded in the eCRF.
- Follow the out-of-range value until the value returns to normal or baseline, or until the value is deemed stable and not clinically significant by the investigator.
- Record as an AE any laboratory test value that is confirmed by repeat and the investigator considers clinically significant, requires a patient to be discontinued from the study, requires a patient to receive treatment, or requires a change or discontinuation of the study drug (if applicable).

8.8.3 Other Tests

The following test history will be reviewed or performed:

- History of latest serology test (ie, HBsAg, HCV antibody, and any confirmatory tests performed at the discretion of the investigator)
- History of HIV
- Serum or urine β-hCG test (females only)

8.8.4 Vital Signs

Vital signs assessments will include temperature (°C), respiratory rate (breaths per minute), systolic and diastolic blood pressure (mmHg), and pulse rate (bpm). Vital signs will be measured after the patient has been resting quietly in a seated position for at least 5 minutes. Any clinically significant abnormal vital sign assessment requires at least one repeat measurement but only the final verified data confirmed by the investigator need be recorded in the eCRF.

A vital signs abnormality that is considered clinically significant initially and on confirmation, requires a patient to be discontinued from the study, requires a patient to receive treatment, or requires a change or discontinuation from the study drug (if applicable) will be recorded as an AE.

8.8.5 Physical Examination

At Screening, comprehensive physical examinations (excluding genital, rectal, and breast examinations [unless indicated) will be performed. In addition, physical examination of the skin will be conducted as a full-body skin assessment, which will serve as subject's baseline skin condition. Abnormal findings will be documented in the patient's eCRF. The investigator may consider photograph the skin condition of the treatment area upon his/her judgement (optional). Subject's baseline skin condition will be used as reference for comparison in the application site examination.

Targeted symptom-driven physical examinations will be performed on Day 1, 3, 6, 8, 15, 22, and 29 of each treatment period and at the end-of-study visit.

An abnormal physical examination finding that is considered clinically significant and requires the patient to be discontinued from the study, requires the patient to receive treatment, or requires a change or discontinuation of the study drug (if applicable) will be recorded as an AE.

8.8.6 Application Site Examination

Application Site Examination will be conducted at Visit 2 to 8 in Part A and Visit 2 to 9 in Part B as indicated in schedule of assessment (Table 2.1, Table 2.2). Application site evaluation will be conducted by comparing the skin of the application site with the baseline skin condition in each visit.

The application site evaluation will include dermatitis, pruritus, paresthesia, erythema, dryness, vesicles, irritation, papules, burning assessed by ICDRG scale (Table 8.2). An abnormal application site finding that is considered clinically significant will be recorded as AE. The investigator may consider photograph the skin condition under the consent of the subject if the investigator considered helpful for the safety assessment in the DSMB meeting (optional).

Table 8.2 Grading score by International Contact Dermatitis Research Group (ICDRG)

Grading	Morphology	Interpretation
–	No reaction	Negative
±?	Erythema only, no infiltration	Doubtful reaction
+	Erythema, infiltration, possibly discrete papules	Weak positive reaction
++	Erythema, infiltration, papules, vesicles	Strong positive reaction
+++	Erythema, infiltration, confluent vesicles	Extreme positive reactions
Ir	Different types of reactions (dermatitis, paresthesia, dryness, burning)	Irritant reaction

8.8.7 Appropriateness of Safety Assessments

Safety evaluations selected for this study are typical of those for this patient population and utilize widely accepted measures.

9 ADVERSE EVENTS

An AE is defined as any untoward medical occurrence in a patient administered a pharmaceutical product during the course of a clinical investigation. An AE can therefore be any unfavorable and unintended sign, symptom, or disease temporally associated with the use of a study drug, whether or not thought to be related to the study drug.

Each AE will be collected from the signing of the ICF until the follow-up/end-of-study visit. Adverse events that are identified at the last assessment visit (or the early termination visit) must be recorded on the AE eCRF with the status of the AE noted. All events that are ongoing at this time will be recorded as ongoing on the eCRF. If the Investigator indicates the AE is "probably", "possibly", or "definitely" related to the study drug, the AE must be followed until they are resolved or medically stable, or until reasonable attempts to determine resolution of the event are exhausted. The investigator should use his/her discretion in ordering additional tests as necessary to monitor the resolution of such events.

