Official Title: A Phase IIa study of the efficacy and safety of oral LAT8881 in neuropathic pain

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Clinical Study Title	**A Phase IIa study of the efficacy and safety of oral LAT8881 in neuropathic pain**
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Drug name	LAT8881
Clinical phase	IIa
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Principal Investigator	[redacted]
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This clinical study will be performed in compliance with Good Clinical Practice (GCP) guidelines, including archiving 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.

Protocol signatures

Investigator's statement

The undersigned Investigator(s) agree:

1. To conduct the study in accordance with the study protocol, ICH Guideline for Good Clinical Practice E6(R2),[1] and applicable regulations and guidelines.
2. To ensure that all persons at their investigational site assisting with the clinical study, are adequately informed and trained about the study protocol, the investigational product and their study-related duties and functions.
3. That alteration of the procedures described in the study protocol, other than to protect subject safety, rights, or welfare, is not allowed without prior written approval from Lateral Pharma Pty Ltd ("Lateral") and if appropriate, the relevant Ethics Committee.
4. That subjects' study-specific data will be kept in the subjects' files and documented in the case report form in a complete and accurate manner. All requested study-related records will be made available for direct access to Lateral's representatives for monitoring or auditing the study.
5. To allow authorised qualified delegates of Lateral to perform regular visits to monitor the study conduct and study data.
6. To ensure that the investigational product is dispensed in accordance with the protocol and only to subjects enrolled in the study.
7. To dispose of used and unused investigational product and materials as instructed by Lateral.

Investigator Name (Print)	Investigational Site
Investigator Signature	Date
Investigator Name (Print)	Investigational Site
Investigator Signature	Date
Sponsor Name (Print)	
Sponsor Signature	Date

[redacted]

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List of Abbreviations

Abbreviation	Definition
µg	Microgram
µl	Microlitre
ADL	Activities of daily living
ADR	Adverse drug reaction
AE	Adverse event
AUC_{0-inf}	Area under LAT8881 concentration time curve from dosing to the last observed concentration value above the limit of quantification, extrapolated to infinity
AUC_{0-t}	Area under LAT8881 concentration time curve from dosing to the last observed concentration value above the limit of quantification
BDI-II	Beck Depression Inventory-II
BLQ	Below limit of quantification
BPI	Brief Pain Inventory
cGMP	Current good manufacturing practice
CI	Confidence interval
C_{max}	Maximum plasma drug concentration
(e)CRF	(electronic) Case report form
CTN	Clinical Trial Notification (scheme)
DPN	Diabetic peripheral neuropathy
EC	Ethics committee
ECG	Electrocardiogram
FAS	Full analysis set
FOCBP	Female of child bearing potential
g	Gram
GCP	Good clinical practice
HbA1c	Glycosylated haemoglobin
hCG	Human chorionic gonadotropin
hGH	Human growth hormone
[redacted]	[redacted]
IASP	International Association for the Study of Pain
ICF	Informed Consent Form
ICH	International Conference on Harmonisation
IMP	Investigational medicinal product
Investigator	A person responsible for the conduct of the clinical trial at a trial site. If a trial is conducted by a team of individuals at a trial site, the investigator is the responsible leader of the team and may be called the principal investigator.

Abbreviation	Definition
kg	Kilogram
m	Metre
m^2	Square metre
MedDRA	Medical Dictionary for Regulatory Activities
mg	milligram
MHRA	Medicines and Healthcare products Regulatory Agency
mL	millilitre
mN	millinewton
[redacted]	[redacted]
n	Number (of subjects)
NeuPSIG	Neuropathic Pain Special Interest Group
NP	Neuropathic pain
NPRS	Numeric pain rating scale
NPSI	Neuropathic Pain Symptom Inventory
[redacted]	[redacted]
PD-Q	painDETECT questionnaire
PGIC	Patient Global Impression of Change
PHN	Postherpetic neuralgia
PIC/S	Pharmaceutical Inspection Co-operation Scheme
PIS	Participant Information Sheet
PK	Pharmacokinetics
PK subjects	Subjects in whom pharmacokinetics are measured
PP	Per protocol
PT	Preferred term
PWT	Paw withdrawal threshold
QST	Quantitative sensory testing
QST subjects	Subjects in whom quantitative sensory testing is undertaken
SAE	Serious adverse event
SAP	Statistical analysis plan
SF-MPQ-2	Short-form McGill Pain Questionnaire 2
SOC	System organ class
SOP	Standard operating procedure
Subject ID	Unique number given to each subject on screening
SUSAR	Suspected unexpected serious adverse reaction
$T_{1/2}$	Terminal elimination half life

