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STATISTICAL ANALYSIS PLAN

A Two-part Proof-of-Concept Study Assessing the Safety and Efficacy of LAT8881 in Lumbar Radicular Pain.

Protocol No.: LAT-NP-002

Product Code: LAT8881

PREPARED FOR: Lateral Pharma Pty Ltd
L45/600 Bourke Street
Melbourne, Vic 3000, Australia

PREPARED BY: [redacted]

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AUTHORS: [redacted]
Caro-Ann Badcock (on-behalf of Lateral Pharma)
Stuart Mudge

SAP APPROVAL

By my signature, I confirm that this SAP has been reviewed and has been approved for use on the LAT-NP-002 study:

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ABBREVIATIONS

AE	Adverse event
AST	Aspartate aminotransferase
BMI	Body mass index
CK	Creatinine Kinase
COVID-19	Novel Coronavirus (Sars-Cov-2)
CRF	Case Report Form
CSR	Clinical Study Report
DSMC	Data and Safety Monitoring Committee
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
FAS	Full Analysis Set
FBC	Full Blood Count
IMP	Investigational Medicinal Product
LOQ	Limit of Quantification
MTD	Maximum Tolerated Dose
PGIC	Patients General Impression of Change
PI	Principal Investigator
PICF	Patient Information and Consent Form
PD	Pharmacodynamic
PK	Pharmacokinetics
PP	Per Population
PT	Preferred term
QST	Quantitative Sensory Test
SAP	Statistical Analysis Plan
SOC	System organ class
TEAE	Treatment Emergent Adverse Event
VAS	Visual Analogue Scale

1. INTRODUCTION

This Statistical Analysis Plan (SAP) provides the details of the planned statistical analyses of the data from the LAT-NP-002 study.

The planned analyses identified in this SAP may be included in clinical study reports (CSRs), regulatory submissions, or future manuscripts. In addition, post-hoc exploratory analyses not necessarily identified in this SAP may be performed to further examine study data. Any post-hoc analyses performed will be clearly identified as such in the CSR.

2. PROJECT OVERVIEW

2.1 Study Design

This is a Proof-of-Concept study that consists of two parts

2.1.1 Part A (single ascending dose study)

Part A will be a double-blind, randomized, placebo-controlled, single ascending dose (SAD) study within 8 healthy volunteers of intravenous administration of LAT8881 over 5 minutes.

The SAD study will enrol 8 participants and each participant will have three treatment days, 1 infusion per dosing day on days 1, 4 and 7 as well as two short visits for safety blood sampling on

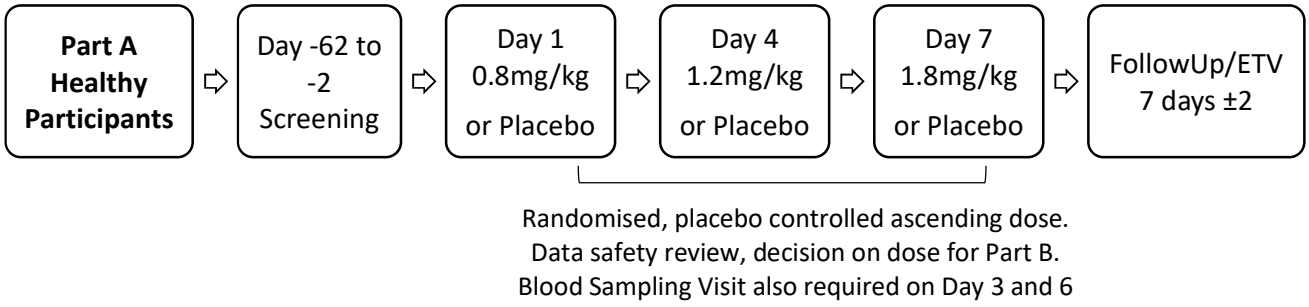
Day 3 and 6 (Figure 1). The 8 participants will be split into two groups of 4 participants each (3 IMP and 1 placebo), with the two groups dosed a few days apart.

Participants will arrive on the morning of each treatment day, receive a single infusion, leave that afternoon (no overnight stay). Participants on a given dosing day will be dosed at staggered intervals as determined by PI.

Treatments will be on Days 1 (0.8 mg/kg), Day 4 (1.2 mg/kg) and Day 7 (1.8 mg/kg) or placebo to allow sufficient washout and consideration of any safety observed following each dosing day. Day 3 and 6 safety blood results will be reviewed prior dosing on the following dosing day.

Participants will fast for 8 hours pre-dose and 4 hours post dose for each dosing occasion. Participants will be randomised, so on each treatment day per group, 3 participants receive LAT8881 and 1 receive placebo (different participants to receive placebo each treatment day). Participants will remain at the clinic until 6 hours post-infusion in order to collect blood samples for PK analysis and for review of safety and tolerability. Safety assessments will be reviewed in a clinic exit visit 7 days after the last infusion.

Figure 1: Part A Study Design



2.1.2 Part B (Cross-Over Study)

Part B will be a placebo-controlled randomized double blind cross-over safety and efficacy study of LAT8881. Up to 20 participants will be randomized into two groups and will receive either a single dose of LAT8881 [the dose selected from Part A of the study] or placebo via intravenous administration over 10 minutes on two consecutive days.

Participants will be randomly assigned to one of two groups, active then placebo or placebo then active (Figure 2).