The procedures specified in Section 9.4 are to be followed for reporting SAEs.

9.1 Recording Adverse Events

Adverse events are to be recorded on the AE page of the eCRF. The following information will be recorded:

- Assessment of whether or not the AE is an SAE (Section 9.2.1)
- Assessment of AE intensity (Section 9.2.2)
- Assessment of AE relationship to study drug (Section 9.2.3)
- Action taken - categorized as dose increased or decreased, dose not changed, drug interrupted, drug withdrawn, not applicable, or unknown, as applicable
- Outcome - recorded as fatal, not recovered/not resolved, recovered/resolved, recovered/resolved with sequelae, recovering/resolving, or unknown, as applicable

9.2 Assessment of Adverse Events

The investigator will assess each AE for seriousness, intensity, and relationship to study drug.

9.2.1 Serious Adverse Events

The investigator is responsible for determining whether an AE meets the definition of an SAE. An SAE is any AE occurring from ICF signing through follow-up that results in any of the following outcomes:

- Death
- A life-threatening adverse drug experience
- Inpatient hospitalization or prolongation of existing hospitalization
- A new persistent or significant disability/incapacity
- A congenital anomaly/birth defect
- An important medical event(s)

Important medical events that may not result in death, be life threatening, or require hospitalization may be considered an SAE when, based upon appropriate medical judgment, they may jeopardize the patient and may require medical or surgical intervention to prevent any of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

Note: SAEs require immediate reporting to the Sponsor. Refer to Section 9.4 for details.

9.2.2 Intensity

The intensity of an AE will be graded according to the following definitions:

- Mild: The patient experiences awareness of symptoms but these are easily tolerated or managed without specific treatment.
- Moderate: The patient experiences discomfort enough to cause interference with usual activity, and/or the condition requires specific treatment.
- Severe: The patient is incapacitated with inability to work or do usual activity, and/or the event requires significant treatment measures.

9.2.3 Relationship to Study Drug

The relationship of an AE to the study drug should be determined by the investigator according to the following criteria:

- Unrelated: This category applies to those AEs that are clearly and incontrovertibly due to extraneous causes (disease, environment, etc).
- Unlikely: This category applies to those AEs that are judged to be unrelated to the test drug/study procedure gut for which no extraneous cause may be found. An AE may be considered unlikely to be related to investigational product/procedure if or when it meets

2 of the following criteria:(1) it does not follow a reasonable temporal sequence from administration of the test drug/study procedure; (2) it could readily have been produced by the patient's clinical state, environmental or toxic factors, or other modes of therapy administered to the patient; (3) it does not follow a known pattern of response to the test drug/study procedure; or (4) it does not reappear or worsen when the drug/study procedure is re-administered.

- Possibly: This category applies to those AEs for which a connection with the test drug/study procedure administration appears unlikely but cannot be ruled out with certainty. An AE may be considered possibly related if or when it meets 2 of the following criteria: (1) it follows a reasonable temporal sequence from administration of the drug/study procedure; (2) it could not readily have been produced by the patient's clinical state, environmental or toxic factors, or other modes of therapy administered to the patient; or (s) it follows a known pattern of response to the test drug/study procedure.
- Probably: This category applies to those AEs that the investigator feels with a high degree of certainty are related to the test drug/study procedure. An AE may be considered probably related if or when it meets 3 of the following criteria: (1) it follows a reasonable temporal sequence from administration of the drug/study procedure; (2) it could not be reasonably explained by the known characteristics of the patient's clinical state, environmental or toxic factors, or other modes of therapy administered to the patient; (3) it disappears or decreases on cessation or reduction in dose (note that there are exceptions where an AE does not disappear upon discontinuation of the drug, yet drug-relatedness clearly exists; for example, as in bone marrow depression, fixed drug eruptions, or tardive dyskinesia); or (4) it follows a known pattern of response to the test drug/study procedure.
- Definitely: This category applies to those AEs that the investigator feels are incontrovertibly related to test drug/study procedure. An AE may be assigned an attribution of definitely related if or when it meets all of the following criteria: (1) it follows a reasonable temporal sequence from administration of the drug/study procedure; (2) it could not be reasonably explained by the known characteristics of the patient's clinical state, environment or toxic factors, or other modes of therapy administered to the patient; (3) it disappears or decreases on cessation or reduction in dose and reoccurs with re-exposure to the drug (if re-challenge occurs); and (4) it follows a known pattern of response to the test drug/study procedure.