Abbreviation	Definition
TEAE	Treatment-emergent adverse event
TGA	Therapeutic Goods Administration
T_{max}	Time to maximum plasma LAT8881 concentration
TYR	Tyrosine
[redacted]	[redacted]

1. Protocol synopsis

Title:	A Phase IIa study of the efficacy and safety of oral LAT8881 in neuropathic pain
Protocol Number	LAT-NP-001
Clinical Phase	IIa
Principal Investigator	[redacted]
Study Site(s)	Emeritus Research, Victoria, Australia Australian Medical Research, New South Wales, Australia AusTrials Pty Ltd, Queensland, Australia University Hospitals Bristol NHS Trust, Bristol, United Kingdom Queen Elizabeth University Hospital, Glasgow, United Kingdom Full contact details are provided in the Site Contact List.
Investigational Medicinal Product (IMP)	LAT8881 [redacted] 30 mg capsules and matching placebo. One capsule to be taken in the morning and one in the evening. Total daily dose of IMP: 0 or 60 mg LAT8881
Indication	Neuropathic pain (NP), associated with either postherpetic neuralgia (PHN) or diabetic peripheral neuropathy (DPN)
Study Description	This is a randomised, placebo-controlled, double-blind, crossover, phase IIa study to investigate the efficacy and safety of oral LAT8881 in neuropathic pain. After a one week baseline period, subjects entered into the study will be randomised to receive IMP (LAT8881 or placebo) twice daily for four weeks. The first treatment period will be followed by a washout period of two weeks and then a second baseline period of one week. Subjects will not take any IMP over these three weeks. After the second baseline period, subjects will cross over to receive the second treatment (either LAT8881 or placebo, whichever treatment was not received in the first treatment period) twice daily for four weeks. The pharmacokinetics (PK) of LAT8881 will be investigated in 15 subjects (PK subjects) at selected Australian sites. Quantitative sensory testing (QST) [redacted] will be performed in up to 20 subjects (QST subjects) in each treatment period, before the first dose and on the last day of each period. No subject will have both PK and QST analyses.
Number of Subjects Planned	It is planned to have 44 subjects complete the study. Assuming a 20% dropout, 55 subjects will be recruited.
Study Objectives	**Primary** • To evaluate the efficacy of oral LAT8881 in NP compared with placebo, when assessed by change in mean pain intensity scores

from baseline to the end of four weeks treatment, based on an 11 point numeric pain rating scale (NPRS)

Secondary

- To investigate the effect of oral LAT8881 in NP compared with placebo at different timepoints (up to 6 hours) following a single dose and after 4 weeks treatment, as measured by the NPRS (PK subjects only)
- To investigate the effect of oral LAT8881 on mean pain scores in NP compared with placebo after 1, 2 and 3 weeks of dosing, as measured by the NPRS
- To determine the proportion of responders to oral LAT8881 in NP compared with placebo
- To investigate the maximum effect of oral LAT8881 in NP, compared with placebo, as determined by the maximum change from mean NPRS baseline after 1, 2, 3 or 4 weeks treatment
- To evaluate the effect of oral LAT8881, compared with placebo, on functioning in subjects with NP when measured by the 7-item short form Brief Pain Inventory (BPI) Interference Scale
- To evaluate the effect of oral LAT8881, compared with placebo, on pain symptoms in subjects with NP, when measured by the short-form McGill Pain Questionnaire 2 (SF-MPQ-2)
- To evaluate the effect of oral LAT8881, compared with placebo, on symptoms in subjects with NP, when measured by the Neuropathic Pain Symptom Inventory (NPSI)
- To evaluate the effect of oral LAT8881, compared with placebo, on emotional functioning when measured by the Beck Depression Inventory-II (BDI-II)
- To evaluate the effect of oral LAT8881, compared with placebo, on overall health and quality of life in subjects with NP, when measured by the Patient Global Impression of Change (PGIC) scale
- To determine the change from baseline in paracetamol rescue medication use during oral LAT8881 administration, compared with placebo
- To evaluate the safety and tolerability of oral LAT8881 in NP after a single dose and after four weeks treatment
- To investigate the pharmacokinetics of twice daily oral LAT8881 in 15 subjects with NP after a single dose and after 4 weeks treatment with oral LAT8881