After passing screening, participants will be admitted for two nights:

1. A study staff member will contact the participant for 3 consecutive days to obtain a verbal pain score out of 10 to confirm that their mean resting radicular pain meets the study inclusion criteria (pain score on each of the 3 days must be ≥3)
2. The participant will arrive the evening prior to dosing, and will complete a final review of inclusion/exclusion criteria.
3. Baseline assessments will be completed on the first day of dosing prior to IMP administration
4. The participant will then receive their first dose.
5. Collection of blood samples for PK/ PD analysis and assessments for review of safety, tolerability and efficacy are listed in the Schedule of Assessments.

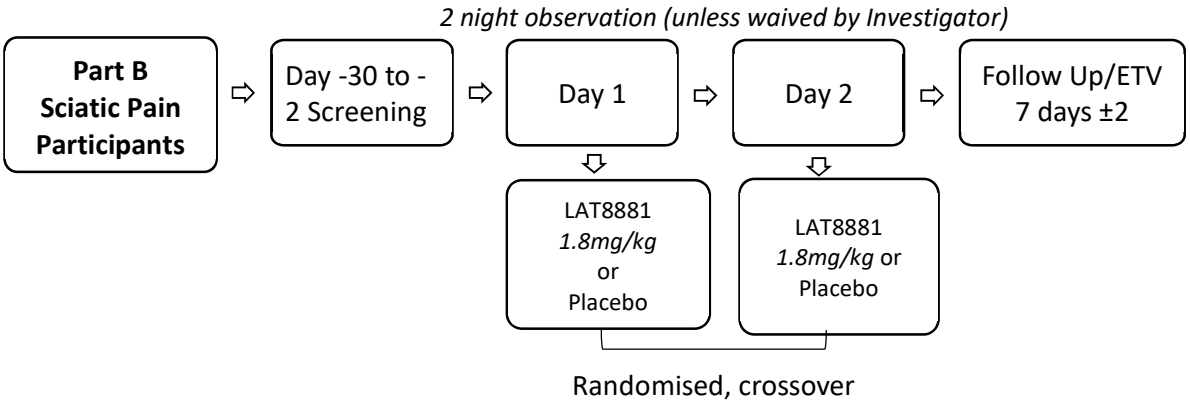
The participants will stay overnight.
If the PK from the Part A demonstrates elimination in <6 hours (assessed by concentration below LOQ of assay),

6. The following morning the participants will cross-over and receive their second dose.
7. Collection of blood samples for PK analysis and assessments for review of safety, tolerability and efficacy are listed in the Schedule of Assessments.
8. Participants will remain at the clinic until 6 hours post the second infusion and then may be discharged.

At the discretion of the Investigator and in consultation with the Study Sponsor, the requirement for subjects to be admitted to the clinic from the evening before Day 1 through to discharge at the end of Day 2 can be waived. In such circumstances, items 1 through 8 above will still apply, with the following modification to item #2:
- During the morning of Day 1 the following will be undertaken prior to dosing: a) a complete final review of inclusion/exclusion criteria, b) a written account of the activities the participant undertook on Day 0.
- Prior to dosing on Day 2, a written account of the activities the participant undertook after discharge at the end of Day 1.

Safety assessments will be reviewed 7 days after the last infusion by clinic exit visit.
Participants will fast for 8 hours pre-dose and 4 hours post dose for each dosing occasion.

Figure 2: . Part B Study Design



2.2 Sample Size

No formal statistical sample size estimation has been performed due to the exploratory nature of this study. The sample size is based on clinical and practical considerations.

For Part A, a total of 8 participants will be dosed on each of three occasions with an increased dose (6 subjects) or placebo (2 subjects). It is expected that the sample size of 8 subjects (split into two groups of 4 subjects each (3 IMP and 1 placebo), with the two groups dosed a few days apart) should be adequate for evaluation of safety, tolerability, PK and PD parameters in this SAD study.

For Part B, a proof-of-concept, up to 20 participants, based on the PI's experience from design and management of lumbar radicular pain subjects, will be enrolled. It is expected that the sample size (10 participants receiving active drug then placebo and 10 receiving placebo then active drug) should be adequate for evaluation of safety and efficacy.

2.3 Study Objectives

2.3.1 Primary Objectives

Part A:

- Evaluate the safety and tolerability of intravenous LAT8881 using an ascending dose schedule

Part B:

- Evaluate the analgesic efficacy of LAT8881 in patients with lumbar radicular pain

2.3.2 Secondary Objectives

Part A:

- Evaluate the plasma concentrations and the PK properties of LAT8881 administered as an IV injection in healthy participants using a dose escalating design
- Establish the dose regimen for Part B of the study

Part B:

- Evaluate the effect of Intravenous LAT8881, compared with placebo, VAS pain scores at rest
- Confirm the safety of LAT8881 in participants with lumbar radicular pain

2.3.3 Exploratory Objectives

Part A:

- Collect blood samples to investigate (and possibly validate) a pharmacodynamic assay and/or biomarkers of LAT8881 activity

Part B:

- Evaluate mechanical Quantitative Sensory Test (QST) assessment on affected lower limb using Von Frey Aesthesiometer on two occasions, once prior to dosing and once post dosing.
- Evaluate the effect of Intravenous LAT8881, compared with placebo, VAS pain scores during straight-leg raise nerve stretch
- Bang Binding Index assessment, whereby participant will be asked to record which dosing occasion they believe they got the active IP.
- Collect blood samples to investigate (and possibly validate) a pharmacodynamic assay and/or biomarkers of LAT8881 activity

2.4 Study Endpoints

2.4.1 Primary Endpoints

<u>Part A</u>
Safety and tolerability

- Incidence, severity, and causality of AEs
- Incidence and severity of clinical laboratory abnormalities
- Change from baseline in vital signs (blood pressure, temperature, respiratory rate, and heart rate)
- Change from baseline in 12-lead ECG parameters
- Incidence and severity of AEs