9.3 Discontinuation due to Adverse Events

Any patient who experiences an AE may be withdrawn at any time from the study at the discretion of the investigator. Patients withdrawn from the study due to an AE, whether serious or nonserious, may be followed by the investigator until the clinical outcome of the AE is determined. The AE(s) should be noted on the appropriate eCRFs and the patient's progress

should be followed until the AE is resolved or medically stable as determined by the investigator. The Sponsor must be notified. If the AE relates to overdose of study treatment, the Investigator's Brochure should be consulted for details of any specific actions to be taken.

9.4 Reporting Serious Adverse Events

In the event of any SAE reported or observed during the study, whether or not attributable to the study drug, site personnel will record and report it to the Sponsor or designee within 24 hours of occurrence or when the investigator becomes aware of the event in accordance with procedures described in the SRM. If the investigator reports the SAE by telephone, a written report must follow within 24 hours including a full description of the event and sequelae in the format detailed in the SAE reporting form.

SAE Report Forms will be provided to the CRU to assist in collecting, organizing, and reporting SAEs and follow-up information.

All SAEs should be followed to their resolution, with documentation provided to the Sponsor on a follow-up SAE Report Form.

Contacts for SAE Reporting:

[redacted]

[redacted]

[redacted]

9.5 Pregnancy

Pregnancies will be captured if they occur in female patients from the time the patient is first exposed to the study drug until 30 days after the last exposure or the last study visit, whichever occurs later. Pregnancies in the sexual partners of male patients will be captured from the time the patient is first exposed to the study drug until 90 days after last exposure to the study drug.

Female patients must be instructed to discontinue all study drugs and inform the study investigator immediately if they become pregnant during the study.

The investigator must report any pregnancy to the Sponsor or designee within 1 business day of becoming aware of the pregnancy per pregnancy reporting procedures described in the SRM. The patient must be immediately discontinued from further treatment with study drug. An uncomplicated pregnancy will not be considered an AE or SAE; however, all pregnancies will be followed through birth and 3 months post delivery.

Any congenital abnormalities in the offspring of a patient who received study drug will be reported as an SAE. The outcome of any pregnancy and the presence or absence of any congenital abnormality will be recorded in the source documentation and reported to the Sponsor.

10 STATISTICAL CONSIDERATIONS

The statistical analysis will be conducted following the principles as specified in ICH Topic E9 (CPMP/ICH/363/96).

All statistical analyses will be described in a separate statistical analysis plan.

10.1 Sample Size Calculation

It is planned to complete 18 subjects in Part A and 90 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.

10.2 Analysis Populations

Pharmacokinetic analysis set (PKAS): The PKAS set 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.

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.

Full analysis set (FAS): The FAS will include all randomized patients who receive at least 1 dose of LT5001 drug product or placebo.

Per-Protocol (PP): The PP population will comprise all FAS patients who complete the study procedures without a major protocol deviation. The PP population will also be used for the analysis of efficacy.

10.3 Randomization

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

For Part A, patients will be randomized into a 2:1 ratio to receive LT5001 drug product or placebo. For Part B, patients will be randomized into a 1:1 ratio to receive LT5001 drug product or placebo.

10.4 Endpoints

10.4.1 Part A Primary Endpoint

- Nature and severity of AEs and number of patients with AEs.

10.4.2 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.

10.4.3 Part B Primary Endpoint

- Change from baseline to end of Week 8 in mean Worst Itching Intensity using NRS.

10.4.4 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.