Exploratory

- To investigate the relationship between baseline subject characteristics, such as clinical diagnosis (PHN or DPN) and QST parameters, and the change in NPRS after oral LAT8881 treatment, compared with placebo
- To investigate the change from baseline on specified QST parameters [redacted] after four weeks treatment with oral LAT8881,

compared with placebo

- To investigate the relationship between plasma LAT8881 concentrations and the change in mean pain score in subjects with NP
- To investigate the impact of variability in NPRS scores during the first baseline period on the difference between baseline and 4 week NPRS scores after LAT8881 or placebo

Endpoints

Primary Endpoint

- Absolute change in mean pain score, using an 11 point NPRS, from baseline to the last week of each treatment period. Pain is recorded once daily in a subject diary, in the evening, and should reflect the subject's average pain over the last 24 hours

Baseline mean pain for each subject is defined as the mean of the last five available ratings of daily pain, recorded in each baseline period.

End of treatment mean pain for each subject is defined as the mean of the last five available ratings of daily pain, recorded in the last 7 days of each 4 week treatment period.

Secondary Endpoints

- Change in NPRS score at 0.5, 1, 2, 4 and 6 hours after the first dose of IMP in each treatment period, compared with the score recorded no more than 60 minutes before the first dose of IMP in that treatment period (PK subjects only)
- Change in NPRS score at 0.5, 1, 2, 4 and 6 hours after a single dose of IMP, following four weeks treatment with IMP in each treatment period, compared with the score recorded no more than 60 minutes before this dose (PK subjects only)
- Change in mean pain scores from baseline after 1, 2 and 3 weeks of dosing with IMP in each treatment period, using an 11 point NPRS. Mean pain scores at weeks 1, 2 and 3 are defined as the mean of the last five available ratings of daily pain in the subject diary, recorded in the previous 7 days of treatment
- 30% responder rate, based on the proportion of subjects achieving ≥ 30% reduction in mean NPRS from baseline to the end of 4 weeks treatment in each treatment period
- 50% responder rate, based on the proportion of subjects achieving ≥ 50% reduction in mean NPRS from baseline to the end of 4 weeks treatment in each treatment period
- Maximum change in mean NPRS from baseline after 1, 2, 3 or 4 weeks treatment in each treatment period
- Change in functioning from baseline to the end of 4 weeks treatment in each treatment period, as assessed by the BPI interference scale
- Change in pain characteristics and intensity from baseline to the end of 4 weeks treatment in each treatment period, as assessed by the SF-MPQ-2
- Change in neuropathic pain symptoms from baseline to the end of 4 weeks treatment in each treatment period, as assessed by NPSI

- Change in emotional functioning from baseline to the end of 4 weeks treatment in each treatment period, as assessed by the BDI-II
- PGIC at the end of each four week treatment period
- Paracetamol (rescue medication) use per week over each treatment period compared with the preceding baseline

Safety Endpoints

- Physical examinations and vital signs
- ECG
- Clinical chemistry and haematology analyses
- Urinalysis
- Number and type of Treatment Emergent Adverse Events (TEAEs), including serious adverse events (SAEs), and suspected unexpected serious adverse reactions (SUSARs)
- Concomitant medications

Pharmacokinetic Endpoints

- Pharmacokinetic parameters: C_{max}, T_{max}, $AUC_{0\text{-}inf}$ in each treatment period, after a single dose and at the end of four weeks treatment in PK subjects

Exploratory Endpoints

- Association between change in mean NPRS from baseline to the end of four weeks treatment and selected subject baseline characteristics, including clinical diagnosis and pre-treatment QST parameters
- Change from baseline in specified QST parameters [redacted] to the end of four weeks treatment, in each treatment period
- Correlation between plasma LAT8881 concentration and the change in mean NPRS from baseline to the end of four weeks treatment in PK subjects
- Change in mean NPRS score from baseline to the last week of each treatment period, after omission of subjects with the 25% most variable first baseline NPRS scores

Study Population: **Inclusion Criteria**

Subjects must meet the following criteria to be entered into the study:

1. Clinical diagnosis of post herpetic neuralgia, with pain persisting for at least 3 months after the onset of herpes zoster rash