Part B

- The change in pain from baseline during and after each infusion on a VAS 0-10 numerical rating scale of “pain now” with measures taken as the infusion starts and at 15 minute intervals for the first hour, then every thirty minutes for an additional two hours, then hourly until 6 hours from infusion commencement

2.4.2 Secondary Endpoints

Part A

- Pharmacokinetic profile

Part B

- Comparison of radicular “pain now” scores as peak change from baseline and area under the curve comparing the two arms over the full six hours
- Comparison of patients’ general impression of change between dosing arms
- Adverse event rates in each dosing arm

2.4.3 Exploratory Endpoints

Part A

- Pharmacodynamic assay and/or biomarkers of LAT8881 activity

Part B

- Mechanical QST assessment using Von Frey Aesthesiometer
- Evaluate the effect of intravenous LAT8881, compared with placebo, on VAS radicular pain scores during straight-leg raise nerve stretch
- Bang Binding Index assessment, whereby participant will be asked to record which dosing occasion they believe they got the active IP.
- Pharmacodynamic assay and/or biomarkers of LAT8881 activity.

2.5 Changes to analyses from protocol

These changes relate to Part B of the study only.

Interim analysis:
The planned interim analysis after at least 10 subjects had completed the study was undertaken after 14 subjects completed the study. The rationale for including 14 subjects within the interim analysis was based on a number of factors, including:

- The observation that 2 of the subjects received less than the full dose (estimated to be 60-65%) due to technical issues with the infusion equipment. Both the sponsor and the PI agreed that it was wise to include at least an additional 2 subjects within the interim analysis
- At the time recruitment approached 12 completed subjects, the recruitment rate was relatively strong, which resulted in 14 subjects completing the study before the interim analysis was initiated.

The planned initial graphical outputs were produced.

No re-estimation of the sample size was undertaken. Based on: (i) the planned graphical outputs, (ii) some additional blinded post-hoc graphical presentations (not discussed in this SAP), (iii) the expectation that 17 subjects were expected to complete the study by 12 May 2023, (iv) dosing an additional 3 subjects to reach the target of 20 could take another 3-6 months, and (v) the inclusion of additional subjects would be unlikely to change any treatment signal in the data to such an extent that continuing recruitment is justified, the recommendation was made to close the study on 12 May 2023, with the last patient last visit then expected on 19 May 2023.

Final analyses:
The data presentation and analysis for the Bang Binding Index assessment has been included in this SAP as it was inadvertently missed in the previous version of the SAP.

After review of the interim analysis outputs where extensive variation in pain scores over time and an unexpected effect of being in the clinic for 24 hours possibly reducing pre-dose pain score on Day 2, particularly for pain at rest, the following decisions were made as to changes to the final analysis outputs.

- Pain at rest:
  - The mean change from baseline from 1 to 2 hours and from 4 to 6 hours are included to provide an easily interpretable summary measure of the pain response profile.
  - The area under the subject profile curve has been removed because it is less meaningful in a clinically useful interpretation of the pain response profile
  - A scatter plot presenting the paired responses for baseline pain with Placebo on the x-axis, LAT8881 on the y-axis, a diagonal line representing no difference and symbols with different shapes and colours representing each treatment sequence to investigate the possible presence of a Day or treatment carry-over effect.
  - Scatter plot in the same format as for baseline pain, for the mean change from baseline from 1 to 2 hours and for the mean change from baseline from 4 to 6 hours to provide a graphical presentation showing the pattern of any treatment differences in the presence of a possible Day effect.

- Pain on leg raise:
  - All analyses completed for pain at rest will be repeated for pain on leg raise. Given the impact of Day 1 on Day 2 pain at rest scores, pain on leg raise may provide more insight as to the “proof of concept” for LAT8881.

3. STATISTICAL CONSIDERATIONS

Data analysis will be performed according to [redacted] Standard Operating Procedures (SOPs).

The general analytical approach for all endpoints will be descriptive in nature
Unless otherwise stated, the following statistical approaches will be taken:

Continuous variables:	Descriptive statistics will include the number of non-missing values, mean, standard deviation (SD), median, minimum, and maximum. The minimum and maximum values will be presented to the same number of decimal places as recorded in the raw data; mean and median will be presented to 1 decimal place more than raw data; and SD will be presented to two more decimal places than the raw data.
Categorical variables:	Descriptive statistics will include frequency counts and percentages per category. Percentages will be rounded to one decimal place, with the denominator being the number of subjects in the relevant population with non-missing data.
Imputation:	No imputation will be performed for missing data.
Confidence intervals (CIs):	If required, CIs will be two sided and will use 95% confidence levels. Any analyses requiring significance testing will use a two-sided test at the 5% significance level.

Unscheduled visits:	Unscheduled visits will be excluded from visit-based summary Tables, but will be included in data listings.
Early withdrawal visits	Early withdrawal visits will be excluded from visit-based summary tables but will be included in data listings.

3.1 Data Capture

3.1.1 Database

The primary method of data collection is via the study database, developed within the chosen Electronic Data Capture (EDC) platform, IBM Clinical Development. The database has been designed based on the final protocol, the system/core configuration, electronic Case Report Form (eCRF) specifications and/or mock eCRF and consistency check specifications.

Data will be entered directly into the EDC system. Site-collected data will be entered directly from source notes at the site and will be verified by Clinical Research Associates (CRAs) to ensure data integrity.

Refer to the Data Management Plan for further details.

