PROTOCOL TITLE:	A Two-part Proof-of-Concept Study Assessing the Safety and Efficacy of LAT8881 in Lumbar Radicular Pain.
Protocol Number:	LAT-NP-002
NCT Number	NCT05298306
Development Phase:	Phase 1b
Document Version:	Protocol Version 5.0 dated 03FEB2023
Sponsor:	Lateral Pharma Pty Ltd 14/114 William St Melbourne, Vic 3000, Australia Phone: +61 (0)400 151 490 Email: dk@lateral-pharma.com
Coordinating Principal Investigator:	Prof. Guy Ludbrook PARC Clinical Research Royal Adelaide Hospital

This clinical study will be performed in compliance with Good Clinical Practice (GCP) guidelines, includingarchiving of essential documents.

Confidentiality statement

All information relating to the investigational product, Investigator's Brochure, Study Protocol, Case Report Forms and any information and results developed during, or arising from the study, is considered confidential and proprietary information of Lateral Pharma Pty Ltd ('Confidential Information'). This Confidential Information shall remain the sole property of Lateral Pharma Pty Ltd and shall not be disclosed to others without prior written consent from Lateral Pharma Pty Ltd and shall not be used except in the performance of this study.

1. Contents

SPONSOR (S) SIGNATURE PAGE

The signature below constitutes approval of this protocol. This study will be conducted in compliance with the clinical study protocol (and amendments), International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) guidelines for current Good Clinical Practice (GCP) and applicable regulatory requirements

Authorised by:

_____	_____	_____
Name	Signature	Date

INVESTIGATOR (S) SIGNATURE PAGE

I have read this protocol and agree that it contains all necessary details for carrying out the study as described. I will conduct this protocol as outlined herein, according to the ethical principles that have their origin in the Declaration of Helsinki, International Conference on Harmonization (ICH) guidelines for Good Clinical Practice (GCP) and applicable laws, rules and regulatory requirement(s).

I agree to obtain the Institutional Review Board (IRB)/Independent Ethics Committee (IEC) approval of the protocol and informed consent prior to the start of the study.

I agree to obtain formal written informed consent in accordance with applicable federal and local regulations and international guidelines from all participants prior to their entry into the study.

I have received and reviewed the Investigator's Brochure including the potential risks and side effects of the product and instructions for use.

I agree to report to the Sponsor any adverse events that occur during the study in accordance with the ICH GCP guideline and the protocol.

I agree to ensure that all associates, colleagues, and employees assisting me with the conduct of the study are informed of their responsibilities in meeting the above commitments and the commitments set forth in the Investigator's Agreement.

I agree to maintain adequate and accurate records and to make those records available for inspection in accordance with the ICH GCP guideline, and federal and local requirements.

I understand that the study may be terminated, or enrolment suspended at any time by the Sponsor, with or without cause, or by me if it becomes necessary to protect the best interests of the study participants.

_____	_____	_____
Name	Signature	Date

1.1. General Study Information

Study Monitor:	Southern Star Research Level 1, 1 Merriwa Street, Gordon NSW 2072 Australia Postal: PO Box 52, Gordon NSW 2072 Australia Contact Phone: + 61 2 9011 6266 Contact Email: info@southernstarresearch.com
Sponsor medical representative	Southern Star Research Level 1, 1 Merriwa Street, Gordon NSW 2072 Australia Postal: PO Box 52, Gordon NSW 2072 Australia Phone: +61 2 9011 6266 Email: jmarjason@southernstarresearch.com

1.2. List Of Abbreviations

AST	Aspartate aminotransferase
BCC	Basal Cell Carcinoma
BMI	Body mass index
CK	Creatinine Kinase
COVID-19	Novel Coronavirus (Sars-Cov-2)
CPI	Coordinating Principal Investigator
CRF	Case Report Form
CT	Computed Tomography
DSMC	Data and Safety Monitoring Committee
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
FAS	Full Analysis Set
FBC	Full Blood Count
MSU	Mid-Stream Urine
MTD	Maximum Tolerated Dose
NHMRC	National Health and Medical Research Council
OTC	Over The Counter
PGIC	Patients General Impression of Change
PICF	Patient Information and Consent Form
PD	Pharmacodynamic
PK	Pharmacokinetics
PP	Per Population
QST	Quantitative Sensory Test
ULN	Upper Limit of normal

2. PROTOCOL SYNOPSIS

Title	A Two-part Proof-of-Concept Study Assessing the Safety and Efficacy of LAT8881 in Lumbar Radicular Pain.
Short Title	LAT-NP-002
Sponsor	Lateral Pharma Pty Ltd
Protocol Number	LAT-NP-002
Study Phase	1b
Primary Objective	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
Secondary Objective(s)	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, on VAS pain scores at rest Confirm the safety of IV LAT8881 in participants with lumbar radicular pain
Exploratory Objectives	Part A: Collect blood samples to investigate 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, on VAS pain scores during straight-leg raise nerve stretch Collect blood samples to investigate (and possibly validate) a pharmacodynamic assay and/or biomarkers of LAT8881 activity
Primary Endpoints	Part A Safety and Tolerability • Incidence, severity, and causality of AEs • Incidence and severity of clinical laboratory abnormalities • Change from baseline in vital signs (BP, temperature, respiratory rate, and heart rate) • Change from baseline in 12-lead ECG parameters

	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
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
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.
Study Design	Part A: This is a double-blind, randomized, placebo-controlled, single ascending dose study within 8 healthy volunteers of intravenous administration of LAT8881 over 5 minutes. Part A of the Study will enrol 8 participants, each participant has 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. The 8 subjects will be split into two groups of 4 subjects each (3 IMP and 1 placebo), with the two groups dosed a few days apart. Participants arrive on the morning of treatment day, receive a single infusion, leave that afternoon (no overnight stay). Participants will be dosed at staggered intervals as determined by PI. . Treatments are 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 must be review prior dosing on the following day. Participants will fast for 8 hours pre-dose and 4 hours post dose for each dosing occasion.

	Participants are 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. <u>Part B</u>: This is a placebo-controlled randomized double blind cross-over safety and efficacy study of LAT8881. Participants will be randomized into two groups and will receive either a single 1.8 mg/kg dose of LAT8881 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. After passing screening, participants will be admitted for two nights: 1. A study staff member will contact the participant for 3 consecutive days the week prior 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.
Sample Size (by treatment group)	Part A: 8 healthy participants Part B: Up to 20 participants with a history of lumbar radicular pain
Inclusion Criteria	Participants who meet **all** the following inclusion criteria may be included in the study: 1. Male or female healthy participants, aged 18-49 years inclusive at screening; 2. Body mass index (BMI) of ≥ 19.0 kg/m^2 to ≤ 32.0 kg/m^2 at screening; 3. The participant must voluntarily provide written informed consent prior to any study procedures being performed and is willing and able to comply with procedures required in this protocol. 4. A female participant is eligible to participate if she is not pregnant, not breastfeeding, and at least 1 of the following conditions applies: a. Not of childbearing potential, defined as surgically sterile (documented hysterectomy, bilateral salpingectomy or bilateral oophorectomy) or postmenopausal (no menses for 12 months without an alternative medical cause. A high follicle stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy; however, in the absence of 12 months of amenorrhea, a single FSH measurement is insufficient); b. Of childbearing potential and agrees to use a highly effective method of contraception consistently during the treatment period and for at least 60 days following completion of study. c. A male participant with a female partner of childbearing potential is eligible to participate if he agrees to use highly effective contraception during the treatment period and for at least 60 days after the last dose of study treatment and refrains from donating sperm during this period; 5. Females of childbearing potential must have a negative pregnancy test at screening (serum) and Day 1 (urine). 6. Willing to be tested for SARS-CoV-2 infection if requested 7. Agree to adhere to the current state and national advice regarding minimizing exposure to severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) from the first Screening visit until the

	EOS/ETV. A SARS-CoV-2 Test will be taken if clinically indicated and in line with local processes. **For Part B of the study, the following criteria is in addition to criteria 3-7:** 8. Male or female participants with sciatic pain, aged 18 years and above 9. Body mass index (BMI) of ≥ 19.0 kg/m^2 10. Presenting with a history of sciatic pain, radiating into a lower limb, of lancinating, burning, stabbing or electric quality, of duration of more than 3 months. 11. Pain scores (VAS) for average daily leg pain at rest at the relevant nerve root of a mean of ≥4/10 and ≤9/10 for 3 days during the week prior to treatment, with a minimum of ≥3/10 on any day. 12. Demonstration of disc herniation within 6 months by CT or MRI at a segmental level consistent with the clinical features. 13. The site of disc herniation must affect L1-2, L2-3, L3-4, L4-5 or L5-S1. 14. The patient is willing to keep all analgesic medication and other therapy usage [such as physiotherapy, acupuncture, or transcutaneous electrical nerve stimulation (TENS)] stable or decreased in the week prior to, and a week after, IP administration. 15. The patient is in good general health, with the exception of the presenting condition under study, as determined by medical and psychiatric history, physical examination, ECG, serum chemistry and hematology, urinalysis and serology.
Exclusion Criteria	**Any** of the following will exclude potential participants from both parts of the study: 1. History or evidence of a clinically significant disorder (including psychiatric), condition, or disease that, in the opinion of the investigator and medical monitor or designee, would pose a risk to participants safety or interfere with the study evaluation, procedures, or completion; 2. History or presence of conditions known to interfere with the distribution, metabolism, or excretion of drugs; 3. Unwillingness to abstain from alcohol from 24 hours prior to investigational product administration, during confinement in the study site until discharge from the confinement period. 4. A positive urine drug screen or alcohol breath test at screening; unless prescribed medication therapy for participants enrolled in Part B 5. History of surgery or major trauma within 12 weeks of screening, or surgery planned during the study; 6. Has any local skin infection that could compromise the injection site or have insufficient venous access. 7. History of significant neurological diseases, including stroke, TIAs, seizures, and vascular malformations. 8. Positive screen for human immunodeficiency virus (HIV), hepatitis B virus surface antigen (HBsAg) or hepatitis C virus antibody (HCV);

	9. Treatment with any investigational product within 30 days or 5 half-lives (whichever is longer) prior to baseline visit, or concurrent participation in a clinical study with an investigational product or device; 10. Use of prescription or over the counter medications within 14 days of investigational product administration and during the study, with the exception of current medications provided the dose has been stable for at least 14 days, contraceptive medications, paracetamol, oral non-steroidal anti-inflammatory agents and vitamins or other medications that, in the opinion of the investigator, will not pose a risk to participants safety or interfere with the study evaluation, procedures or completion; 11. History of cancer, with the exception of successfully treated non-metastatic basal cell and squamous cell carcinoma; 12. Treatment involving chemotherapy or the known possibility of chemotherapy in the future 13. Participant has a known history of active or latent TB, except documented and complete adequate treatment of TB; 14. Has clinically significant laboratory abnormality as determined by the investigator deemed clinically significant by the investigator; inclusive of Alanine aminotransferase (ALT) and aspartate aminotransferase (AST) ≥ 1.5 × the upper limit of normal (ULN) 15. Has a history of substance abuse in the past 5 years or as determined by PI. 16. Is unwilling to refrain from donating blood products or plasma within 30 days prior to or post the study drug administration. 17. Patient has a documented history of allergy or intolerance to components of the study drug. **<u>For Part B of the study, the following criteria is in addition to criteria 1-18:</u>** 18. Has a history of significant pain unrelated to disc herniation that, in the opinion of the investigator, would significantly compromise assessment of leg radicular pain. 19. Has radiological evidence of foraminal stenosis or of clinically significant spinal stenosis . 20. Has had lumbar back surgery related to the specific disc(s). 21. Has received an epidural corticosteroid injection within 3 months of screening. 22. Has an ongoing worker's compensation claim, disability claims, or litigation related to any pain problem. 23. Has a history of chronic infection, including TB, Hep.B, Hep.C, or HIV. 24. Has a history of demyelinating disease such as Multiple Sclerosis, Neuromyelitis Opticia, or Optic Neuritis. 25. Has significant spinal stenosis or spondylolisthesis (Grade 2 or higher). 26. Has a history of diabetic neuropathy or peripheral neuropathy in the lower extremities.