OR

2. Clinical diagnosis of distal painful polyneuropathy due to Type I or Type II diabetes mellitus with:
   a) symmetrical, bilateral pain in the lower extremities for at least 3 months and
   b) diabetes under control for at least 3 months prior to randomisation, as indicated by a glycated haemoglobin level

(HbA1c) of ≤ 11% (97 mmol/mol) and on a stable dose of insulin or oral diabetic medication for 3 months prior to screening, and

c) no change in diabetic medication planned for the duration of the study

3. Positive sensory symptoms (mechanical or thermal) associated with neuropathic pain, confirmed by:

   a) painDETECT questionnaire (PD-Q) and

   b) Clinical assessment, showing signs of neuropathic pain in either a dermatomal (PHN) or distal symmetrical distribution (DPN)

4. Aged 18 to 75 years

5. Subjects must be sufficiently competent in English to understand the purposes and risks of the study and able to give voluntary written informed consent to participate in the study

6. Willing and able to comply with all study procedures

7. Completion of at least five NPRS scores during the week preceding randomisation

8. An average daily pain score on the NPRS of at least 4 and no more than 8 in the last five diary entries before randomisation

9. No more than one score on the NPRS of 9 or more, and no more than one score of 2 or less, in the last five diary entries before randomisation

10. Females of child bearing potential must have a negative pregnancy test at Visit 1 (Screening) and at Visit 2 (Day 1) prior to administration of IMP

11. Female subjects must be:

    a) of non child-bearing potential [surgically sterilised or post–menopausal (12 months with no menses without alternative medical cause)] OR

    b) not pregnant, breast feeding or planning to become pregnant AND willing to comply with the medically acceptable contraceptive requirements of the study from Screening to at least 28 days after the last IMP administration

Exclusion Criteria

Subjects who meet any of the following criteria will be excluded from the study:

1. Presence of moderate to severe pain from other causes that may confound assessment or self-evaluation of NP.

2. Subjects with both DPN and PHN

3. Skin conditions in the affected area that could alter sensation or assessments

4. History of or current clinically significant gastrointestinal, hepatic, renal, cardiovascular, respiratory, endocrine, oncological, immunological, neurological, ophthalmological, haematological or psychiatric disorder or any other condition, which in the opinion of the investigator or sponsor

would jeopardise the safety of the subject or the validity of the study results

5. Medical history of, or currently active, human immunodeficiency virus, hepatitis B or hepatitis C virus
6. Clinically significant abnormal 12-lead electrocardiogram (ECG)
7. Immunocompromised state, or conditions known to be associated with an immunocompromised state
8. Clinically significant or unstable medical or psychological condition that would compromise participation in the study
9. Recent history of malignancy within 5 years preceding screening (except resected cervical or skin cancer [except melanoma]). Subjects who have had no evidence of disease in the last 5 years are eligible
10. Active herpes zoster infection on screening
11. Current alcohol abuse, illicit or illegal drug use
12. Use of prohibited medication (see study medications)
13. Previous treatment with LAT8881 (formerly identified as AOD9604) within the last 5 years
14. Participation in an investigational trial within 60 days or 5 half-lives (whichever is longer) prior to screening
15. History of significant hypersensitivity to LAT8881 or drugs of a similar pharmacological class (e.g. somatropin)
16. Surgical or medical conditions which could significantly alter drug absorption, distribution, metabolism or excretion
17. An employee of the sponsor or research site personnel directly affiliated with this study, whether biological or legally adopted, or their immediate family members, defined as a spouse, parent, sibling, or child
18. Previous neurolytic or neurosurgical therapy for PHN or DPN
19. PK subjects:
    a) Blood or plasma donation of more than 500 mL during the 3 months prior to randomisation
    b) History of fainting during phlebotomy

Study Medications

Permitted medications

The following medications are permitted:

- Subjects may take their usual oral medications for PHN or DPN, providing the dose has been stable for at least 30 days before randomisation and is maintained for the duration of the study until the end of study visit
- Diabetics must be on stable diabetic medication for at least 3 months before randomisation, and the medication must be maintained at the same dose until the end of study visit
- Subjects may also take the following medications, provided the regimen is stable for 30 days before randomisation and remains

steady from randomisation to the end of study visit:

- benzodiazepine
- anxiolytic, such as buspirone
- serotonin and noradrenaline (norepinephrine) reuptake inhibitor
- oral aspirin (≤ 150 mg/day)
- tricyclic antidepressant

- In addition, up to 4 g per day of paracetamol (rescue medication) may be taken except within 4 hours of the first and last clinic visit in each treatment period

Prohibited medications

The following medications are prohibited.