3.1.2 Third Party Data

3.1.2.1 *Safety Laboratory*

Central safety laboratory data will be received at [redacted] from PARC Clinical Research.
This data transfer will occur once the central safety laboratory, SA Pathology, transfers the data to PARC as specified in the Data Transfer Specification. Data transfers are being processed at the end of each cohort throughout the study, with each transfer being reconciled against the CRF data.

The final data transfer(s) will be incorporated into the End of Study analysis once the final transfer has been received, reconciled and all issues are considered resolved.

No unit conversion of laboratory data is planned.

3.1.2.2 *PK Laboratory*

PK samples will be analyzed by HMS Trust Laboratory. PK analyses will be documented in a separate PK Analysis Plan and analyses will be performed by PKPD Systems. The PK Analysis Report will be incorporated directly into the appendices of the CSR.

3.1.2.3 *PD Laboratory*

PD samples will be analysed by collaborators selected by Lateral Pharma. Analysis of PD data will be considered outside the scope of this SAP.

3.2 Statistical Programming

3.2.1 Baseline

Baseline will be defined as the last available assessment prior to the first IMP administration. For part B, baseline will be assigned separately for the two treatment periods..

3.2.2 Change from Baseline

Part A: $change\ from\ baseline$=($postbaseline\ value$)−($baseline\ value$)
Part B, Period 1:

$change\ from\ baseline$=($postbaseline\ value$)−($period\ 1\ baseline\ value$)
Percentage change from baseline=100 x change from baseline/(period 1 baseline value)
Mean change from baseline over 1-2 hours = [change from baseline at 1 hr + change from baseline at 1.5 hr + change from baseline at 2 hr]/3
Mean change from baseline over 4-6 hours = [change from baseline at 4 hr + change from baseline at 6 hr]/2

Part B, Period 2:

$change\ from\ baseline$=($postbaseline\ value$)−($period\ 2\ baseline\ value$)
Percentage change from baseline=100 x change from baseline/(period 2 baseline value)
Mean change from baseline over 1-2 hours = [change from baseline at 1 hr + change from baseline at 1.5 hr + change from baseline at 2 hr]/3
Mean change from baseline over 4-6 hours = [change from baseline at 4 hr + change from baseline at 6 hr]/2

3.2.3 Study Day

Part A: Study Day will be derived as the number of days relative to date of first administration of study drug, where the day of first administration = 1.
Part B: Study Day will be number of days relative to date of administration of study drug for each period, where the day of administration = 1.

3.2.4 Listings, Tables and Figures

Listings, tables and figures will be delivered as individual .rtf files in accordance with the mock listings, tables and figures, with separate sets of outputs for each study part.

Data listings will present all data, with subjects grouped by treatment regimen (part A) or treatment sequence (part B).

3.2.5 Treatment groups – Part A

Tabulations will summarize data by treatment group, the pooling of all the study drug, and total (all groups). All placebo participants will be grouped in a single cohort for tabulation summaries.

For Part A, treatment groups within tables are planned to be presented as:

LAT8881 (0.8mg/kg) (N=X)	LAT8881 (1.2mg/kg) (N=X)	LAT8881 (1.8mg/kg) (N=X)	LAT8881 (All Doses) (N=X)	Placebo (N=X)	Total (N=X)

3.2.6 Treatment groups – Part B

LAT8881 will be administered at a dose of 1.8 mg/kg via an infusion pump at a constant rate over 10 minutes.
The placebo formulation will be presented as above but without the LAT8881 active.

Tabulations for part 2 will summarise data as follows:

Demographics and baseline characteristic data, will be summarised by:

- LAT8881 1.8 mg/kg /Placebo
- Placebo/LAT8881 1.8 mg/kg
- Total

Visit based tabulations will be summarised by treatment received (LAT8881 1.8 mg/kg or Placebo) and total, and timepoint relative to within period dosing. Treatment will be assigned to individual records based on the treatment period. Timepoints will be:

- Screening (summarised as total only)
- Day 1- predose/Day 2-predose (combination of Day 1 and Day 2, summarised by treatment)
- Day 1- dose/Day 2-dose (combination of Day 1 and Day 2, summarised by treatment)
- Day 1- 5min/Day 2-5min (combination of Day 1 and Day 2, summarised by treatment)
- Day 1- 10min/Day 2-10min (combination of Day 1 and Day 2, summarised by treatment)
- Day 1- 15min/Day 2-15min (combination of Day 1 and Day 2, summarised by treatment)
- Day 1- 20min/Day 2-20min (combination of Day 1 and Day 2, summarised by treatment)
- Day 1- 30min/Day 2-30min (combination of Day 1 and Day 2, summarised by treatment)
- Day 1- 45min/Day 2-45min (combination of Day 1 and Day 2, summarised by treatment)
- Day 1- 1hr/Day 2-1hr (combination of Day 1 and Day 2, summarised by treatment)
- Day 1- 1.5hr/Day 2-1.5hr (combination of Day 1 and Day 2, summarised by treatment)
- Day 1- 2hr/Day 2-2hr (combination of Day 1 and Day 2, summarised by treatment)
- Day 1- 2.5hr/Day 2-2.5hr (combination of Day 1 and Day 2, summarised by treatment)
- Day 1- 3hr/Day 2-3hr (combination of Day 1 and Day 2, summarised by treatment)
- Day 1- 3.5hr/Day 2-3.5hr (combination of Day 1 and Day 2, summarised by treatment)
- Day 1- 4hr/Day 2-4hr (combination of Day 1 and Day 2, summarised by treatment)
- Day 1- 5hr/Day 2-5hr (combination of Day 1 and Day 2, summarised by treatment)
- Day 1- 6hr/Day 2-6hr (combination of Day 1 and Day 2, summarised by treatment)
- Day 9/ETV (summarised as total only)