Investigational Product	LAT8881 is administered via an infusion pump at a constant rate. The LAT8881 formulation will be presented in a pre-filled syringe containing the following: - LAT8881 10 mg/ml (active) - DSPE-PEG2000 20 mg/ml (Buffer) - Mannitol 47 mg/ml (Tonicity) - Sodium Hydroxide 0.33 mg/ml (Buffer) The placebo formulation will be presented as above but without the LAT8881 active.
Dosage Regimen	Part A: LAT8881 (or placebo) is administered at a dose of 0.8 mg/kg, 1.2 mg/kg and 1.8 mg/kg via an infusion pump at a constant rate over 5 minutes. Part B: LAT8881 (or placebo) is administered at a dose of 1.8 mg/kg via an infusion pump at a constant rate over 10 minutes.
Duration of Treatment	Part A: Three single doses of LAT8881 or placebo (Day 1, Day 4 and Day 7) Part B: Two single doses, one of LAT8881 and one of placebo over two dosing occasions.
Statistical Methods	A maximum of 8 participants in Part 1 and 20 participants in Part 2 will be randomised to the trial, to achieve a sample size of up to 28 participants completing all study interventions. There will be an interim analysis after at least 10 participants in Part B complete the Study Per Protocol.

3. SCHEDULE 1 OF OBSERVATIONS AND PROCEDURES PART A

Procedure	Day -30 to -2	Day 1/Day 4/Day 7 (hours)												Day 3/ 6	Day 14/ ETV
	Screening	Pre-Dose	Dose	5 min	0.25	0.5	1	1.5	2	2.5	3	4	6 Discharge	Day prior dosing [5]	+/- 2 day
Informed consent	×														
Medical history	×	×													
Inclusion/exclusion criteria	×														
Demography	×														
Physical examination, height, weight	×														
Symptom-directed physical exam		×											×		×
Pregnancy test (WOCBP) [1]	×	×													×
Urine drug screen, Urinalysis and Alcohol breath test [2]	×	×													
SARS-CoV-2 Test [3]															
HIV, Hepatitis B & C screening	×														
Clinical laboratory tests	×													x	×
12-lead ECG	×	×							×			×			×
Vital signs	×	×				×	×	×	×	×	×	×	×		×
Spot pulse oximetry	×	×				×	×	×	×	×	×	×	×		×
Randomization		×													
Dose administration [4]			×												
AE review				×	×	×	×	×	×	×	×	×	×		×
Concomitant medication review		×	×	×	×	×	×	×	×	×	×	×	×		×
PK [6]		×		×	×	×	×		×			x	x		
PD [6]		x		x	x	x	x		x			x	x		
Discharge													×		

*# Participants who withdraw early from the study will be encouraged to return to the clinic for an ETV assessment.

* Participants may require an unscheduled visit to address safety issues and/or for any additional PK and/or PD sample collection as required.

1 All WOCBP will have a serum pregnancy test at Screening and at the ETV visit, if applicable. Urine pregnancy tests will be performed for WOCBP at all other specified subsequent visits. If a urine pregnancy test is positive, it must be confirmed by a serum pregnancy test.

2. Urine Drug Screen and Alcohol Breath Test will be performed in clinic. A urine dipstick will be completed at all visit. In the event of positive Leukocytes and/or nitrates that urine sample will be sent to the local labortaotry for a microscopic examination.

3. SARS-CoV-2 Test will be taken if clinically indicated and in line with local processes.
4. All participants will fast 8 hours prior and 4 hours after the study drug administration
5. Samples must be taken with enough time that results are available prior to planned IP dosing on the following morning.
6. Pre-dose, 5 ± 1 min, 15 ± 2 min, 30 ± 2 min, 60 ± 5 min, 2 h ± 10 min, 4h ± 20 min, 6h ± 30 min post-dose.

4. SCHEDULE 1 OF OBSERVATIONS AND PROCEDURES PART B

Procedure	Day -30 to -2	Day 1/Day 2 (hours)																	Day 9/ ETV
	Screening	Pre Dose	Dose	5min	10 min	15 min	20 min	30 min	45 min	1	1.5	2	2.5	3	3.5	4	5	6	+/- 1 day
Informed consent	×																		
Medical history	×																		
Inclusion/exclusion criteria	×	×																	
Demography	×																		
Physical examination, height, weight	×																		
Symptom-directed physical exam		×																×	×
MRI or CT if >6mths [6]	×																		
Sciatic Pain History	×																		
3 Day NRS Pain Scores [5]		×																	
Pregnancy test (WOCBP) [1]	×	×																	×
Urine drug screen, Urinalysis and Alcohol breath test[2]	×	×																	
SARS-CoV-2 Test [3]																			
HIV, Hepatitis B & C screening	×																		
Clinical laboratory tests	×	x																x	x
12-lead ECG	×	×										×				×		×	
Vital signs	×	×								×		×		×		×	×	×	
Spot pulse oximetry	×	×								×		×		×		×	×	×	
Pain scores (VAS)		×				×		×	×	×	×	×	×	×	×	×	×	×	

Provocation Assessment with VAS		x				x		x	x	x	x	x	x	x	x	x	x	
Patient General Impression of Change [9]																	x	
QST (von Frey) [7]		×										×				×		
Randomization		×																
Dose administration [4]			×															
AE review				×		×		×	×	×	×	×	×	×	×	×	×	×
PK Sampling[8]		X		x	x		x	x	x	x							x	
PD Sampling[8]		x		x	x		x	x	x	x							x	
Concomitant medication review				×														x
Bang Binding Index assessment [9]																	×	
Discharge [9]																	×	

*# Participants who withdraw early from the study will be encouraged to return to the clinic for an ETV assessment.

* Participants may require an unscheduled visit to address safety issues and/or for any additional PK and/or PD sample collection as required.

1 All WOCBP will have a serum pregnancy test at Screening and at the ETV visit, if applicable. Urine pregnancy tests will be performed for WOCBP at all other specified subsequent visits. If a urine pregnancy test is positive, it must be confirmed by a serum pregnancy test.

2. Urine Drug Screen and Alcohol Breath Test will be performed in clinic. A urine dipstick will be completed at all visit. In the event of positive Leukocytes and/or nitrates that urine sample will be sent to the local labortaotry for a microscopic examination.

3. SARS-CoV-2 Test will be taken if clinically indicated and in line with local processes.

4. All participants will fast 8 hours prior and 4 hours after the study drug administration

5. Staff to contact the participant for 3 consecutive days during the week prior to dosing for documentation of daily pain scores

6. Not required if participant has current imaging available within the last 6 months

7. Mechanical Quantitative Sensory Test (QST) assessment using Von Frey Aesthesiometer will be completed by trained staff members

8. Pre-dose, 5 (mid infusion) , 10 (end of infusion) ± 1 min, 20 ± 1 min, 30 ± 2 min, 45 min ± 5 min, 60 min ± 5 min, 6h ± 30 min from the start of the infusion of the dose.

9. Completed 6 hours post dose on Day 2 only

5. INTRODUCTION

5.1. Background

Neuropathic pain

Neuropathic pain (NP) is defined as pain caused by a lesion or disease of the somatosensory nervous system.[2] The damage may be located either centrally or peripherally. Examples of central neuropathic pain include pain in Multiple Sclerosis or Parkinson's disease and pain after a stroke; examples of peripheral neuropathic pain include painful diabetic neuropathy, phantom limb pain, post-herpetic neuralgia, chemotherapy induced polyneuropathy, and trigeminal neuralgia.

The symptoms of peripheral neuropathic pain vary, depending upon the type of nerves that are damaged. Typical descriptions of the pain include shooting, stabbing, electric shock, burning, tingling, tight, numbness, prickling, itching and a sensation of pins and needles. Symptoms may also include allodynia, hyperalgesia, anaesthesia dolorosa, with sensory gain or loss. The impact of neuropathic pain on both the individual and on society is substantial. In addition to the morbidity associated with the pain itself, patients with neuropathic pain have a decreased quality of life, increased use of healthcare resources, increased absenteeism and decreased productivity at work.

The development of validated questionnaires for neuropathic pain has enabled better assessment of its prevalence in the general population. A recent systematic review of epidemiological studies of neuropathic pain estimated that the prevalence of pain with neuropathic characteristics ranged from 7- 10%.[3] This is likely to increase as the population ages, when there will be an increased incidence of risk factors for neuropathic pain, such as diabetes, cancer and cancer chemotherapy.

The treatment of neuropathic pain is challenging as it is generally not possible to alleviate the cause of the pain. Rather, therapy focuses on treating the symptoms. Non-pharmacological treatments, such as physical exercise, cognitive behavioural therapy and meditation have been proposed but there is only weak evidence for the efficacy of such approaches.[4] Pharmacological therapy is the mainstay of treatment. A recent review of 229 randomised double-blind studies of oral and topical pharmacotherapy for neuropathic pain by the Neuropathic Pain Special Interest Group (NeuPSIG) of the International Association for the Study of Pain (IASP) recommended gabapentin, gabapentin extended release/enacarbil, pregabalin, duloxetine, venlafaxine and tricyclic antidepressants as first line therapy.[5] However, it was found that outcomes with these agents were generally only modest, with 4 to 10 patients requiring active treatment for a 50% reduction in pain, compared with placebo treatment. Moreover, many of these therapies have side effects, such as somnolence, dizziness, motor imbalance and cognitive impairment, which restrict a patient's activities and diminish their quality of life.[6]

There is clearly an unmet need for more effective therapies to treat neuropathic pain. LAT8881 has a different mechanism of action to current therapies and has shown promising activity in animal models of neuropathic pain. It also has a good pre-clinical and clinical

safety record. This is the first clinical study to investigate this compound (by intravenous dosing) in neuropathic pain.

LAT8881

LAT8881 (Tyr-hGH$_{177-191}$) is a 16 amino acid peptide fragment based on the C-terminus of human-growth hormone (hGH$_{177-191}$) with an additional tyrosine at the N-terminus. It was initially developed for the treatment of obesity, (known during that time as AOD9604), but Phase 2 clinical studies did not show a statistically significant weight loss in obese subjects and development for this indication was discontinued.

Subsequent to these clinical trials in obesity, LAT8881 was successfully investigated in a variety of animal models of neuropathic pain:

- An analgesic effect was demonstrated in a number of *in vivo* preclinical studies after administration of LAT8881 at doses ranging from 1.0 to 10 mg/kg, including when administrered intravenously, orally and subcutaneously .
- *In vitro* electrophysiological studies suggested that LAT8881 inhibits neuronal activity in a manner consistent with a reduction in pain signalling.
- Mechanism of action studies identified the target of LAT8881 to be LANCL1, an inner cell-membrane hub protein ubiquitously expressed but high in the nervous system, respiratory tissue, and testis, known to be involved in protection from cell stressors by engaging several pathways (such as AKT/mTORC, Eps8, GSH, and de-ubiquitination)[7] but, until now, not known as a potential therapeutic target for the treatment of neuropathic pain.

The proposed repurposing of LAT8881 as a treatment for neuropathic pain via a novel and unique mechanism is underpinned by the preclinical and clinical safety data obtained when it was investigated as an obesity treatment, as detailed in the study Investigational brochure.

5.2. Findings From Nonclinical and Clinical Studies

A comprehensive nonclinical safety program with LAT8881 was completed prior to the initiation of the obesity clinical program:

- Conventional repeat-dose studies were undertaken in rats and monkeys, with LAT8881 administered intravenously on a daily basis for 28 consecutive days in both species and orally for 26 and 39 weeks in the rat and monkey respectively. Maximum doses were 10 mg/kg/day to both rat and monkey when given intravenously and 100 mg/kg/day in the rat and 50 mg/kg/day in the monkey when given orally. No concerning toxicities were observed.
- Following review of studies to assess genotoxic potential, it was concluded that LAT8881 does not pose a genotoxic risk for humans under therapeutic conditions.
- Reproductive studies were undertaken in rats and rabbits, at doses up to 50 mg/kg/day (rabbit) and 100 mg/kg/day (rat). No effect on reproduction was observed in these studies.