- Patch containing 8% capsaicin (Qutenza), if applied within the last six months before randomisation
- Current or recent (within 7 days of randomisation) use of any other topically applied pain medication
- Cryotherapy, intrathecal/epidural opioids, systemic corticosteroids or botulinum toxin if administered in the last 6 months. Topical or inhaled corticosteroids are permitted. .A short course (< 7days) of oral prednisolone or equivalent for other conditions, up to 4 weeks preceding Day 1, is allowed
- Steroid or local anaesthetic nerve blocks within the last 12 months

Study Procedures

Screening (Days -28 to -1)

Potential subjects will be required to provide written informed consent prior to any study-specific screening procedures being performed. A unique Screening Number (Subject ID) will be assigned.

There will be two stages within the screening procedure. In the first stage (Screening Stage 1, Days -28 to Day -8), subjects will undergo screening assessments including medical history, height, weight, PD-Q, 12-lead ECG, vital signs, and physical examination. Concomitant medications will be recorded. Blood will be collected for routine haematology and clinical chemistry screening and, in female subjects of child-bearing potential, to test for pregnancy. A urine sample will be collected for urinalysis.

Subjects deemed likely to be eligible for the trial after completion of the above screening tests will be given access to a diary and training on how to record daily pain scores.

In the second screening stage (Screening Stage 2, First Baseline Period, Days -7 to -1) subjects will complete their diary from Days -7 to -1 inclusive. This will be their first baseline period if confirmed to be eligible and enrolled in the study.

Up to 20 potentially eligible subjects will also have QST scheduled within seven days of the first treatment.

First Treatment Period (Days 1-28)

Subjects will return to the unit on Day 1 (Visit 2) with their diary completed

from Days -7 to -1 inclusive. Diary records will be reviewed to assess pain scores. Other assessments, including weight, PD-Q, ECG, vital signs and a targeted physical examination will also be conducted on Day 1. Concomitant medications will be recorded. Blood and urine samples will be taken for safety monitoring. Urine samples in female subjects of child-bearing potential will be tested for evidence of pregnancy. Results from safety monitoring tests are not required prior to dosing. Eligible subjects will be enrolled and randomised to LAT8881 or placebo.

Subjects will complete baseline assessments for Patient Reported Outcomes (interference scale of the short form BPI, SF-MPQ-2, NPSI, BDI-II). In PK subjects, a pre-dose NPRS will be completed and a pre-dose blood sample taken for PK analysis. QST subjects will have a pre-dose QST assessment, if not completed within the previous 7 days.

Subjects (except PK subjects) will take their first dose of IMP and remain in the clinic for up to one hour to check for any adverse events.

PK subjects will take their first dose of IMP and remain in the clinic for at least 6 hours. At scheduled times over this period, blood samples will be taken for PK analyses and NPRS assessments.

All subjects will leave the unit with sufficient IMP for the first treatment period.

On Day 14 (Visit 3), subjects will take their morning IMP dose and return to the clinic. Weight, vital signs, a targeted physical examination, concomitant medications and adverse events will be recorded. Subject compliance with medication and diary entries will be checked. Subjects will be reminded to continue their medication and to record daily entries into their diary.

On the morning of Day 28 (Visit 4, Last Day of First Treatment Period), subjects will not take their morning dose of IMP. They will make their morning diary entry and return to the clinic. At the clinic, weight, ECG, vital signs, a targeted physical examination, concomitant medications and adverse events will be recorded. Blood and urine samples will be taken for safety analysis. Subjects will complete assessments for Patient Reported Outcomes (interference scale of the short form BPI, SF-MPQ-2, NPSI, BDI-II, PGIC). In PK subjects, a pre-dose NPRS will be completed and a pre-dose blood sample will be taken for PK analysis.

Subjects (except PK and QST subjects) will then take their morning dose of IMP and leave the clinic. PK subjects will take their morning dose of IMP and stay for at least 6 hours. At scheduled times over this period, blood samples will be taken for PK analyses and NPRS assessments will be undertaken.

QST subjects will take their morning dose of IMP and will have specified QST parameters [redacted] assessed 2 hours after this dose. An appointment for a QST assessment will be scheduled within seven days of the first dose of the second treatment period.