10.5 Pharmacokinetic Analysis Part A (only)

The following PK parameters will be determined for LT5001 drug product:

C_{trough}	Lowest observed blood concentration prior to next application

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

Adjusted PK parameter = C_{trough}/ Actual Dose

The actual dosing in each patient will be determined by subtract the weight of each returned study drug from the initial weight (T_0). In addition, the original blood PK parameter (without dose adjustment) versus time will also be analyzed.

Pharmacokinetic parameters will be listed by subject and treatment using the SAS, and summarized by treatment using the using the pharmacokinetic analysis set (PKAS) and the following summary statistics: n, arithmetic mean, standard deviation (SD), CV%, minimum, median, and maximum. Geometric mean and geometric CV% will also be presented for all PK parameters.

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.

10.6 Safety Analysis

All safety analysis will be performed on the SAS for both Part A and Part B.

Adverse events will be coded by System Organ Class and Preferred Term using the current version of MedDRA. Incidences of TEAEs (ie, events that started after 1st dose of the study drug or worsened in severity after 1st dosing), will be presented by dose group. Incidences of TEAEs will also be presented by maximum severity and relationship to study medication.

Safety data will be summarized through appropriate data tabulations, standard descriptive statistics, and graphical presentations. For each continuous laboratory parameter, results will be categorized as low, normal, or high based on the laboratory normal ranges. Frequencies and percentages will be presented by dose group for patients who had a shift to low and for patients who had a shift to high from baseline to any post-dosing assessment.

The association of AEs, clinical laboratory tests, vital sign measurements with the actual dosing of the study drug or systemic exposure of LT5001 drug product may also be explored. If appropriate, statistical modeling will be performed to further characterize the associations mentioned above. All out-of-range and clinically significant laboratory results will be identified in patient data listings. The number and percentage of patients in each dose group with normal and abnormal physical examination results will be presented for evaluations at baseline and final visit.

For each body system, changes in the patients' findings from baseline to final visit (no change, normal to abnormal, or abnormal to normal) will be tabulated for each dose group.

Application site examination (observed and change from baseline) will be summarized by time point using appropriate descriptive statistics.

The number and percentage of patients reporting any treatment-emergent AE will be tabulated by system organ class and preferred term (coded using MedDRA). Treatment-emergent AEs will be further classified by severity and relationship to treatment.

10.7 Efficacy Analysis

The efficacy of LT5001 drug product will be assessed via the following:

Part A:

- Change in mean Worst Itching Intensity using NRS.
- 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 in mean Worst Itching Intensity using NRS.
- 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.

Mixed-effect model repeated measures analysis of covariance will be applied to compare the treatment groups for efficacy endpoints (i.e. change of NRS, change from baseline in 5-D Itch Scale, change from baseline in total Skindex-10), with baseline itch and prior anti-itch medication use as covariates, and patient as a random effect.

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.

10.8 Other Statistical Considerations

Continuous data will be summarized using descriptive statistics as number of observations, mean, median, standard deviation, minimum, and maximum. Categorical data will be summarized by number, frequency, and percentage.

10.9 Dropouts, Premature Termination, and Missing Values

The dropouts, premature termination of study medication, and withdrawal will be summarized and analyzed by treatment groups. A listing of patients with withdrawal, as well as those with premature termination of study medication along with the date and reasons for termination, will be provided. Generally, the last-observation-carried-forward procedure will be used to estimate the missing data for efficacy variables. No imputation will be done for estimating the missing values for safety variables and time to event data.

10.10 Interim Analysis

After completion of Part A, an evaluation of all safety data will be performed. DSMB will review interim analysis and give comments on safety or any medical concern to determine whether the study continued 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.

11 ACCESS TO SOURCE DATA/DOCUMENTS

The investigator will provide direct access to source data and documents for individuals conducting study-related monitoring, audits, IEC review, and regulatory review. The investigator must inform the study patient that his/her study-related records may be reviewed by the above individuals without violating the patient's privacy of personal health information in compliance with Health Insurance Portability and Accountability Act of 1996 regulations.