Six clinical studies have been completed with LAT8881 in healthy volunteers and in healthy obese subjects. The product was well tolerated when given intravenously in the first two clinical studies and orally in the next four studies. When the studies are described in this

Protocol, the emphasis is on the safety outcomes, as weight loss was not an objective of the neuropathic pain study. These studies are described below and in greater detail in the body of this protocol:

- The first clinical study with LAT8881 was a placebo-controlled Phase I study conducted in 2001 (METAOD001). LAT8881 was administered intravenously to healthy male volunteers in single doses ranging from 25 to 400 µg/kg. Each subject was randomised to receive active drug on three occasions and placebo on another. The number of subjects per LAT8881 dose ranged from 4 to 10. LAT8881 was well tolerated over the dose range. There were no clinically significant adverse events (AEs), or significant abnormalities in vital signs, safety laboratory tests or electrocardiograms (ECGs) during the study. The most common treatment-related AEs were fatigue, headache and dizziness, with no apparent relationship to dose.
- The second study (METAOD002) was a Phase IIa, double-blind placebo-controlled 4×4 Latin Square design study in which 23 healthy clinically obese males participated. LAT8881 was administered as an intravenous infusion in single doses of 25, 50 and 100 µg/kg. Each subject was randomised to receive active drug on three occasions and placebo on another. LAT8881 was well tolerated over the dose range: there were no study drug-related withdrawals, serious AEs, clinically significant AEs, or changes of clinical significance in vital signs, safety laboratory tests, or ECGs during the study. One subject reported severe chest pain, considered possibly related to treatment, after 50 µg/kg, but not after other doses. The most common related adverse event was mild or moderate euphoria. This was not observed after placebo.
- The first study with the oral LAT8881 formulation was a single dose, double-blind, placebo-controlled, 4×4 Latin Square designed study to evaluate safety, tolerability and pharmacodynamic endpoints in healthy, clinically obese males (METAOD003). The study was completed with each of 15 subjects receiving three oral doses (capsule formulation) of LAT8881 (9, 27 and 54 mg) and placebo. In addition, one subject received LAT8881 at all doses (not placebo) and another subject received LAT8881 (9 mg and 54 mg only).

  LAT8881 was well tolerated over this dose range. There was one SAE, considered unrelated to treatment (hospitalisation for bronchial pneumonia). Two subjects withdrew because of AEs, these were not considered related to treatment. There were no clinically significant AEs, or changes of clinical significance in vital signs, safety laboratory tests or ECGs during the study. The most common treatment-related AEs were headache and diarrhoea. All AEs were mild or moderate, except for severe diarrhoea in one subject and the bronchiolitis noted above.
- The next study to be conducted was designed to assess the safety of multiple daily oral dosing of LAT8881 (METAOD004) in healthy, clinically obese male volunteers. This study was a double-blind, placebo-controlled, dose escalation study with 3 cohorts, each of 12 subjects. Subjects in each cohort were randomised, so that 9 received active study drug (9, 27 or 54 mg LAT8881, capsule formulation) and 3 received placebo. Treatment at each dose was daily for 7 days. Dose escalation was approved by the sponsor after a safety review of the previous cohort.

LAT8881 was well tolerated over the oral dose range. There were no withdrawals from the study, serious adverse events (SAEs), clinically significant AEs, or changes of clinical significance in vital signs, safety laboratory tests or ECGs during the study. There were no observable trends in the incidence of AEs between the 9 mg and 27 mg LAT8881 and placebo treatment groups. The highest dose administered (54 mg) was associated with an increased incidence of events involving the digestive system (diarrhoea, dyspepsia, flatulence, nausea and eructation) and general body symptoms of abdominal pain and headache. All were all of mild to moderate intensity. No anti-LAT8881 antibodies were detected in sera collected from subjects treated with LAT8881 for 7 days.

- A Phase IIb study was then conducted in 300 healthy clinically obese subjects (METAOD005). This was a double-blind, randomised, placebo-controlled parallel group study carried out in five centres in Australia. After a 2 week placebo run-in period, 300 subjects were randomised to receive capsules of placebo or LAT8881 (1, 5, 10, 20 or 30 mg), once daily for 12 weeks.

  LAT8881 was well tolerated over the dose range. There were no changes of clinical significance in vital signs or safety laboratory tests during the study. Some abnormal, clinically significant ECG recordings were recorded, but these did not show a dose-relationship and, when such information was available, were classified as mild and unrelated. The incidence and severity of adverse events was similar in all dose groups and placebo. Five patients reported at least one SAE, none of which was considered to be related to study medication. There were 10 withdrawals from treatment because of AEs, only one of which was considered related to treatment (depression). The most common treatment-related AEs were headache and gastrointestinal symptoms (abdominal distention, abdominal pain, constipation, diarrhoea and flatulence). All related AEs were of mild to moderate severity, except in three subjects who each had one severe related symptom (itchy skin, headache or diarrhoea). No antibodies to LAT8881 were detected in sera collected throughout the treatment period.

  Evaluation of weight loss in the METAOD005 study suggested a non-linear bimodal dose response and the final clinical study (METAOD006) was conducted at lower doses of LAT8881 (0.25, 0.5 and 1 mg). The safety data from this final study is of limited significance to the neuropathic pain study because of these low doses.

- METAOD006 was a Phase IIb randomised, double-blind, placebo-controlled study in obese adults to assess the safety, tolerability and effect on body weight of LAT8881, in combination with a diet and exercise program. The study consisted of a four-week single-blind placebo run-in period, followed by 24 weeks of LAT8881 tablets once per day. A total of 534 subjects were enrolled in the study, 502 were randomised at the end of the 4-week placebo run-in period and all 502 subjects were included in the safety analysis.

  The incidence of AEs was similar between groups. There were 18 SAEs reported, two of which were considered related to treatment (syncope after placebo and after 0.25 mg). Fourteen subjects withdrew from treatment because of AEs, two (fatigue, itchy skin) were considered related to treatment. The most common related AEs were

headache, dysgeusia, diarrhoea, nausea and increased gamma glutamyl transferase, with no clear dose relationship. All were mild to moderate severity.

Overall, it was concluded that LAT8881 displayed a good safety and tolerability profile in this study that was indistinguishable from placebo. However, there were no statistically significant changes in weight loss in any treatment group, and it was decided to discontinue the clinical program.

A further two clinical studies were conducted with 30 mg oral capsules, one in peripheral neuropathic pain, the other in acute migraine:

- LAT-NP-001 was a randomised, placebo-controlled, double-blind, crossover, phase IIa study to investigate the efficacy and safety of oral LAT8881 in neuropathic pain (post-herpetic neuralgia or diabetic neuropathy). After a one-week baseline period, subjects were randomised to receive LAT8881 30mg or placebo capsules twice daily for four weeks, followed by a washout period of two weeks, a second baseline period of one week, and then crossover to receive the other treatment for four weeks. A total of 48 subjects completed both treatment periods.

  LAT8881 was well tolerated in subjects with neuropathic pain due to PHN or DPN, but did not reduce the pain or associated symptoms under the conditions of the study

- LAT-MIG-001 was a randomised, placebo-controlled, double-blind, crossover Phase IIa proof of concept study to investigate the efficacy and safety of oral LAT8881 in acute migraine. A total of 16 subjects were randomised to receive 2 capsules of 30 mg IMP (LAT8881 60 mg or placebo), to be taken at the onset of a migraine of moderate to severe intensity. After treatment the subjects returned to the clinic for re-evaluation and crossover to the second treatment.

  LAT8881 was well tolerated in subjects with migraine, but it did not reduce migraine pain significantly compared to placebo under the conditions of the study.

Given the following observations, it is a reasonable to assume that the failure to reduce the symptoms of pain in clinical studies is due to a lack of systemic exposure to LAT8881 from oral dosing: (i) the extensive supporting nonclinical data in neuropathic pain models, (ii) no detectable levels of LAT8881 were measured within the blood of a subset of patients in LAT-NP-001 that were included within a pharmacokinetic sub-study, and (iii) the oral bioavailability of LAT8881 is estimated to be less than 1%.

The preclinical and clinical data with LAT8881 available to date do not suggest any significant safety concerns. There are no established SAEs associated with administration of LAT8881, and no pattern of severe, related AEs. There is some evidence of a small increase in mild gastrointestinal disorders in one of the oral trials. Some mild ECG changes were noted after LAT8881 in two studies (METAOD005 and METAOD006) but not in the other four studies. Only one of these ECG changes was considered possibly related to treatment (a subject in Study METAOD006 who had a mild ectopic supraventricular rhythm after 0.5 mg LAT8881).

Sciatica, a subtype of neuropathic pain, is also referred to as radicular pain, which is defined as pain radiating from the lower back to one or both buttocks or legs. The condition occurs when either disc injury or compression of spinal nerve roots, or both, leads to irritation, inflammation, and nerve injury with resultant radicular pain and associated neuropathologic changes.

In general, sciatica is a self-limiting condition with up to 80% of patients recovering within 8 weeks of onset and up to 95% of patients recovering within 1 year. It is recommended that treatment for patients with sciatica should be conservative in nature for the first 6 weeks after symptom onset.

Patients with sciatica are often initially treated with rest and oral analgesics, which include nonsteroidal anti-inflammatory drugs (NSAIDs) and opioids. However, these may have limited effectiveness initially, and/or on perisistent pain. Further, prolonged opioid use is associated with undesirable sequelae, both on the patient (tolerance, dependence) and in the community (diversion risk). Alternate treatments for persistent neuropathic pain, such as gabapentinoids and antidepressants, have limited efficacy, or poorly tolerated side effects, or both. The use of epidural steroids is relatively common, but has not been convincingly shown to provide sustained benefit, and conveys the risks of an invasive procedure. Surgical options are also invasive, and outcomes are often poor in terms of improved pain. Based on the positive findings for neuropathic pain in pre clinical studies further examination of this study in participants with neuropathic pain is indicated.

6. STUDY OBJECTIVES

6.1. Hypothesis

When administered as an IV infusion at a dose of 0.8 mg/kg to 1.8 mg/kg as determined in Part A , LAT8881 reduces neuropathic pain in subjects with lumbar radicular pain, with peak pain relief achieved within six hours post-dose, and with no dose limiting side effects.

6.2. Primary Objective

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

6.3. 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

6.4. Experimental 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 at 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

7. STUDY DESIGN

7.1. Overall design

LAT-NP-002 consists of two parts.

Part A**:**
A Double blind, Randomized Cross-over Placebo-controlled Pharmacokinetic, Safety and Tolerability Study of Ascending doses of LAT8881 in Healthy Participants to determine the dose level for Part B.

Part B:
A Randomized Placebo-controlled Double-blind Cross-over Proof-of-Concept safety and efficacy study of LAT8881 in participants with lumbar radicular pain

At the conclusion of Part A of the study, safety data and PK data will be collated and presented to HREC along with the justification for dose level and dose interval for Part B, noting that a different cohort of subjects will commence Part B.

7.2. Justification of Study Design

The study has been designed to look for a Maximum tolerated IV dose of LAT8881 in healthy participants followed by assessment of this dose to treat lumbar radicular pain.

Part A:

- Confirm the maximum tolerated dose within the target dose range
- Characterise the pharmacokinetic (PK) profile of LAT8881 and of its metabolites
- Seek to validate a pharmacodynamic (PD) marker and identify a PK/PD relationship to guide dosing in future efficacy studies.

Part B:

- Demonstrate proof-of-concept that LAT8881 can reduce pain in patients with lumbar radicular neuropathy – acute pain relief design allows for the limitations imposed by requiring an IV infusion of investigational product
- Further validate the PK/PD relationship through association with pain relief in neuropathic pain subjects
- Post-hoc analysis of subjects who demonstrate a clinical response to the treatment will inform future clinical work and the optimal target product profile.

7.3. Sample Size

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

- Part A follows a dose escalation design where 8 subjects will be dosed on each of three occasions with an increased dose (6 subjects) or placebo (2 subjects). The 8 subjects will be split into a maximum of two groups of 4 subjects each (3 IMP and 1 placebo), with the groups dosed at least a few days apart. The MTD will be the highest dose level at which no more than 1 of 6 subjects on active dose experience a dose-limiting toxicity.
- In Part B of the study, a proof-of-concept, the sample size will be expanded up to n=20 based on the PI's experience from design and management of lumbar radicular pain subjects.