All subjects will take their second Day 28 IMP dose in the evening.

Washout (Days 29 to 42)

Subjects will be asked to discontinue their IMP after their evening dose on Day 28. Daily diary NPRS entries should be continued.

Second Baseline Period (Days 43 to 49)

Subjects will continue daily diary entries and will not take any IMP over Days 43 to 49 inclusive (second baseline).

Second Treatment Period (Days 50-77)

Subjects will return to the unit on Day 50 (Visit 5) with their diary completed from Days 29 to 49 inclusive. QST subjects will have a pre-dose QST assessment, if not completed within the previous 7 days.

On Day 50, assessments including weight, ECG, vital signs, a targeted physical examination and concomitant medications will be recorded and the subject's pain diary (Days 43-49 inclusive) will be reviewed. Blood and urine samples will be taken for safety monitoring. Results from safety monitoring tests are not required prior to dosing.

Subjects will complete their second baseline assessments for Patient Reported Outcomes (interference scale of short form BPI, SF-MPQ-2, NPSI, BDI-II). In PK subjects, a pre-dose NPRS will be completed and a pre-dose blood sample taken for PK analysis.

Subjects (except PK subjects) will take their allocated IMP and remain in the clinic for up to one hour to check for any adverse events.

PK subjects will take their allocated IMP and remain in the clinic for at least 6 hours. At scheduled times over this period, blood samples will be taken for PK analyses and NPRS assessments will be undertaken.

All subjects will leave the unit with sufficient IMP for the second treatment period.

On Day 63 (Visit 6), subjects will take their morning IMP dose and return to the clinic. Weight, vital signs, a targeted physical examination, concomitant medications and adverse events will be recorded. Subject compliance with medication and diary entries will be checked. Subjects will be reminded to continue their medication and to record daily entries into their diary.

On the morning of Day 77 (Visit 7, Last Day of Second Treatment Period), subjects will not take their morning dose of IMP. They will make their morning diary entry and return to the clinic. At the clinic, weight, ECG, vital signs, a targeted physical examination, concomitant medications and adverse events will be recorded. Blood and urine samples will be taken for safety analysis. Subjects will complete assessments for Patient Reported Outcomes (interference scale of the short form BPI, SF-MPQ-2, NPSI, BDI-II, PGIC). In PK subjects, a pre-dose NPRS will be completed and a pre-dose blood sample will be taken for PK analysis.

Subjects (except PK and QST subjects) will then take their morning dose of IMP and leave the clinic. PK subjects will take their morning dose of IMP and stay for at least 6 hours. At scheduled times over this period, blood samples will be taken for PK analyses and NPRS will also be monitored. QST subjects will take their morning dose of IMP and will have QST [redacted] assessed two hours after this dose.

All subjects will take their second Day 77 IMP dose in the evening. They will be asked to discontinue their IMP after taking the Day 77 evening dose.

End of Study (Day 91)

At the end of study visit, weight, vital signs, a targeted physical examination, concomitant medications and adverse events will be recorded. Blood and urine samples will be taken for safety analysis.

Early withdrawal

Subjects who withdraw early will be asked to attend an end of study visit. This visit should be scheduled approximately two weeks after the last dose was taken.

Statistical Analysis

With a total sample size of 44 evaluable subjects there is 90% power to demonstrate a statistically significant difference in the mean change from baseline NPRS for the active treatment compared with placebo of at least 1 unit. This assumes that the standard deviation of the change from baseline NPRS is 2, the correlation between active and placebo responses within a subject is 0.5 and there is a 2-sided test at the 5% level of significance. Assuming a 20% dropout rate, it is aimed to enrol at least 55 subjects to obtain 44 evaluable subjects.

The number of subjects within each treatment group is also sufficient to show a statistically significant change from baseline of 2 or more points on the NPRS.

The primary efficacy endpoint is the change from baseline mean NPRS score to the end of treatment mean NPRS score after LAT8881, compared with the change from baseline after placebo treatment. This will be analysed in the per protocol (PP) population, which will be defined in a statistical analysis plan (SAP) before database lock. The PP will be based on the duration of IMP treatment and protocol deviations.

Mixed effects regression models will be used to compare the absolute and percentage changes from baseline to the end of each treatment for the mean NPRS scores. The models will have fixed effects for period and treatment. Baseline mean pain score within each period by treatment combination will be included as a covariate. A random effect for subject will be included to capture the repeated measures nature of the design.