- Event based tabulations (e.g. adverse events, concomitant medications and deviations) will be summarised by treatment and total. Treatment will be assigned to individual records based on the treatment period of the start date of the event.
  - Adverse Events:
    - Events started prior to the Day 1 study drug administration will only be considered as Medical History.
    - If start date is after Day 1 study drug administration, then it will be assigned to the treatment received in Period 1.
    - If start date is after the Day 2 study drug administration, then it will be assigned to the treatment received in Period 2.
  - Protocol Deviations:
    - If date is before Day 1 then it will be assigned to Screening
    - If date of deviation is after Day 1 study drug administration,then it will be assigned to the treatment received in Period 1.
    - If start date is after the Day 2 study drug administration, then it will be assigned to the treatment received Period 2.
  - Concomitant Medications:

- Based on start and end dates – if subject was on medication within a given period then that medication will be summarised within that period. If subject took medication across both periods then it would be counted in both treatment columns.

- Treatment Exposure will be summarised by sequence and total

4. ANALYSIS SETS

Four (4) analysis sets will be used for the analyses: Full Analysis Set, Per Protocol population, Safety Population and PK/PD Population. Analyses planned for the PK/PD Population will be documented separately.

4.1 Analysis Population Descriptions

4.1.1 Full Analysis Set

The Full Analysis Set (FAS) consists of all participants enrolled and randomised into the study. The FAS population will be used for summaries of participant disposition, demographic and baseline characteristics. Participants will be analysed according to the treatment group they were assigned at randomisation.

4.1.2 Per Protocol population

A per-protocol (PP) population will be based on duration of IMP treatment and protocol deviations. This population may exclude participants with inadequate exposure to IMP or who have other protocol deviations. The PP population is the primary population to analyse efficacy endpoints. Demographic and baseline characteristics of the PP population will also be presented.

4.1.3 Safety population

The safety population consists of all randomised participants who received at least one dose of IMP and had at least one post dose safety assessment. The safety population will be used for the analysis of safety and tolerability. Participants will be analysed as treated, regardless of the randomised treatment assigned, if this differs from that to which the participant was randomised.

4.1.4 PK and PD population

The PK and PD population will include all participants who received at least one dose of IMP, had at least one post dose sample collection for PK and PD analysis and who did not have any clinically significant events or major protocol deviations that may have compromised the integrity of the PK and PD results.

5. PROTOCOL DEVIATIONS

Analysis Set: FAS

All protocol deviations will be listed, grouped by participant and treatment group.

The protocol deviation summary table will include:

- The total number of minor protocol deviations
- The total number of major protocol deviations
- The number of participants who reported at least one minor protocol deviation
- The number of participants who reported at least one major protocol deviation

6. SUBJECT DISPOSITION

Analysis Set: FAS

6.1 General Subject Disposition

A listing of subject disposition will present:

- Date of informed consent
- Date of randomization
- Date of first treatment
- Date of last treatment
- Date of completion / early withdrawal
- Primary reason for early withdrawal

The number and percentage of subjects entering and discontinuing the study will be summarised along with the reason for discontinuation.
The subject disposition summary table will include:

- Number of subjects who received at least one dose of study medication
- Number of subjects who completed the full study
- Number of subjects withdrawn early
- Reason for early withdrawal

6.2 Death

Death related details will be listed only if required.

7. DEMOGRAPHIC AND BASELINE CHARACTERISTICS

Analysis Set: FAS

7.1 Demographics

7.1.1 Parameters

- Date of birth
- Age (years)
- Sex (male/female)
- BMI
- Race
- Ethnicity
- Child-bearing potential
- Menopausal status
- Smoking Habits

7.1.2 Biostatistical methods

Demographic data, inclusive of but not restricted to that listed in 7.1.1 above, will be listed for each participant and summarized using descriptive statistics, tabulated overall for Part A and by treatment sequence and overall for Part B.

7.2 Medical history

All medical history data will be listed.

Medical history (other than disease under study) will be coded using the Medical Dictionary for Regulatory Activities (MedDRA®) and summarised by system organ class (SOC) and preferred term (PT).

7.3 Lumbar Radicular Pain History

All lumbar radicular pain history will be listed for each participant by treatment sequence for Part B only.

7.4 Pregnancy Test

Pregnancy test data will be listed for positive results only.

7.5 Eligibility

All eligibility data will be listed.

7.6 Urine Drug and Alcohol Breath Test

Any positive urine drug screen and alcohol screen tests will be listed.

7.7 SARS-CoV-2 Screening

Any positive SARS-CoV2 screening results will be listed.

8. TREATMENT EXPOSURE

Analysis Set: Safety Population

8.1.1 Parameters

- Date of drug infusion
- Start time of infusion
- End time of infusion
- Date/Time of last meal
- Study drug dose (mg)
- Total volume to be infused (mL)
- Actual volume infused (mL)

8.1.2 Biostatistical methods

All study drug administration data will be listed.

Extent of exposure to LAT8881 and placebo will be summarised for Part A and B as:

- Total IMP administered (mg): Sum of all doses (mg)
- Total Number of participants exposed to study treatment: Sum of all participants treated with LAT8881
- Duration of exposure (hours): (Date / Time last treatment – Date / Time of first treatment) + 1

9. PHARMACOKINETICS

Analysis Set: PK Population

Refer to PK Analysis Plan

All results of pharmacokinetic assays will be reported in listings.

10. PHARMACODYNAMICS

Refer to PD Analysis Plan.