Attention is drawn to the regulations promulgated by the FDA under the Freedom of Information Act providing, in part, that information furnished to clinical investigators and IECs will be kept confidential by the FDA only if maintained in confidence by the clinical investigator and IEC. By signing this protocol, the investigator affirms to the Sponsor that the investigator will maintain, in confidence, information furnished to him or her by the Sponsor and will divulge such information to the IEC under an appropriate understanding of confidentiality with such board.

12 QUALITY CONTROL AND QUALITY ASSURANCE

Sponsor or designated CRO will implement and maintain quality control and quality assurance procedures with written SOPs to ensure the study is conducted and data are generated, documented, and reported in compliance with the protocol, GCP, and applicable regulatory requirements.

12.1 Conduct of Study

This study will be conducted in accordance with the provisions of the Declaration of Helsinki and all revisions thereof (Tokyo 2004), and in accordance with FDA CFR (§312.50 and §312.56) and the ICH E6 Guidelines on GCP (CPMP/ICH/135/95). Specifically, this study is based on adequately performed laboratory and animal experimentation; the study will be conducted under a protocol reviewed by an IEC; the study will be conducted by scientifically and medically qualified persons; the benefits of the study are in proportion to the risks; the rights and welfare of the patients will be respected; the physicians conducting the study do not find the hazards to outweigh the potential benefits; and each patient will give his or her written, informed consent before any protocol-driven tests or evaluations are performed.

The investigator may not deviate from the protocol without a formal protocol amendment having been established and approved by an appropriate IEC, except when necessary to eliminate immediate hazards to the patient or when the change(s) involve only logistical or administrative aspects of the study and are approved by the Sponsor. Any deviation may result in the patient having to be withdrawn from the study, and may render that patient nonevaluable.

12.1.1 Protocol Deviations

A protocol deviation is defined as any intentional or unintentional change to, or noncompliance with, the approved protocol procedures or requirements. Deviations may result from the action or inaction of the patient, investigator, or site staff.

At the outset of the study, a process for defining and handling protocol deviations will be established. This will include determining which violations will be designated “key,” requiring immediate notification to Lumosa Therapeutics Co., Ltd. The investigator is responsible for seeing that any known protocol deviations are recorded and handled as agreed.

12.2 Protocol Amendments

Only the Sponsor may modify the protocol. Amendments to the protocol will be made only after consultation and agreement between the Sponsor and the investigator. All amendments that have an impact on patient risk or the study objectives, or require revision of the ICF, must receive approval from the IEC prior to their implementation.

12.3 Monitoring of Study

The investigator will permit the site monitor to review study data as frequently as is deemed necessary to ensure data are being recorded in an adequate manner and protocol adherence is satisfactory.

The investigator will provide access to medical records for the monitor to verify eCRF entries. The investigator is expected to cooperate with the Sponsor or a designee in ensuring the study adheres to GCP requirements.

The investigator may not recruit patients into the study until the Sponsor or a designee has conducted a site initiation visit (in-person or via teleconference) to review the protocol and eCRF in detail.

13 ETHICS

13.1 Institutional Review Board/Independent Ethics Committee Approval

13.1.1 Ethics Review Prior to Study

The investigator will ensure that the protocol and ICF are reviewed and approved by the appropriate IEC prior to the start of any study procedures. The IEC will be appropriately constituted and will perform its functions in accordance with FDA regulations, ICH GCP guidelines, and local requirements as applicable.

13.1.2 Ethics Review of Other Documents

The IRB/IEC will approve all protocol amendments (except for Sponsor-approved logistical or administrative changes), written informed consent documents and document updates, patient recruitment procedures, written information to be provided to the patients, available safety information, information about payment and compensation available to patients, the investigator's curriculum vitae and/or other evidence of qualifications, and any other documents requested by the IRB/IEC and regulatory authority as applicable.

13.2 Written Informed Consent

The nature and purpose of the study will be fully explained to each patient. The patients must be given ample time and opportunity to inquire about details of the study, to have questions answered to their satisfaction, and to decide whether to participate. Written informed consent must be obtained from each patient prior to any study procedures being performed.