Overall, a total of 8 subjects (healthy volunteers) are planned for Part A of this study, and up to 20 subjects with lumbar radicular pain are planned to be enrolled in Part B.

7.4. Justification of Dose

The proposed starting dose was calculated based on the no-observed-adverse-effect level in previous clinical trials.

8. STUDY POPULATION

8.1. Inclusion Criteria

Participants who meet **all** the following inclusion criteria may be included in the study:

1. Male or female healthy participants, aged 18-49 years inclusive at screening;
2. Body mass index (BMI) of ≥ 19.0 kg/m^2 to ≤ 32.0 kg/m^2 at screening;
3. The participant must voluntarily provide written informed consent prior to any study procedures being performed and is willing and able to comply with procedures required in this protocol.
4. A female participant is eligible to participate if she is not pregnant, not breastfeeding, and at least 1 of the following conditions applies:
    a. Not of childbearing potential, defined as surgically sterile (documented hysterectomy, bilateral salpingectomy or bilateral oophorectomy) or postmenopausal (no menses for 12 months without an alternative medical cause. A high follicle stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy; however, in the absence of 12 months of amenorrhea, a single FSH measurement is insufficient);
    b. Of childbearing potential and agrees to use a highly effective method of contraception consistently during the treatment period and for at least 60 days following completion of study.
    c. A male participant with a female partner of childbearing potential is eligible to participate if he agrees to use highly effective contraception during the treatment period and for at least 60 days after the last dose of study treatment and refrains from donating sperm during this period;

5. Females of childbearing potential must have a negative pregnancy test at screening (serum) and Day 1 (urine).
6. Willing to be tested for SARS-CoV-2 infection if requested
7. Agree to adhere to the current state and national advice regarding minimizing exposure to severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) from the first Screening visit until the EOS/ETV. A SARS-CoV-2 Test will be taken if clinically indicated and in line with local processes.

For Part B of the study, the following criteria is in addition to criteria 3-7:

8. Male or female participants with sciatic pain, aged 18 years or over;
9. Body mass index (BMI) of ≥ 19.0 kg/m^2
10. Presenting with a history of sciatic pain, radiating into a lower limb, of lancinating, burning, stabbing or electric quality, of duration of more than 3 months.
11. Pain scores (VAS) for average daily leg pain at rest at the relevant nerve root of a mean of ≥4/10 and ≤9/10 for 3 days during the week prior to treatment, with a minimum of ≥3/10 on any day.
12. Demonstration of disc herniation within 6 months by CT or MRI at a segmental level consistent with the clinical features.
13. The site of disc herniation must affect L1-2, L2-3, L3-4, L4-5 or L5-S1.
14. The patient is willing to keep all analgesic medication and other therapy usage [such as physiotherapy, acupuncture, or transcutaneous electrical nerve stimulation (TENS)] stable or decreased in the week prior to, and a week after, IP administration.
15. The patient is in good general health, with the exception of the presenting condition under study, as determined by medical and psychiatric history, physical examination, ECG, serum chemistry and hematology, urinalysis and serology.

8.2. Exclusion Criteria

Any of the following will exclude potential participants from both parts of the study:

1. History or evidence of a clinically significant disorder (including psychiatric), condition, or disease that, in the opinion of the investigator and medical monitor or designee, would pose a risk to participants safety or interfere with the study evaluation, procedures, or completion;
2. History or presence of conditions known to interfere with the distribution, metabolism, or excretion of drugs;
3. Unwillingness to abstain from alcohol from 24 hours prior to investigational product administration, during confinement in the study site until discharge from the confinement period.
4. A positive urine drug screen or alcohol breath test at screening; unless prescribed medication therapy for participants enrolled in Part B
5. History of surgery or major trauma within 12 weeks of screening, or surgery planned during the study;
6. Has any local skin infection that could compromise the injection site or have insufficient venous access.
7. History of significant neurological diseases, including stroke, TIAs, seizures, and vascular malformations.

8. Positive screen for human immunodeficiency virus (HIV), hepatitis B virus surface antigen (HBsAg) or hepatitis C virus antibody (HCV);
9. Treatment with any investigational product within 30 days or 5 half-lives (whichever is longer) prior to baseline visit, or concurrent participation in a clinical study with an investigational product or device;
10. Use of prescription or over the counter medications within 14 days of investigational product administration and during the study, with the exception of current medications provided the dose has been stable for at least 14 days, contraceptive medications, paracetamol, oral non-steroidal anti-inflammatory agents and vitamins or other medications that, in the opinion of the investigator, will not pose a risk to participants safety or interfere with the study evaluation, procedures or completion;
11. History of cancer, with the exception of successfully treated non-metastatic basal cell and squamous cell carcinoma;
12. Treatment involving chemotherapy or the known possibility of chemotherapy in the future
13. Participant has a known history of active or latent TB, except documented and complete adequate treatment of TB;
14. Has clinically significant laboratory abnormality as determined by the investigator deemed clinically significant by the investigator; inclusive of Alanine aminotransferase (ALT) and aspartate aminotransferase (AST) ≥ 1.5 × the upper limit of normal (ULN)
15. Has a history of substance abuse in the past 5 years or as determined by PI.
16. Is unwilling to refrain from donating blood products or plasma within 30 days prior to or post the study drug administration.
17. Patient has a documented history of allergy or intolerance to components of the study drug.

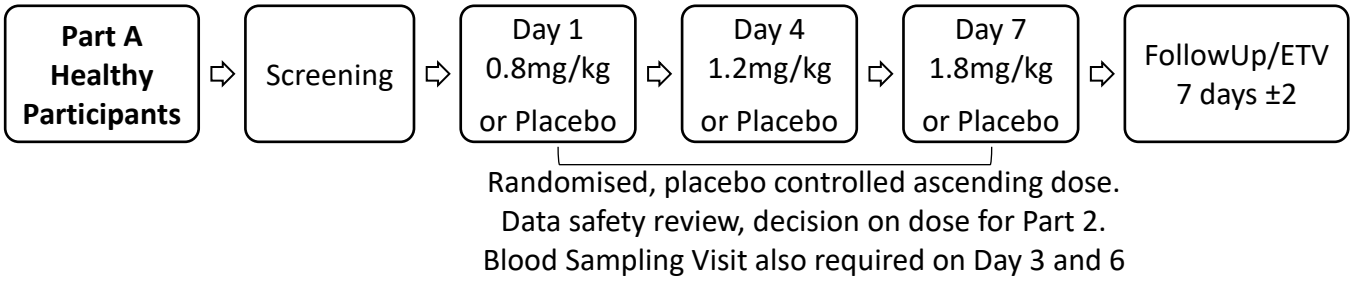
For Part B of the study, the following criteria is in addition to criteria 1-18:

18. Has a history of significant pain unrelated to disc herniation that, in the opinion of the investigator, would significantly compromise assessment of leg radicular pain.
19. Has radiological evidence of foraminal stenosis or of clinically significant spinal stenosis .
20. Has had lumbar back surgery related to the specific disc(s).
21. Has received an epidural corticosteroid injection within 3 months of screening.
22. Has an ongoing worker's compensation claim, disability claims, or litigation related to any pain problem.
23. Has a history of chronic infection, including TB, Hep.B, Hep.C, or HIV.
24. Has a history of demyelinating disease such as Multiple Sclerosis, Neuromyelitis Opticia, or Optic Neuritis.
25. Has significant spinal stenosis or spondylolisthesis (Grade 2 or higher).
26. Has a history of diabetic neuropathy or peripheral neuropathy in the lower extremities.

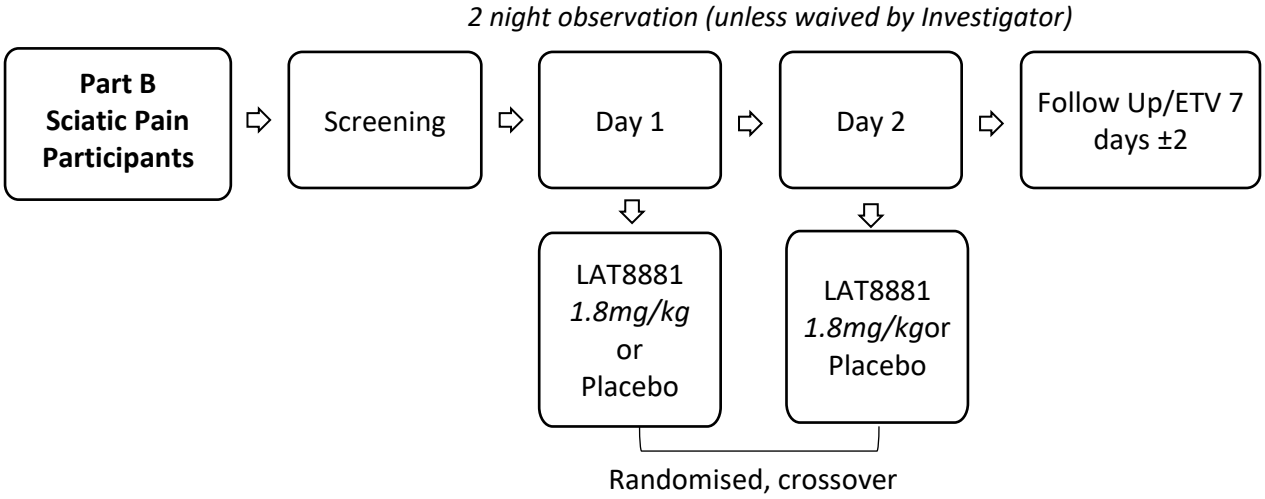
8.3. Screen Failures

Screen failures are defined as participants who consent to participate in the clinical study but are not subsequently entered in the study.
Individuals who do not meet the criteria for participation in this study (screen failure) may be rescreened once at the discretion of the Investigator.
A minimal set of information will be collected on all screen failures who were never chosen for participation: demography, screen failure details and eligibility criteria.

PART A: Evaluate the safety and tolerability of multiple ascending single doses of LAT8881



PART B: Evaluate the efficacy of Lat8881 in participants with lumbar radicular pain.



9. STUDY PROCEDURES

9.1. Recruitment

Participants will be recruited from the PARC Clinical Research database along with advertsing for Part B of the study.

9.2. Informed Consent

Potential participants will be provided with the Participant Information and Consent Form (PICF) and given adequate opportunity to read this document, consult with anyone they wish, and to ask questions of the study team, before deciding whether or not to take part. A signed consent form will be obtained from each participant prior to performing any study-specific procedures, including screening activities. Informed Consent must only be received by study

team members designated to this duty on the site Delegation Log. In most cases, the Site Principal Investigator or sub Investigators will be responsible for receiving Informed Consent for the study. The original copy of the PICF will be retained in the Investigator Site File and a copy will be provided to the participant. The date of consent, as well as document version and date will be recorded on the Electronic Data Capture (EDC).

9.3. Screening

For Part A, the screening visit must occur no more than 60 days prior to dosing.

For Part B. the screening visit must occur no more than 28 days prior to dosing.

For Part B; if the investigator deems appropriate the screening assessments may be split over two vists with Informed Consent Form, Medical History, Sciatic Pain Review and CT or MRI completed prior to additional assessments.

9.4. Randomisation

The results of all assessments conducted in the screening visit will be recorded in the EDC and must be reviewed by the Site Principal Investigator to confirm eligibility prior to randomising a patient to the study. Once the Site PI confirms participant eligilibity for the trial, the participant will undergo randomisation.

The methodology for assigning study numbers is discussed in section 14.1 below.

9.5. Follow Up

Participants will be requested to complete a Follow-Up Visit 1 week after the end of the treatment period (Day 14 for Part A and Day 9 for Part B). The focus of this visit will be completion of safety assessment and monitoring of AE's and Concomitant medications.

9.6.ASSESSMENTS

9.6.1. Demography

Collection of the participants details including initials, gender, age, race, ethnicity

9.6.2. Physical Exam

A complete physical examination will include, at a minimum, assessments of the General Appearance, HEENT, Neck (incl Thyroid), Cardiovascular, Respiratory, Gastrointestinal, Renal, Neurological, Musculoskeletal, and Skin. Height and weight will also be measured and recorded at the Screening Visit.

A Symptom Directed Physical Exam will be performed if necessary at the Day 7 Follow Up and/or ETV.