11. EFFICACY (PART B ONLY)

Analysis Set: Full Analysis Set and Per Protocol population

Parameters:

- Pain now VAS score:
  - Change from Baseline to hours 0.25, 0.5, 0.75, 1, 1.5, 2, 2.5, 3, 3.5, 4, 5 and 6,
  - Percentage change from baseline to hours 0.25, 0.5, 0.75, 1, 1.5, 2, 2.5, 3, 3.5, 4, 5 and 6
  - Peak change from baseline over 6 hours
  - Mean change from baseline over 1 to 2 hours
  - Mean change from baseline over 5 to 6 hours
- Pain on leg raise VAS score:
  - Change from Baseline to hours 0.25, 0.5, 0.75, 1, 1.5, 2, 2.5, 3, 3.5, 4, 5 and 6,
  - Percentage change from baseline to hours 0.25, 0.5, 0.75, 1, 1.5, 2, 2.5, 3, 3.5, 4, 5 and 6

  - Peak change from baseline over 6 hours
  - Mean change from baseline over 1 to 2 hours
  - Mean change from baseline over 5 to 6 hours
- Patients general impression of change at hour 6 on Day 1 and on Day 2
- Mechanical QST assessment using Von Frey Aesthesiometer
- Bang Binding Index assessment at 6 hours on Day 2

11.1.1 Biostatistical methods

Efficacy will be assessed based on the difference between treatments in the following measures:

Pain NowScores (VAS)

"Pain now" scores, change from baseline, percentage change from baseline and summary scores (i.e. maximum change from baseline, mean change from baseline over 1 to 2 hours and mean change from baseline over 4 to 6 hours) will be listed for all study participants at each timepoint by treatment sequence.

Descriptive statistics including the number of participants, mean, standard deviation, median, minimum and maximum for the VAS "pain now" score at each timepoint along with the change from baseline and percentage change from baseline will be presented by treatment group within treatment period and overall. The mean, standard deviation, median, minimum and maximum for the change from baseline over 6 hours, the mean change from baseline over 1 to 2 hours and the mean change from baseline from 4 to 6 hours will be presented by treatment group within treatment period and overall.

Graphical presentations will include those presented for the interim analysis:

1. Individual subject VAS scores-time profiles by timepoint and by sequence (left panel LAT8881-Placebo, right panel Placebo-LAT8881)
2. Group mean VAS scores by timepoint and day, two sequences combined (one panel only)
3. Group mean VAS scores by timepoint and day in each panel, and by sequence (left panel LAT8881-Placebo, right panel Placebo-LAT8881)

Additional graphical presentations will include:

4. Individual subject change from baseline -time profiles by post-dose timepoint and by sequence (left panel LAT8881-Placebo, right panel Placebo-LAT8881)
5. Group mean change from baseline by post-dose timepoint by treatment, two sequences combined (one panel only)
6. Group mean change from baseline by post-dose timepoint and by sequence (left panel LAT8881-Placebo, right panel Placebo-LAT8881)
7. Difference between treatments in the change from baseline at each post-dose timepoint by sequence (left panel LAT8881-Placebo, right panel Placebo-LAT8881)
8. Difference between treatments in the change from baseline at each post-dose timepoint by treatment (one panel only)
9. A scatter plot for baseline scores with Placebo score on the x-axis, LAT8881 score on the y-axis, a diagonal line with slope=1 representing no difference between treatments will be overlaid on the plot, symbols and symbol colour will be used to identify treatment sequence.
10. Maximum change from baseline will be presented using the same scatter plot format as for baseline scores
11. Mean change from baseline over 1 to 2 hours will be presented using the same scatter plot format as for baseline scores
12. Mean change from baseline over 5 to 6 hours will be presented using the same scatter plot format as for baseline scores

To estimate the difference between LAT8881 and Placebo in the change from baseline “pain now” VAS over all session time points, a generalised linear mixed effects model will be fitted. Fixed-effects will include treatment, session time point and period (i.e. Day) factors; baseline will be included as a covariate. Random effects for participants and participant by period will be included to take into account the repeated measures on each participant and the cross-over nature of the study. The covariance structure for the random effects is assumed to follow a compound symmetry structure. The estimated adjusted (least squares) mean change from baseline for each treatment at each session time, the difference between the treatments, the 95% confidence interval for the difference and the p value for the difference will be presented. A p value of <0.05 will be declared statistically significant. The model assumes no carry-over treatment effect and assumes that any period (i.e Day) effect will affect subjects in both treatment sequences in a similar manner.

The same model will be fitted to the change from baseline “pain on leg raise” VAS scores.
As reflected in the scientific literature and regulatory authority guidelines, what consitutes a minimally significant change in baseline pain score can vary from subject-to-subject, whether the pain is acute or chronic, and on the mechanism of the pain. For the purposes of this study, the sponsor considers a 0.9 cm reduction to represent a minimally clinically significant change in pain as reported on the VAS, with the desired target reduction from baseline in the range of 0.9 to 3 cm.

Provocation Assessment with VAS

The pain on leg raise VAS score, change from baseline, percentage change from baseline, maximum change from baseline, mean change from baseline from 1 to 2 hours and mean change from baseline from 4 to 6 hours will be listed for all study participants at each timepoint by treatment sequence as for the “pain now” endpoints. Descriptive summary tables and analyses will be as per the “pain now” endpoints.

Patients general impression of change
The assessment responses will be listed for all participants by treatment sequence and visit.

The number and percentage of participants in each rating category will be summarised by treatment within period (i.e. Day) and overall.

A graphical presentation will take the form of a heat map with the rating categories for Placebo on the x-axis and the rating categories for LAT8881 on the y-axis. Each cell will contain the percentage of subjects with the corresponding combination of PGIC and will be colour-coded to represent the weight of evidence for the corresponding percentage.