14 DATA HANDLING AND RECORD KEEPING

14.1 Data Reporting and Case Report Forms

14.1.1 Case Report Forms

The investigator will be provided with eCRFs, and will ensure all data from patient visits are promptly entered into the eCRFs in accordance with the specific instructions given. The investigator must sign the eCRFs to verify the integrity of the data recorded.

14.1.2 Laboratory Data

A list of the normal ranges for all laboratory tests to be undertaken forms part of the documentation to be collated prior to study start. The investigator must maintain source documents such as laboratory reports and complete history and physical examination reports.

14.1.3 Retention of Source Documents

The investigator must maintain source documents such as laboratory reports, x-rays, ECGs, consultation reports, and complete history and physical examination reports.

14.2 Retention of Essential Documents

The study essential documents must be maintained as specified in the ICH guidelines for GCP and the applicable regulatory requirements. The investigator/institution should take measures to prevent accidental or premature destruction of these documents.

Essential documents should be retained until at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or until at least 2 years have elapsed since the formal discontinuation of clinical development of the study drug. These documents should be retained for a longer period; however, if required by the applicable regulatory requirements or by an agreement with the Sponsor. It is the responsibility of the Sponsor to inform the investigator/institution as to when these documents no longer need to be retained.

15 ADMINISTRATIVE INFORMATION

15.1 Financing and Insurance

Financing and insurance will be addressed in a separate agreement between the Sponsor and the investigator.

15.2 Publication Policy

The Sponsor will retain ownership of all data. All proposed publications based on this study will be patient to Sponsor's approval requirements.

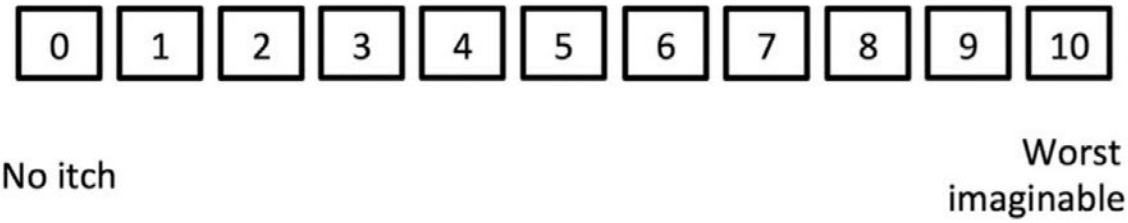
16 REFERENCES

Pisoni RL, Wikstrom B, Elder SJ, et al. Pruritus in haemodialysis patients: International results from the Dialysis Outcomes and practice patterns Study (DOPPS). Nephrol Dial Transpl. 2006;21(12):3495-3505.

[redacted]

Pereira MP, Ständer S. Assessment of severity and burden of pruritus. Allergol Int. 2017 Jan;66(1):3-7.

APPENDIX A Numerical Rating Scale



Numerical Rating Scale (NRS), an unidimensional scale, which may be the most widely used is a validated measurement of UP intensity in HD patients. The intensity can be quickly measured with monodimensional scales that are routinely used in clinical care and RCTs (Pereira 2017). Patients can be asked to rate their itch intensity from 0 ("no itch") to 10 ("worst imaginable itch") with the NRS. Pruritus intensity measured using NRS can be categorized into no (0 point), mild (1–3 points), moderate (4–6 points), severe (7–8 points), and very severe pruritus (≥ 9 points).

APPENDIX B Skindex-10 Scale

During the past WEEK, how often have you been bothered by:

1. Your itching
2. The persistence/recurrence of your itching
3. The appearance of your skin from scratching
4. Frustration about your itching
5. Being annoyed about your itching
6. Feeling depressed about your itching
7. Feeling embarrassed about your itching
8. The effects of your itching on your interactions with others (for example: interactions with family, friends, close relationships, etc.)
9. The effects of your itching on your desire to be with people
10. The effect of your itching making it hard to work or do what you enjoy

Patients fill one of seven bubbles ("0 [never bothered], 1, 2, 3, 4, 5, and 6 [always bothered]") for each of the questions. The total score 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)

APPENDIX C 5-D Itch Scale

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

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

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

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

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

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

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

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

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

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

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