9.6.3. Medical History

A complete medical history will be reviewed at Screening and will include evaluation for past or present cardiovascular, respiratory, gastrointestinal, renal, hepatic, neurological, endocrine, metabolic, lymphatic, hematologic, immunologic, dermatologic, psychiatric, genitourinary and surgical history or any other diseases or disorders (including cancer).

9.6.4. Sciatic Pain Assessment and History for Part B

In addition to the physical exam assessment of sciatic pain and history will occur at the screening visit for participant in Part B.

Special attention will required during the examination of the lower back and neurologic assessment of the lower limbs. This will particularly seek to determine motor function in the affected leg and will assess and record any sensory change that might coincide with the dermatomal representation of the affected nerve root. Assessment will include straight leg raise and qualities of pain in affected leg.

9.6.5. Prior and Concomitant Medications

Prior medications are those medications that are initiated and stopped prior to first study drug administration, while concomitant medications are medications taken at least once after first study drug administration. All medications stopping on the same day as first study treatment will be considered as concomitant medications. SARS-Cov-2 vaccination is acceptable, if > 2 week prior to dosing.

9.6.6. Vital Signs

Vital signs include blood pressure, heart rate, pulse oximetry, temperature, and respiratory rate (in semi supine or supine position after a 5-minute rest). Vital signs will be collected at the timpoints in Schedule 1 and 2.

9.6.7. Electrocardiograms

Electrocardiogram values will be summarized at each protocol scheduled time point. In addition, a frequency tabulation of ECG results (Normal, Abnormal Not Clinically Significant or Abnormal Clinically Significant) will be presented at each protocol scheduled time point.

9.6.8. Average Daily Pain Scores (NRS) for Part B

Study staff will contact the participant at the same time each day for 3 consecutive days during the week prior to Day 1 to obtain the participants average **leg** pain scores for the preceding 24 hours. Pain scores need to be at least ≥ 3/10 each day however the 3 day mean must meet the inclusion criteria of between ≥ 4/10 and ≤ 9/10.

9.6.9. Clinical Safety Blood and Urine

Urinalysis, Urine Drug Screen and Pregnancy testing will occur at Screening, prior to each dosing occasion and Follow up visit or ETV, if applicable.
For Part A only, Local laboratory Clinical Safety Blood results from samples taken on Day 3 and 6 are required to be available and reviewed by PI/ designee prior to dosing occasions 2 and 3.

The following bloods will be performed via a locally contracted pathology laboratory (local laboratory):

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
	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.		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)		

9.6.10. Urinalysis

A urinalysis test (dipstick) will be performed for each participant. Urinary analysis will be performed at Screening and other times according to the timepoints listed in Schedule 1 and 2 .If abnormality is noted for nitrite or leukocyte esterase (and at the discretion of the

Investigator) a microscopic examination of RBC, WBC, bacteria and casts will be performed by the local laboratory.
Macroscopic urinalysis parameters to be tested are:

- pH (PH)
- Specific Gravity (SPGRAV)
- Creatinine (CREATININE)
- Protein (PROT)
- Glucose (GLUC)
- Ketones (KETONES)
- Total Bilirubin (BILI)
- Occult Blood (OCCBLD)
- Nitrite (NITRITE)
- Urobilinogen (UROBIL)
- Leukocytes (WBC)

9.6.11. Urine Drug Screen

A Urine drug screen will be performed at screening and other times according to the study schedule.
Urine drug screen to include at minimum:

- Amphetamines
- Barbiturates
- Cocaine
- Opiates
- Cannabinoids
- Benzodiazepines

A positive drug screen will result in exclusion from the study unless there is documentation of a stable dose of prescribed medication therapy for participants enrolled in Part B.

9.6.12. Pregnancy Screen

All WOCBP will have a serum pregnancy test at Screening and at the ETV visit, if applicable. Urine pregnancy tests will be performed pre-dose for WOCBP at all other specified subsequent visits. Urine pregnancy tests may be performed in the clinic using a human chorionic gonadotropin (hCG) pregnancy test.
If a urine pregnancy test is positive, it must be confirmed by a serum pregnancy test.

9.6.13. Alcohol Breath Test

An alcohol breath test will be performed at screening and other times according to the study schedule. A negative result is required for entry and continuation in the study.

9.6.14. CT or MRI Imaging

Part B only: Assess the radiological validation of the herniated disc (MRI or CT Scan within the last 6 months). If an MRI or CT scan does not exist, it is important to order this

investigation for review prior to administration of the IMP to fulfil necessary validation of entry criteria. MRI is the preferred imaging report unless not appropriate due to metal implants.

9.6.15. Pain assessment (VAS), Patient General Impression of Change (PGIC) and Bang Binding Index Assessment (Part B only)

Pain Assessments will be completed using a Visual Analogue Scale (VAS). VAS scores will be collected at the timepoints in Schedule 2.
The Patient General Impression of Change will be collected at the timepoints in Schedule 2.
Bang Binding Index Assessment will be collected at the timepoints in Schedule 2

9.6.16. PK and PD Sampling

PK and PD sample analysis will be performed using validated or fit-for-purpose methods as outlined in the Laboratory Manual.

The Sponsor will supply complete written instructions for handling, processing, storage, and shipping of samples prior to study initiation.

Pharmacokinetic and Pharmodynamic samples will be taken at the timepoints in schedule 1 and 2. The samples will be sent to a certified Central Laboratory for analysis.

Blood samples for plasma PK and PD will be obtained at the following time points:
Part A: Predose, 5, 15, 30 minutes, 1, 2, 4 and 6 hours post IV injection.
Part B: Predose, 5, 10, 20, 30, 45 minutes, 1 and 6 hours from the start of the IV infusion.
Collecting 4 mLs in a K2EDTA tube for the PK sample and 8mls for the PD Samples.

The PK Population will include all randomized participants who received LAT8881, with exploitable PK data and without relevant deviations interfering with the PK evaluations.
The PK Population will be used for the summaries and analyses of all PK data.

9.6.17. Mechanical QST assessment using Von Frey Aesthesiometer (Part B only)

Evalutate mechanical Quantitative Sensory Test (QST) assessment to detect sensory changes to light touch on affected and non-affected dermatomes using von Frey Aesthesiometer on six occasions, once prior to dosing and once 2 hours and 4 hours post dosing. This will occur for each dosing occasion.

QST measurements will be completed by staff trained on performance of this test.

10. INVESTIGATIONAL PRODUCT (IP) DISPENSING AND ACCOUNTABILITY

LAT8881 will be stored and handled by the pharmacist(s) according to study Pharmacy Manual (provided by the Sponsor or its designee), the pharmacy's standard operating procedures, applicable laws, and regulatory requirements.

The investigator or designee must confirm appropriate temperature conditions have been maintained during transit for all investigational product received and any discrepancies are reported and resolved before use of the investigational product.

Only participants enrolled in the study may receive investigational product and only authorized site staff may supply or administer investigational product. All investigational product must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labeled storage conditions with access limited to the investigator and authorized site staff. The investigator is responsible for investigational product accountability, reconciliation, and record maintenance (i.e., receipt, reconciliation, and final disposition records). Further guidance and information for the final disposition of unused investigational products are provided in the Study Pharmacy Manual.

11. Administration

Part A:

LAT8881 is administered at a dose of 0.8 mg/kg, 1.2 mg/kg and 1.8 mg/kg via an infusion pump at a constant rate over 5 minutes. The LAT8881 formulation will be presented in a polypropylene luer lock syringe containing the following:

- LAT8881 10 mg/ml (active)
- DSPE-PEG2000 20 mg/ml (Buffer)
- Mannitol 47 mg/ml (Tonicity)
- Sodium Hydroxide 0.33 mg/ml (Buffer)

Part B:

LAT8881 is 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.

To minimise potential local infusion site irritation or reaction, the LAT8881 infusion will be administered in line with a continuous infusion of 5% Dextrose Solution (50 g of glucose in water for injection, or equivalent). The dextrose solution infusion will commence approximately 30 minutes pre-dose and continue until the participant ceases fasting.

The rate of dextrose solution will be 80mls/hr. The IV dosing/ Normal Saline infusion cannula will be inserted into the opposite arm to the PK sampling IV Cannula to avoid any dilution of the PK samples.

Further details on the administration process can be found in the Pharmacy Manual.

12. Investigational Product Compliance

The participant will receive investigational product directly from the investigator or designee, under medical supervision. The date and time of each dose administered in the clinic will be recorded in the source documents. The dose of investigational product and study participant identification will be confirmed at the time of dosing by a member of the study site staff other than the person administering the investigational product.

13. COVID-19 CONSIDERATIONS AND CONTINGENCY PLANNING

Information regarding COVID-19 risk and considerations is included in the PICF, to ensure that study participants are cogniscent of the potential impact on the study and schedule. All participating sites must confirm that they are compliant with local infection control policies related to COVID-19.

14. BLINDING, PACKAGING AND SHIPPING

The IP for all sites will be manufactured and packaged by a contracted certified pharmacy. Treatment packs will be shipped to study sites on completion of a remote Site Initiation Visit (SIV).

IP will be labelled with:

- Study Protocol Number
- Randomisation number and participant details
- Instructions for Storage
- Instructions for Use

All participant-facing study personnel, including the CPI, Site PIs, and site study teams (including central coordinating team), will be blinded to treatment allocation until data collection is completed for all participants and the database is locked.

To maintain blinding for participant-facing study personnel, the study drug and placebo will be presented in identical sized syringes with clear liquid, and the packaging will also be identical for both study drug and placebo. Treatment allocation will not be discernable by differences in appearance. The study interventions do not differ across the treatment groups, and study SOPs guiding data collection, particularly participant-reported data, assist with reducing risk of inadvertent unblinding and discourage speculation regarding treatment allocation.

14.1. Method for assigning subject study number

At screening, each subject will, in chronological order, be allocated a unique Screening Number (Subject ID).
At randomisation on Day 1, the subject will be manually assigned a unique Randomisation Number, which will be allocated in ascending order according to their chronological order of inclusion in the study. Confirmation of the randomisation number allocated to each subject will be documented in the drug accountability records and recorded in the CRF.

For Part A, randomisation will be employed is to identify subjects have placebo on the three treatment days. For Part B, randomisation is to identify the treatment sequence.

The Subject ID number will be used to identify the subject throughout the study period and on all study-related documentation.

15. UNBLINDING

Blinding of treatment assignment is critical to the integrity of this clinical study. In the event of a medical emergency or pregnancy in an individual participant in which knowledge of the IP is critical to the participant's management, the blind for that participant may be broken. The participant's safety takes priority over any other considerations in determining if a treatment assignment should be unblinded.

If a decision is made to unblind a participant, the Site PI will access to an envelope containing the unblinding information. For any participant unblinded and/or withdrawn from the study, the appropriateness and requirements for further monitoring blood tests and urine tests as per the Study Schedule following emergency unblinding will be decided by the Site PI. This will depend on the clinical circumstances surrounding unblinding.

Any request to unblind a participant for non-emergency purposes should be discussed with the Sponsor.

16. SAFETY ASSESSMENTS

Safety bloods will be performed at each study timepoint, and any early termination visit. Participants will undergo physical examination at study visits, as described in the Schedule of Events. AEs will be identified via:

- Participant report
- Observations (e.g. vital signs, physical examination)
- UA via dipstick
- Safety blood tests (and MSU, if applicable)
- Fasting pre-dose and in the immediate post dose period

16.1. Pregnancy Testing

WOCBP must have a negative serum pregnancy test (βHCG) at screening and a negative urine pregnancy test prior to dosing on each occasion.
Participants who are pregnant or breastfeeding are excluded from the study. Participants who return a positive urine pregnancy test at any study visit will be discontinued from study drug and a serum pregnancy test conducted. If the serum pregnancy test is also positive, the patient will be discontinued from the study and an early termination visit will be undertaken.

17.WITHDRAWAL

Participants will be informed that they are free to withdraw from the study.
The CPI may discontinue the study drug and/or withdraw a participant from the study if, in the Investigator's opinion, it is not in the best interest of the participant to continue the study, or the participant demonstrates a consistent pattern of non-compliance with study procedures. Site PIs should discuss with the CPI any participant cases where withdrawal should be considered.