The categories of general impression of change:

- Very much improved
- Much improved
- Slightly improved
- No change
- Slightly worse
- Much worse
- Very much worse

Quantitative Sensory Test (QST) assessment
The Affected and Non-affected dermatome monofilament pain assessment data will be listed for all study participants at each timepoint by treatment sequence.

The number and percentage of participants with pain at each filament will be summarised by type of dermatome and treatment sequence at each timepoint with the number of subjects, mean, standard deviation, median, minimum and maximum by treatment group within treatment period and overall.

Bang Binding Index assessment

The Bang Binding Index assessment identifying which Day the subject believed they were treated with the active treatment will be listed for all study participants.

The number and percentage of participants who correctly identified when they were using active treatment will be presented by treatment sequence and overall.

Sub-group Assessment of Demographic Factors
The contribution of demographic factors (listed in 7.1.1 above) to any differences in efficacy between treatment groups will be investigated.

12. SAFETY

Analysis Set: Safety Population

The following Safety analyses will be performed if there is enough data to warrant the analysis tables. If there is not enough data, we will write a paragragh describing the safety events.

12.1 Adverse Events (AEs)

AEs will be coded using the current version of the Medical Dictionary for Regulatory Activities (MedDRA, version 24.1) by system organ class (SOC) and preferred term (PT), classified from verbatim terms.

All AEs recorded during the study will be listed, grouped by participant and treatment group.

A Treatment Emergent Adverse Event (TEAE) is defined as any untoward medical occurrence reported or observed after the start of dosing with study drug and prior to the End of Study visit. Conditions present before the first dose of study drug that increase in severity after the first study drug administration will also be considered TEAEs. Where an AE start date is partially or fully missing, and it is unclear as to whether the AE started after treatment administration, it will be assumed to be a TEAE.
AE summaries will be restricted to TEAEs only.

An overview summary table of TEAEs will be provided for:

- Part A by treatment group and overall
- Part B by treatment within sequence, by treatment and overall

Table will include number of participants reporting at least one of the following:

- TEAE
- Grade 3+ TEAE
- Related TEAE
- Serious TEAE
- Serious and related TEAE

Number of participants discontinued from treatment due to a TEAE
Number of participants withdrawn from the study due to a TEAE
Number of deaths

For the TEAE summaries, participants who experience the same TEAE more than once will be counted only once for that event within each category (PT, SOC or overall).

The number and percentage of participants experiencing a TEAE, will be summarised for each SOC and PT by cohort and overall for the following categories of events, by severity:

- All TEAEs
- All TEAEs related to the study drug
- All Grade 3+ TEAEs
- All serious TEAEs
- All serious TEAEs related to the study drug

The number and percentage of participants experiencing a TEAE will be summarised for each SOC and PT by maximum severity and cohort for all TEAEs and all TEAEs related to study medication. If a participant experiences the same AE at more than one severity grade, the most severe rating or the stronger causal relationship to investigational product will be given precedence. Only severities that are populated will be reported.

12.2 Prior and Concomitant Medication

Prior and concomitant medications will be coded using The WHO Drug Dictionary September 2021 release, with Preferred Name (PN) and Anatomical Therapeutic Chemical (ATC) code.

A prior medication will be defined as a medication that was commenced prior to the first study drug administration. A concomitant medication will be defined as a medication taken after first study drug administration. Medications stopped on the same day as first study drug administration will be considered as prior medication only.

Prior and concomitant medication summaries will be presented in separate tabulations. All medications will be listed for each participant, with each medication flagged as to whether they are a prior medication, concomitant medication, or both. For part A, prior medications will be presented overall and concomitant medications will be presented by treatment group and overall
For part B, prior medications will be presented by treatment sequence and overall, and concomitant medications and safety measure summaries will be presented by treatment within each treatment period and overall.

Table summaries will be presented using frequency counts and percentages. For the summaries of prior and concomitant medications, subjects who take the same medication (in terms of the lowest level ATC) more than once will be counted only once for that medication.

12.3 Laboratory

12.3.1 Parameters

Laboratory Tests	**Parameters**		
Hematology	Haemoglobin Red blood cell count (RBC) Red cell distribution width (RCD) Haematocrit/Packed cell volume (PCV)	RBC Indices: Mean cell volume (MCV) Mean corpuscular haemoglobin (MCH) Mean platelet volume (MPV) Platelets	White blood cell (WBC) count with Differential: Neutrophils Lymphocytes Monocytes Eosinophils Basophils
Clinical Chemistry	Sodium Potassium Chloride Bicarbonate Anion Gap Urea Creatinine	Albumin Alkaline phosphatase (ALP) Gamma-glutamyl transferase (GGT) Alanine Aminotransferase (ALT)	Creatinine Kinase (CK)
	eGFR Uric acid Glucose (non-fasting) Calcium Ionised Calcium	Phosphate Total Protein Globulin Bilirubin	Aspartate Aminotransferase (AST) Lactate dehydrogenase (LD)
Routine Urinalysis (if positive urine dipstick)	Bilirubin, Specific gravity, pH, Nitrate, Protein, Leucocyte esterase, Blood, Ketones, Glucose, Urobilinogen, Creatinine.		Microscopic examination (if blood or protein is abnormal)

Pregnancy testing	Highly sensitive serum
FSH	FSH for confirmation of post memopausal status
Other Tests	Serology: (HIV antibody, hepatitis B surface antigen [HBsAg], and hepatitis C virus antibody)

12.3.2 Biostatistical methods

Individually for Part A and Part B, all laboratory parameters will be listed with flags for values outside the reference ranges and values considered to be clinically significant by the investigator.