Patients withdrawing from the study early should be strongly encouraged to perform the early termination visit as soon as possible following the last dose of study drug and the Follow-Up visit should be performed 7 days (+/- 2 days) after the last dose of study drug is taken. If the participant does not want to return to the clinic for the Early Termination or Follow-up visit, a phone call visit should be made to collect as much information as possible.

17.1. Replacement of participants

In Part A, a subject who is withdrawn from the Study before Day 4 (the second dose) for any reason other than a dose limiting toxicity will be replaced. A subject who has withdrawn after Day 4 is completed will not be replaced. This will ensure that two subjects take placebo at end dose level.

In Part B, a subject who is withdrawn from the Study before completion of Day 1 (the first dose) for any reason other than a dose limiting toxicity will be replaced. A subject who has withdrawn after Day 1 dosing is completed will, if possible, be replaced at the discresion of the sponsor and the Investigator.

Replaced subjects will take the same treatment as the original subject that is being replaced.

A termination case report form (CRF) page should be completed for every subject who received study medication whether or not the subject completed the study. The reason for any early discontinuation from the study will be indicated on this form.

17.2. General Considerations for Stopping Criteria

For Part A of the Study:

- If 1 or more participants exhibits an SAE, or a significant AE, that is determined to be related to the study drug,(ie Serious Adverse Reaction or a Suspected Unexpected Severe Adverse Reaction) the study will be halted. No further dosing, dose escalation or inclusion of any further participants at the same dose will occur without recommendation by the Data Safety Monitoring Committee (DSMC) as per the agreed DSMC charter.
- If 2 or more participants exhibit a moderate AE determined to be related to the study drug in the same system organ class (SOC, e.g., immune or gastrointestinal system, no further dosing, dose escalation or inclusion of any further participants at the same dose will occur without recommendation by the DSMC.
- If any participant exhibits a mild or moderate AE that in the Investigator's opinion may be an allergic reaction the study may be halted. No further dosing, dose escalation or inclusion of any further participants at the same dose will occur without recommendation by the DSMC.

For Part B of the Study:

- If 1 or more participants exhibits an SAE, or a significant AE, that is determined to be related to the study drug (i.e. aSerious Adverse Reaction or a Suspected Unexpected Severe Adverse Reaction) the study will be halted. No further dosing will occur without recommendation by the DSMC.
- If 2 or more participants exhibit a moderate AE determined to be related to the study drug in the same system organ class (SOC, e.g., immune or gastrointestinal system), the study will be halted. No further dosing, will occur without recommendation by the DSMC.

- If any participant exhibits a mild or moderate AE that in the Investigators opinion may be an allergic reaction the study may be halted. No further dosing, will occur without recommendation by the DSMC.

18. PROHIBITIONS AND RESTRICTIONS IN THE STUDY

18.1. Prohibited medications

Participants must abstain from alcohol for 24 hours prior to each dosing occasion. Illicit drugs are prohibited. Participants should also avoid caffeine for 48 hours and grapefruit juice for 24 hours prior to arrival to study visit.

Use of prescription or over the counter medications and vaccines are prohibited within 14 days of investigational product administration and during the study, with the exception of current medications provided the dose has been stable for at least 14 days, contraceptive medications, paracetamol, oral non-steroidal anti-inflammatory agents and vitamins;

Participants should also not receive any other investigational products during the study.

Participants should also not initiate any new exercise or physical therapy regimens during the study. Exercise and physical therapy regimens that were in place at the Screening visit may be continued in a stable manner during the study.

18.2. Contraception

A female participant is eligible to participate if she is not pregnant, not breastfeeding, and at least 1 of the following conditions applies:

- Not of childbearing potential, defined as surgically sterile (documented hysterectomy, bilateral salpingectomy or bilateral oophorectomy) or postmenopausal (no menses for 12 months without an alternative medical cause. A high follicle stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy; however, in the absence of 12 months of amenorrhea, a single FSH measurement is insufficient);
- Of childbearing potential and agrees to use a highly effective method of contraception consistently during the treatment period and for at least 60 days following completion of study.
- A male participant with a female partner of childbearing potential is eligible to participate if he agrees to use acceptable contraception during the treatment period and for at least 60 days after the last dose of study treatment and refrains from donating sperm during this period;

To prevent pregnancy in a female subject of child bearing potential (FOCBP), the FOCBP must use a highly effective method of contraception (failure rate of <1%), during the study and for 60 days after the last dose of IMP. Such methods include:

- Abstinence from heterosexual intercourse. This should be the subject's usual and preferred lifestyle OR
- Consistent and correct use of a highly-effective form of contraception, such as:
  - combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation (oral, intravaginal or transdermal administration),

- progestogen-only hormonal contraception associated with inhibition of ovulation (oral, injectable or implantable administration)
- intrauterine device
- intrauterine hormone-releasing system
- bilateral tubal occlusion OR

- Vasectomised partner, provided that the partner is the sole sexual partner and that the vasectomised partner has received medical assessment of the surgical success of the vasectomy

Periodic abstinence (e.g. calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception.

19. Study Oversight

19.1. Suspension or premature termination of the study

Conditions may arise during the study that could prompt the study to be halted or the study site to be terminated. The sponsor may terminate part of, or the entire study for safety, administrative, or commercial reasons. Conditions that may prompt such considerations include, but are not limited to, the following:

• The discovery of unexpected, serious, or unacceptable risk to participants enrolled in the study;
• A decision on the part of Sponsor to suspend, discontinue, or shorten the study;
• Study conduct at a study site may warrant termination under conditions that include the following:

o Failure of investigator(s) to enrol eligible participants into the study;
o Failure of the investigator to comply with country-specific regulations;
o Submission of false information from the research facility to the sponsor, the clinical monitor, or
a regulatory authority;
o Insufficient adherence to protocol requirements;
o A conflict of interest of the investigator, his/her institution, or site personnel that could negatively
impact the integrity of the clinical study;
o Institution or Ethics Committee under investigation for cause by a regulatory authority.

Any decision by the sponsor on stopping or restarting the study must be discussed with the investigator. All actions are to be documented and the Ethics Committee (EC) and regulatory (competent) authority notified in writing as required by local regulations. Should a protocol amendment be required, this will be managed in accordance with Section 22.4. The study must not recommence recruitment or dosing until approval is received in writing from the EC (if/as required by the EC). If the study is to be terminated for safety reasons, any further administration of IMP will be stopped.
If the study is terminated for safety reasons, participants will be followed up for a minimum of one week following the last exposure to IMP, at which time an End of Study visit should be conducted. Refer to Schedule 1 and 2 for follow up assessments. Any AEs/SAEs ongoing at the time of the End of Study visit will be followed to resolution or stabilisation (whichever is the sooner).

19.2. Continuation on to Part B

At the conclusion of Part A of the study safety data and PK data will be collated and presented to HREC along with the justification for dose level and dose interval for Part B.

20.ADVERSE EVENTS

20.1. Adverse event

An adverse event is any untoward medical occurrence in a patient or clinical investigation participant administered a pharmaceutical product and may not necessarily have a causal relationship with the administered treatment.

An AE can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not it is related to the medicinal (investigational) product. This includes an exacerbation of pre-existing conditions or events, intercurrent illnesses, drug interaction or any worsening (i.e. any clinically significant adverse change in frequency and/or intensity) of a pre-existing condition, which is temporally associated with the use of the sponsor's product. Anticipated fluctuations of pre-existing conditions, including the disease under study, that do not represent a clinically significant exacerbation or worsening need not be considered AEs.

Laboratory reference ranges are defined by upper or lower limits of parameters of the respective laboratory. The investigator should ensure that each parameter out of the normal range is assessed for clinical significance and the potential for being an AE (refer to Schedule 1 and 2). An adverse event is defined as 'serious' when it meets one of the pre-defined outcomes as described in Section 12.1.6.

20.2. Adverse drug reaction/Suspected adverse (drug) reaction

An adverse drug reaction (ADR) is any AE for which there is a reasonable possibility that the drug caused the AE. Reasonable possibility means there is evidence to suggest a causal relationship between the IMP and the adverse event.

20.3. Suspected unexpected serious adverse reactions

Suspected unexpected serious adverse reactions (SUSARs) are Aes that are believed to be related to an IMP and are both unexpected (i.e. the nature or intensity is not expected from the information provided in the Investigator's Brochure) and serious. SUSARs are participant to expedited reporting to the applicable regulatory authorities.

For regulatory reporting purposes, SUSARS will be unblinded.

20.4. Causality

The investigator must assign causality to each adverse event in relation to the IMP based on the following definitions:

Not related: AE with an incompatible time relationship to IMP administration, and that could be explained by underlying disease or other drugs or is incontrovertibly not related to the Investigational Product

Possibly related: AE with a reasonable time relationship to IMP administration, but which also could be explained by concurrent disease or other medications.

Probably related: AE with a reasonable time relationship to IMP administration that is unlikely to be attributed to concurrent disease or other medications.

Definitely related: AE with plausible time relationship to IMP administration and which cannot be explained by concurrent disease or concomitant medications.

20.5. Severity (Intensity) of adverse event

Grade refers to the intensity of an AE and should not be confused with seriousness

Grade 1 Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.

Grade 2 Moderate; minimal, local or noninvasive intervention indicated; limiting age appropriate instrumental Activities of Daily Living (ADL*).

Grade 3 Severe or medically significant but not immediately life-threatening; hospitalisation or prolongation of hospitalisation indicated; disabling; limiting self-care ADLs.

Grade 4 Life-threatening consequences; urgent intervention indicated.

Grade 5 Death related to AE.

20.6. Serious adverse event

A serious adverse event (SAE) is any untoward medical occurrence or effect that, at any dose:

- Results in death,
- Is life-threatening.

Life-threatening in the definition of serious refers to an event in which the participant was at risk of death at the time of the event, it does not refer to an event which hypothetically might have caused death if it were more severe.

- Requires inpatient hospitalisation or prolongation of existing hospitalisation.

Hospitalisation is defined as inpatient admission or care regardless of duration. Out-patient treatment in an emergency room is not in itself an SAE, although the reasons for it may be. Elective surgery, or hospital admissions and/or surgical operations planned before or during this study are not considered Aes if the illness or disease existed before the participant was enrolled in the study, provided that it did not deteriorate in an unexpected way during the study.

- Results in persistent or significant disability/incapacity.
- Is a congenital anomaly/birth defect.
- Is medically important or is a medically significant event.

Medical and scientific judgement is required to decide if prompt notification is required in situations that the investigator regards as medically important that did not strictly meet the criteria above but may have jeopardised the participant or required intervention to prevent one of the outcomes listed above, or that would suggest any significant hazard, contraindication, side effect or precaution that may be associated with the use of the IMP. Such events should also be considered as serious.

20.7. Recording of adverse events

For Australian sites, all events from Screening to prior to the first dose of IMP will be captured as medical history. All events occurring during and following the first administration of IMP will be reported as Aes or SAEs (if criteria met) until the completion of the End of Study Evaluation visit.

AEs that are ongoing at the End of Study Evaluation visit will be followed up until the event has resolved or stabilised. All follow-up information will be recorded in the participant's source records. All spontaneously volunteered and enquired for, as well as observed AEs, will be recorded in the participant's source records as well as the CRF.

It is preferable that AEs and SAEs be reported as diagnoses if available, rather than individual signs and symptoms. SAEs should be reported and documented in accordance with the procedures in listed below The following data should be documented for each AE: the description of the event, start and stop dates, intensity, causality and outcome must be recorded, as well as any actions taken.

20.7.1. Clinical lab abnormalities and other abnormal assessments

Abnormal laboratory findings (e.g., clinical chemistry, haematology, and urinalysis) or other abnormal assessments (e.g., ECG, vital signs) per se are not reported as AEs. However, those abnormal findings that are deemed clinically significant or are associated with signs and/or symptoms must be recorded as AEs (and recorded as an SAE if they meet the criteria of being serious) as described previously. Clinically significant abnormal laboratory or other abnormal findings that are present at baseline and worsen after first dose of IMP are to be considered AEs (and SAEs if serious).
The investigator should exercise his or her medical and scientific judgment in deciding whether an abnormal laboratory finding or other abnormal assessment is clinically significant. Usually, the abnormality should be associated with a clinically evident sign or symptom, or be likely to result in an evident sign or symptom in the near term, to be considered clinically significant. A clinically significant laboratory abnormality in the absence of clinical symptoms may jeopardize the subject and may require intervention to prevent immediate consequences.