Each parameter will be summarised descriptively (including actual values and changes from baseline) by visit and treatment.

Categorical interpretations of each record (Normal, Abnormal – Not Clinically Significant (NCS), Abnormal – Clinically Significant (CS)) will be summarised for each scheduled visit, as well as the worst case, in a separate set of tables, ordered as follows from best to worst case: Normal, Abnormal – NCS, Abnormal – CS. The worst case finding will reflect all post-baseline assessments, including unscheduled and early discontinuation visits.

Maximum shift tables will also be presented for hematology and chemistry variables, presenting a summary of the shifts from baseline values to the most extreme post-baseline value, where all scheduled and unscheduled visit results will be assessed to determine the maximum shift. The maximum shift will be determined based on the absolute change from baseline, considering both shifts in the negative and positive direction. Both the baseline and maximum shift values will then be converted to “Low”, “Normal” or “High” using the associated reference ranges.

12.4 Vital Signs

12.4.1 Parameters

- Systolic Blood Pressure (SBP) (mmHg)
- Diastolic Blood Pressure (DBP) (mmHg)
- Heart Rate (beats/minute)
- Respiratory Rate (breaths/minute)
- Temperature (°C)

12.4.2 Biostatistical methods

Individually for Part A and Part B:
All vital signs data will be listed for all participants , with flags for values outside the site's reference range.

Vital sign parameters will be summarized by presenting summary statistics for observed values and change from baseline values for each scheduled visit and timepoint.

The incidence rates of notable vital sign abnormalities will be summarized using the following set of normal ranges:

- Systolic Blood Pressure (mmHg)
- Diastolic Blood Pressure (mmHg)
- Heart Rate (beats/min)
- Pulse Oximetry (%)
- Respiratory Rate breaths/min)
- Temperature (°C)

12.5 Body Measurements

12.5.1 Parameters

- Weight (kg)
- Height (cm)
- Body mass index (BMI) (kg/m^2)

12.5.2 Biostatistical methods

BMI, height and weight data, will be listed for all participants.

Body measurement data will also be summarised.

12.6 Physical Examination

12.6.1 Parameters

- Gastroinstestinal (GI)
- Cardiovascular
- Dermatological
- Extremities
- General appearance
- HEENT (Head, Eyes, Ears, Nose, Throat)
- Renal
- Musculoskeletal
- Neurological
- Respiratory
- Thyroid
- Other (free text)

12.6.2 Biostatistical methods

Physical examination data will be listed for all paricipants by scheduled visit.

12.7 12-Lead ECG

12.7.1 Parameters

- The following ECG parameters are collected in triplicate for each timepoint:
  - PR interval (msec)
  - QRS interval (msec)
  - QT interval (msec)
  - Heart rate (beats/minute)
  - QTcB Interval (msec)
  - QTcF Interval (msec)
- ECG result (Normal, Abnormal – Not clinically significant, Abnormal – Clinically significant)
- ECG abnormality (as appropriate)

12.7.2 Biostatistical methods

ECG parameters will be listed for all participants and time points.

Observed values, and absolute change from baseline, will be summarised descriptively for all ECG parameters by scheduled visit and timepoint for part A and by sequence and overall for part B.

The number and percentage of participants with ECG findings will also be summarized by scheduled visit and timepoint part A and by sequence and overall for part B. This table will include a summary of the number and percentage of participants with abnormal results for each parameter at each timepoint, using the set of normal ranges provided.

A maximum shift table will also be presented for ECG Result, presenting a summary of the shifts from baseline values to the most extreme post-baseline value, where all scheduled and unscheduled visit results will be assessed to determine the maximum shift, ordered (best to worst case) by Normal, Abnormal – NCS, Abnormal – CS.

13. HANDLING OF MISSING DATA

Only recorded data will be analysed/presented and any subjects who have missing data will only have observed data reported, with no imputation for missing data.

14. CHANGES AND CLARIFICATIONS TO THE PLANNED ANALYSIS

Any changes to the statistical analysis plan will be described and justified in the final report.

15. INTERIM ANALYSES

In Part B, a blinded interim analysis was undertaken after 14 subjects have completed both periods. Enrolment will continue while the interim analysis is undertaken.

The interim analysis was to be done in two parts. Initially, 6 tables comprising a listing and table for separately for pain assessment score for pain at rest and pain following leg raise; a listing and summary table for patients general impression of change, will developed.
In addition, the pain scores will be summarised graphically as follows:

- Figure 1: Group mean VAS scores at Rest by timepoint, two sequences combined (one panel only)
- Figure 2: Group mean VAS scores at Rest by timepoint and by sequence (left panel Treatment A then Treatment B, right panel Treatment B then Treatment A)
- Figure 3: Group mean VAS scores following leg raise by timepoint, two sequences combined (one panel only)
- Figure 4: Group mean VAS scores following leg raise by timepoint and by sequence (left panel Treatment A then Treatment B, right panel Treatment B then Treatment A)

All analyses had subject numbers assigned randomly and treatment sequence labelled A and B to maintain blind. The results were used to make an initial futility assessment. If the decision is made to proceed then, secondly, the full interim analysis was to be completed as per full listings and tables within this document.

The DSMC team will provide additional insight regarding potentially stopping the study for futility. Details will be provided in the DSMC charter.

16. SOFTWARE

The following software will be used to perform the statistical analyses: Statistical Analysis System (SAS®) Version 9.4 or higher (SAS Institute, Cary, North Carolina, USA).

17. REFERENCES

1) LAT8881 Protocol Version 5.0 - 03 Feb 2023
2) Lateral LAT-NP-002_4.1_Annotated.pdf