20.8. Reporting of serious adverse events

Any SAE must be reported by the investigator if it occurs during the clinical study or within 2 weeks of the participant having received the last dose of IMP, whether or not the SAE is considered to be related to the IMP. This shall include pregnancy in a female participant or in a female partner of a male study participant. Instances of death, congenital abnormality or an event that is of such clinical concern as to influence the overall assessment of safety, if brought to the attention of the investigator at any time after cessation of IMP administration and linked by the investigator to this study, should be reported to the sponsor.
The investigator must report an SAE on an SAE Report Form and forward the SAE Report Form, the AE form and the concomitant medication form to the sponsor or delegate **within 24 hours of becoming aware of the SAE** and **regardless of causality**. All pregnancies in a female participant or in a female partner of a male study participant should be reported on a Pregnancy Report Form following the same reporting process and timelines required for SAEs.

The investigator should not wait to receive additional information to document fully the event before notification of a SAE, though additional information may be requested. Where applicable, information from relevant laboratory results, hospital case records and autopsy reports should be obtained.

Follow-up information on SAEs must also be reported by the investigational site to the sponsor within the same time frame. If a non-serious AE becomes serious, this and other relevant follow-up information must also be provided within 24 hours of the investigator becoming aware. All SAEs will be recorded in the participant's source documents and the CRF.

It is the responsibility of the sponsor to determine whether a reported SAE fits the classification of a SUSAR (refer to Section 12.1.3). If the sponsor considers the SAE to be drug related (i.e. an adverse drug reaction), unexpected and fulfils the criteria for a Suspected Unexpected Serious Adverse Reaction (SUSAR), the sponsor has the responsibility to expedite the reporting to all concerned investigators, to the EC where required, and to the appropriate regulatory authorities within the pre-defined timelines.

The investigator must notify their EC of SAEs occurring at the site, within the time period and in accordance with requirements specified by the EC. The sponsor and/or delegate will promptly notify all relevant investigators and the regulatory authorities of findings that could adversely affect the safety of participant's, impact on the conduct of the study or alter the ethics approval/favourable opinion of the study.

20.9. Follow-up of adverse events and serious adverse events

All AEs and all SAEs must be followed by the investigator until resolution, or until in the opinion of the investigator, the AE has stabilised or is recognised as permanent, or until the participant is lost to follow up, whichever comes first. Follow-up investigations may be necessary according to the investigator's medical judgement.

21. STATISTICAL ANALYSIS

21.1. General considerations

An analysis of Part A will be conducted when all subjects in Part A have completed Part A.

A final analysis of Part B will be conducted when all subjects have completed Part B.

The statistical analysis principles described below will be supplemented by a comprehensive statistical analysis plan (SAP) which will be finalised before the database is locked. This will contain details of methods for handling missing data and early withdrawals. Any changes to the statistical analysis plan will be described and justified in the final report.

Descriptive statistics will be used to analyse the data in both Part A and Part B of the study. The descriptive summary for the categorical variables will include counts and percentages. The descriptive summary for the continuous variables will include number of participants (n), means, medians, standard deviations, and minimum and maximum values. Pharmacokinetic measures will be analysed as for continuous variables.

In Part A and Part B, data will be tabulated and analysed with respect to subject enrolment and disposition.

In Part A, demographic, baseline characteristics and prior medications summaries will be presented overall. Concomitant medications, PD, PK and safety measure summaries will be presented by active treatment dose, placebo and overall. Note that results for the subjects on placebo across all doses will be combined for summary purposes.

In Part B, demographic, baseline characteristics (including history of lumbar radicular pain) and prior medications will be presented by treatment sequence and overall. Efficacy, PD, PK, concomitant medications and safety measure summaries will be presented by treatment within each treatment period and overall.

As this is a Proof-of -Concept study, no formal statistical hypotheses are being specified although some may be investigated as part of the data presentation, in which case corresponding 95% confidence intervals will be presented for treatment differences and p-values of <0.05 will be declared statistically significant. Treatment comparisons will take into account the paired nature of the treatment responses where feasible and treatment period order will be ignored in any treatment comparisons.

All data will be listed for all subjects to support each table and to present all data. All statistical analyses will be performed using SAS unless otherwise stated in the SAP.

21.2. Analysis populations

21.2.1. 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.

21.2.2. 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. Rules for this population will be included in the SAP. The PP population is the primary population to analyse efficacy endpoints. Demographic and baseline characteristics of the PP population will also be presented.

21.2.3. 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.

21.2.4. 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 protocol deviations that may have compromised the integrity of the PK and PD results.

21.2.5. Participant disposition

The total number of participants will be summarised. The duration on study, and number of participants terminating the study treatment early, along with the reason for early study treatment termination will also be summarised.

21.3. Analysis of safety data

Safety observations and measurements include study drug exposure, AEs, safety laboratory tests, vital signs, physical examinations and ECGs.

21.3.1. Extent of exposure

The number of participants exposed to study treatment, duration of exposure and total IMP administered, will be summarised for Part A and for Part B.

21.3.2. Adverse events

Adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) (Version 20.0 or later) and summarised by system organ class (SOC) and preferred term (PT).

A summary of the number and percentage of participants with the following adverse events will be prepared for Part A: by dose (with all placebo subjects combined) and overall; Part B: by treatment within sequence, by treatment and overall :

- All adverse events
- Serious adverse events
- Adverse events leading to premature discontinuation of IMP
- Adverse events by intensity
- Adverse events by relationship to IMP

21.3.3. Clinical laboratory evaluations

Individually for Part A and Part B, safety laboratory data (haematology, clinical chemistry, and urinalysis) will be summarised by visit and treatment. All laboratory data will be included in the data listings. In addition, a separate listing of laboratory data for participants with clinically significant abnormal results will be prepared.

21.3.4. Other safety measures

Individually for Part A and Part B:

- Vital signs (body temperature, respiratory rate, heart rate, and blood pressure) will be summarised by baseline and treatment overall and for each treatment within the treatment sequence. Changes over time in vital signs will be summarised.
- Physical examination data will be listed only.
- The number and percentage of participants receiving concomitant medications will be tabulated overall and by medication received.

21.4. Analysis of pharmacokinetic data

The following pharmacokinetic parameters will be derived from the plasma concentrations of LAT8881 and metabolites, where practicable:

- C_{max} Maximum plasma LAT8881 concentration
- T_{max} Time to maximum plasma LAT8881 concentration
- $AUC_{0\text{-}t}$ Area under LAT8881 concentration time curve from dosing to the last observed concentration value above the limit of quantification. It will only be calculated if there are at least three quantifiable data points.

- $AUC_{0\text{-}inf}$ Area under LAT8881 concentration time curve from dosing to the last observed concentration value above the limit of quantification, extrapolated to infinity
- $T_{1/2}$ Terminal elimination half life, will only be determined if there are at least three quantifiable elimination phase data points.

Plasma LAT8881 values (or those of its metabolites) below the limit of quantification will be labelled as (BLQ) in the plasma LAT8881 data listings and set to zero if recorded pre-dose.

21.5. Analysis of efficacy data (Part B only)

The primary population for analysis of efficacy data is the PP population. All summary tables and results of statistical analyses will be presented for the PP population for all efficacy endpoints. In addition, all summary tables and results will be presented for the FAS population.

Individual pain score-time profiles for each treatment within each subject will be presented graphically. The difference between the VAS pain scores for "Pain Now" at each timepoint for LAT8881 compared with placebo within each subject will be estimated and presented graphically. The number of subjects, mean, standard deviation, minimum and maximum VAS pain score at each timepoint, change from baseline, difference between treatments at each timepoint and change from baseline difference between treatments will be presented for each treatment overall and within each treatment period.

21.6. Analysis of exploratory endpoints

Part A and B: Exploratory analysis of pharmacodynamic assay and/or biomarkers of LAT8881 activity will be completed pre and post dose on each dosing occasion throughout Part A and B of the study.

Part B: Exploratory analyses will be undertaken to determine the relationship between change in current VAS pain scored from baseline through to 6 hours post treatment.

The approaches to these investigative analyses will be detailed in the statistical analysis plan.

21.7. Planned Interim Analyses

The DSMC will monitor blinded safety data on an ongoing basis and at the completion of Part A of the study. The DSMC will also review PK data from Part A, provide to HREC to determine the MDT dose for Part B.

In Part B, an interim analysis will be undertaken after 'at least 10 subjects' have completed both periods Per Protocol. Enrolment will continue while the interim analysis is undertaken. The interim analysis will include results for only the 10 (or less) subjects that have completed both periods. The aim of the analysis includes but is not limited to:

- Providing additional insight regarding potentially stopping the study for futility. Details will be provided in the DSMC charter.
- Undertaking a sample size re-estimation based on the primary endpoint of the change in VAS "Pain Now" score from baseline through the 6 hours post-infusion. The standard deviation for the change from baseline while on placebo treatment and the correlation between the changes from baseline while on placebo and on active treatment will be used to estimate a sample size required to detect a clinically significant difference in the change from baseline while on active treatment compared with placebo, with a power of 80% and type I error (alpha) of 5%. Full details on this interim analysis will be included within the SAP.

22. STUDY MANAGEMENT

22.1. Regulatory compliance and ethical conduct

This study must be conducted in compliance with the study protocol, the requirements and obligations of the International Conference on Harmonisation (ICH) and Good Clinical Practice (GCP) guidelines, Integrated Addendum to ICH E6(R1): Guideline for Good Clinical Practice E6(R2),1 the World Medical Association Declaration of Helsinki23 and its amendments and all applicable local guidelines, laws and regulations. Investigators and other site personnel will undergo appropriate study-specific training during the study site initiation visit. Before initiation of the study at the site(s), the written approval / favourable opinion of the local and/or national independent Ethics Committee(s) and relevant Health Authority(ies) will be sought and obtained.

22.2. Ethics Committee review

Prior to the initiation of the study, the protocol and associated documentation (including all materials used to recruit participants for the study) must be given a favourable opinion by an Ethics Committee (EC). A copy of this written approval and any correspondence with the EC will be provided to the sponsor. The investigator must obtain approval from the sponsor before potential participants can undergo any study specific screening procedures. The investigator will comply with any additional requirements imposed by the EC. The investigator must submit progress reports to the EC according to local regulations and guidelines. The investigator must also provide their EC with any reports of SAEs from the study site in accordance with the EC's requirements and timelines.

22.3. Informed consent process

The investigator will ensure that the participant is given full and adequate oral and written information about the nature, purpose, possible risks and potential benefits of the study. Participants must also be notified that they are free to discontinue from the study at any time. The participant should be given the opportunity to ask questions and should be allowed time to consider the information provided. The participant's signed and dated informed consent must be obtained before conducting any procedure specifically for the study. The investigator must store the original, signed ICF with the participant's medical records. A copy of the signed and dated ICF must be given to the participant. Participants who are incompetent and unable to freely provide informed consent and participants who are unable to read or speak English without the assistance of an interpreter will not be invited to participate in the study.
If new information arises during the study that may affect the safety of the participants, the protocol and ICF will be amended as appropriate and submitted to the EC as outlined in Schedule 1 nd 2. Following approval by the EC, participants will be advised by letter of any safety related updates that may impact during the post-study period and be invited to discuss any concerns with the investigator. When applicable, participants may be requested to re-consent to ongoing their participation in the study.

22.4. Protocol amendments

Modification of the signed, EC-approved protocol must not be changed without the agreement of the sponsor. If it is necessary for an EC-approved study protocol to be amended, the relevant EC and, if required, the local regulatory authority must be informed and asked for its opinion as to whether a reevaluation of the ethical aspects of the study is necessary. In the UK, a substantial amendment to the protocol will be submitted to the Medicines and Healthcare Products Regulatory Agency for approval. The investigator must not implement any deviation from, or change to the protocol, without agreement by the sponsor and prior review and documented approval/favourable opinion of the amendment from the

relevant EC, except where it is necessary to eliminate an immediate hazard to study participants, or where the change(s) involve(s) only logistical or administrative aspect(s) of the study, for example, change in monitor(s) or change of telephone number(s).
If a protocol amendment requires a change to the Participant Information Sheet (PIS) or Informed Consent Form (ICF), approval of the revised PIS and ICF by the sponsor and EC is required before the updated document can be used. Following approval, the sponsor (or delegate) will distribute new versions of amended documents (e.g. protocol, PIS, ICF) to the site.

22.5. Protocol deviations

No deviations from or changes to the protocol will be implemented without documented approval from the EC of an amendment, except where necessary to eliminate an immediate hazard(s) to study participants or when the change(s) involves only logistical or administrative aspects of the study. Any deviations from or changes to the protocol which were implemented to eliminate an immediate hazard and the proposed amendment, if appropriate, should be submitted to the EC for review and approval as soon as possible. Should any protocol deviation occur, it must be reported to the study monitor as soon as is reasonably practical. If a major protocol deviation occurs, the investigator must notify the sponsor and the appropriate EC as soon as possible or as per local requirements.

All instances of noncompliance with the requirements of the Study Protocol will be captured in a Protocol Deviation Log. The deviation and the reason for its occurrence must be documented, reported to the relevant EC (if required) and included in the clinical study report.

23. QUALITY CONTROL AND QUALITY ASSURANCE

23.1. Training of staff

Each individual involved in the study must be qualified by education, training and experience to perform his or her respective tasks. Site staff may be trained at investigator meetings and initiation visits by the sponsor or their designees.

23.2. Study monitoring

The study will be independently monitored in accordance with ICH GCP1, and applicable local regulations. Before the start of the study, a study monitor appointed by the sponsor will evaluate the investigational site to ensure facilities are adequate and to discuss responsibilities with the site staff with regards to following the protocol and regulatory and ethical requirements. During the study, the study monitor will regularly visit the site to monitor and confirm protocol, regulatory and ethical adherence, confirm data accuracy and provide information and support as needed. The investigator is responsible for maintaining source documents. The investigator must agree to allow the study monitor direct access to all relevant documents at each monitoring visit, including electronic medical records, and to allocate their time and the time of their staff to the study monitor to discuss findings and any relevant issues. Site staff will be provided with contact details for the study monitor and back-up persons in the event they have queries or require assistance.

23.3. Data management and quality control

The sponsor (or delegate) will be responsible for activities associated with the data management of this study. This will include setting up a database and data transfer mechanisms, along with appropriate validation of data and resolution of queries.

Data generated within this clinical study will be handled according to the relevant SOPs of the sponsor and/or their delegate(s). An electronic CRF (eCRF) will be created by the data management group for recording of the required data and integration into the study database. All data (including electronically available data, i.e. eCRF and laboratory data) will be integrated into a validated Data Management System with full audit trail capability (i.e. a computerised log of all subsequent changes to the data will be recorded). Automated checks will be made against the data to ensure completeness and consistency.

The database and check programs will be validated before implementation. AEs will be coded using MedDRA (Version 20.0 or later) and medications will be coded using the current version of the WHO Drug Dictionary. Missing or inconsistent data will be queried via system generated queries to the investigator for clarification. Subsequent modifications to the database will be documented. Data collection and entry into the eCRF will be completed by authorised study site personnel designated by the investigator. Appropriate training and security measures will be completed with the investigator and all authorised study site personnel prior to the study being initiated and any data being entered for any study participants. The eCRFs should always reflect the latest observations on the participants participating in the study; therefore, the eCRFs are to be completed as soon as possible during or after the participant's visit. The investigator must verify that all data entries in the eCRFs are accurate and correct. If some assessments are not done, or if certain information is not available or not applicable or unknown, this should be indicated in the eCRF. The investigator will be required to sign off on the final clinical data. During the study the study monitor will review the eCRFs and evaluate them for completeness and consistency. The eCRF will be

compared with the source documents to ensure that there are no discrepancies. All entries, corrections and alterations are to be made by the investigator or designee. The study monitor cannot enter data into the eCRFs. If corrections are needed, the responsible study monitor or data manager will raise a query and the appropriate investigational staff will be required to provide an answer. All queries and resultant data changes will have an electronic audit trail, meaning that the name of the investigational staff responding to the query, time and date stamp are captured.

The eCRF is considered a data entry form and should not constitute the original, or source document, unless otherwise specified. Source documents are documents used by the investigator or study site that relate to the participant's medical record, that verify the existence of the participant, the inclusion and exclusion criteria and all records covering the participant's participation in the study. They include, but are not limited to, laboratory reports, hospital records, participant files, etc. eCRFs will be completed for participants who have signed the ICF, are eligible for this study and have been enrolled in the study.

23.4. Audits and inspections

An audit is a systematic and independent examination of study related activities and documents to determine whether the evaluated study activities were conducted and the data were recorded, analysed and accurately reported according to the protocol, the sponsor's standard procedures or those of the sponsor's designees, ICH GCP and applicable regulatory requirements. In accordance with ICH GCP, this study may be selected for audit. Inspection of site facilities (e.g. pharmacy, medication storage areas, laboratories) and review of study-related records may occur by the sponsor, sponsor's representative, Ethics Committee or regulatory authority to evaluate the study conduct and compliance with the protocol, ICH GCP, and applicable regulatory requirements. The regulatory authority or Ethics Committee inspectors are responsible for contacting and visiting the investigative site for the purpose of inspecting the facilities, if required, and, upon request, inspecting the various records of the study (e.g. source documents, CRFs, essential documentation, and other pertinent data) ensuring that participant confidentiality is respected.

The investigator should contact the sponsor or designee immediately if they are contacted by a regulatory agency or Ethics Committee about an inspection at their centre. If an audit or inspection occurs, the Investigator and institution agree to allow the auditor/inspector direct access to all relevant documents and allocate their time and the time of their staff to the auditor/inspector to discuss findings and any relevant issues.

24. DOCUMENTATION, RECORD ACCESS AND ARCHIVING

24.1. Maintenance of essential documents/supplements at study site during the study

At the beginning of the study, an Investigator's Study File will be established at the study site. The investigator/institution is responsible for maintaining the study documents during the study as specified in the ICH GCP1 guidelines and applicable regulatory requirement(s). The investigator/institution must take measures to prevent accidental or premature destruction of these documents. These files must be suitable and available for inspection at any time by the sponsor, study monitor, and/or applicable regulatory authorities.

24.2. Data protection

To protect the participant's identity, a unique participant identification code (Participant ID) will be assigned by the investigator to each study participant and used in lieu of the participant's name when the investigator reports SAEs and/or other study-related data. The participant's study number, rather than the

participant's name, will appear on all documents and will be cross referenced by the participant's date of birth. Personal information will be treated as confidential, but may need to be reviewed by authorised representatives of the sponsor (and/or delegate), the EC and regulatory authority(ies). The participant's consent to direct access to his/her original medical records for data verification purposes must be obtained prior to that participant's involvement in the study. Participants will be informed that data will be held on file by the sponsor and that these data may be viewed by staff including the study monitor and by external auditors on behalf of the sponsor and appropriate regulatory authorities. Participants will also be informed that a study report will be prepared and may be submitted to regulatory authorities and that the study results may be published. However, participants will be identified in such reports only by study identification number (Participant ID), gender and age. All participant data will be held in strict confidence.

The PIS will explain that electronic study data will be stored in a computer database, maintaining confidentiality in accordance with the applicable local privacy regulations. Participant data in the database will be identified by Participant ID number only. Electronic CRFs will also identify participants by Participant ID only and will be maintained and stored in accordance with the applicable local privacy regulations. The PIS will also explain that for data verification purposes, authorised representatives of the investigator, sponsor, regulatory authorities or ECs may require direct access to parts of the hospital or practice records relevant to the study including the participant's source documents and/or medical record.

24.3. Data retention & archiving

All study records (including the Investigator's Study File containing Essential Documents as defined in ICH GCP1) and source data must be available for retrospective review or audit.

Source documents are original documents, data, and records from which the participant's CRF data are obtained. These include, but are not limited to: hospital records, participant's source documents/files, clinical and office charts, laboratory and pharmacy records, diaries, radiographs, IMP accountability logs, and correspondence. CRF entries may be considered source data if the CRF is the site of the original recording (i.e., there is no other written or electronic record of data). In this case, a note to the file should indicate which CRFs data points are considered source data. At completion of the study the investigator is responsible for the archiving of the study records for their site.

All source data, clinical records and laboratory data relating to the study must be archived for no less than 2 years after the last approval of a marketing authorisation application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region, or at least two years have elapsed after formal discontinuation of clinical development of the IMP. Study documents should be retained for a longer period as required by local regulatory requirements or by an agreement with the sponsor. In Australia and UK, records should be retained by the trial sponsor for at least 15 years following completion of the trial. It is the responsibility of the sponsor to inform the investigator/Institution as to when the documents no longer need to be retained.

No study document should be destroyed without prior written agreement between the sponsor and the investigator. If the investigator leaves the Institution, the responsibility for all study documents must be transferred to another person at the institution. If the investigator wishes to assign the study records to another party or move them to another location, he/she must notify the sponsor in writing of the new responsible person and/or the new location.

25. STUDY ADMINISTRATION

25.1. Study agreements

Financing and insurance of this study will be outlined in separate agreement(s) between the sponsor and all relevant parties.

Payments will relate to the number of participants as well as the cost of clinical visits, laboratory investigations and other services outside of normal routine examinations and specifically connected with the conduct of this study. This agreement will cover payment for eCRFs fully completed in conformity with the protocol. The fee for participants who withdraw prematurely from the study will be on a pro-rata basis reflecting the percentage of study activities completed. Neither the sponsor nor its designee is financially responsible for further testing/treatment of any medical condition that may be detected during the screening process. In addition, in the absence of specific arrangements, neither the sponsor nor its designee is financially responsible for further treatment of the participant's condition beyond the time period specifically outlined in this protocol. The investigator(s) must comply with all the terms, conditions and obligations of the study agreement for this study. In the event of any inconsistency between this protocol and the study agreement, the study agreement shall prevail.

25.2. Confidentiality

In signing the final protocol, every participating investigator agrees to keep all information and results concerning the study and the investigational product confidential for as long as the data remain unpublished. The confidentiality obligation applies to all personnel involved at the study site. However, authorised regulatory officials and the sponsor's personnel (or their representatives) will be allowed full access to inspect and copy the records. All IMPs, participant bodily fluids and/or other materials collected shall be used solely in accordance with this protocol, unless otherwise agreed to in writing by the sponsor and the EC.

All CRFs as well as all reports and communications relating study involvement will identify each participant only by the participant identification code (Participant ID). The investigator will maintain a current confidential Participant Identification List of full names of all participants in this study. This list will allow the investigator to reveal the identity of the participants if they need to be contacted for safety reasons. This information will be held in the strictest confidence and will only be used if needed for emergency purposes.

25.3. Insurance

The sponsor has appropriate liability insurance cover available to enable it to indemnify and hold the investigator(s) and relevant staff as well as any hospital, institution, EC or the like, harmless from any claims for damages for unexpected injuries, including death, that may be caused by the IMP but only to the extent that the claim is not caused by the fault or negligence of the participants or investigator(s). This insurance is held in accordance with the applicable local legal requirements. Further details of this and financial arrangements are specified in the agreements with the study site.

25.4. Reporting

A final integrated clinical/statistical report will be prepared that is compliant with the ICH Note for Guidance: Structure and Content of Clinical Study Reports (CPMP/ICH/137/95)24.

25.5. Publication policy

By signing the study protocol, the investigator agrees with the use of results of the study for the purposes of national and international registration, publication and information for medical professionals. If necessary, the authorities will be notified of the investigator's name, address, qualifications and extent of involvement.

An investigator shall not publish any data related to this study (poster, abstract, paper, slide presentation, etc.) without having consulted with the sponsor in advance. The objectives, the content and the results of the present study should be considered confidential. All data and results are the exclusive property of the sponsor.

Except for legal reasons, the investigator will not reveal the result of the study to a third party without a mutual agreement about the analysis and interpretation of the data with the sponsor.
AEs will be assessed by the Site PI, and in the event of an SAE, the CPI and Sponsor must be notified by the Site PI or delegate **within 24 hours** of observing or being informed of the event.

26. REFERENCES

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