The models for the primary endpoint will be expanded to compare the absolute and percentage changes from baseline for the mean NPRS scores after 1, 2 and 3 weeks of dosing with IMP in each treatment period. The model will also include a fixed effect for week (1, 2, 3 and 4), the interaction between treatment and week to assess whether the change from baseline for each treatment is different.

Daily NPRS scores for all enrolled subjects will be listed. Mean and standard deviation of scores during the baseline period and weeks 1, 2, 3 and 4, and the absolute and percentage change from baseline in each period, will be listed and summarised for LAT8881 and placebo treatments overall and within treatment sequence for all randomised subjects and for the PP population. The maximum change in mean NPRS from baseline, determined for each subject after LAT8881and placebo, will be listed and summarised. In PK subjects, NPRS scores at specified times up to 6 hours on Days 1, 28, 50 and 77 will be listed and summarised. Change from pre-dose values will also be listed and summarised. Changes over time will be analysed using the same modelling approach as for the primary endpoint.

The proportion of subjects achieving at least 30% and 50% reduction in pain after four weeks treatment, as assessed by the mean NPRS score, will be summarised with the 95% confidence interval for the percentage reduction, estimated by Clopper Pearson Exact methodology. A mixed effects logistic regression model, including the same fixed and random effect terms as for the primary endpoint, will be used to assess the odds of achieving a reduction in pain after four weeks treatment with LAT8881 compared to placebo.

Baseline and end of treatment values for the BPI interference scale, SF-MPQ-2, NPSI and BDI-II will be listed for LAT8881 and placebo. Values at each timepoint and the change from baseline will be summarised. Similarly, baseline and end of treatment values for QST parameters [redacted] will be listed for LAT8881 and placebo, and values at each timepoint and change from baseline will be summarised. Differences between the LAT8881 and placebo treatments in the change from baseline reported outcomes will be analysed using the same model as for the primary endpoint.

PGIC will be tabulated at the end of each treatment period and summarised.

Paracetamol (rescue medication) use at baseline and weekly over the treatment period will be listed for each subject. The average weekly and cumulative dose of rescue paracetamol medication in each treatment period will be summarised by visit and treatment

All randomised subjects who receive at least one dose of IMP and have at least one post dose safety assessment will be included in the safety analysis. Adverse events will be listed individually and will be summarised by body system and preferred term. Summaries will include the number and percentage of subjects with any adverse event, with serious adverse events, adverse events leading to premature discontinuation of IMP, adverse events by intensity and adverse events by relationship to IMP. Safety laboratory data will be summarised by visit and treatment, subjects with clinically significant abnormal results will be listed.

Plasma drug concentrations and any derived pharmacokinetic parameters will be listed and summarised descriptively for all subjects who received at least one dose of IMP, had at least one post-dose sample collection for PK analysis and who did not have any clinically significant events or protocol deviations that may have compromised the integrity of the PK results.

Anticipated Study Duration: Recruitment approximately 9 months, study duration approximately 13 months

Subject Duration:	Maximum participation duration is 17 weeks: screening and first baseline (up to 4 weeks), first treatment (4 weeks), washout (2 weeks) second baseline (1 week), second treatment (4 weeks), follow up (2 weeks).

2. Study schedule of assessments and procedures

2.1 Screening, First Baseline Period, First Treatment Period and Washout

	Screening Stage 1	Screening Stage 2 (First Baseline)	First Treatment Period			Washout
Visit No	**1**		**2**	**3**	**4**	
Study Day	**-28 to -8**	**-7 to -1**	**1**	**14 ± 1**	**28 ± 1**	**29 (+/-1) to 42 (+/-1)**
Written informed consent	X					
Eligibility assessment	X					
Pain diary training	X					
Confirmation of eligibility			X			
Enrolment			X			
Randomisation			X			
Medical history, demographics	X					
Height,[1] weight	X		X	X	X	
PD-Q	X		X			
12 lead ECG	X		X[2]		X[2]	
Vital signs	X		X[3]	X	X	
Physical examination[4]	X		X[5]	X[5]	X[5]	
Concomitant medications	X		X	X	X	
Clinical laboratory safety testing[6]	X		X[2,7]		X[2]	
Pregnancy test[8]	X[9]		X[10]			
QST sensory phenotype assessment[11]			X[12]		X	
IMP administration			X[13]	X	X[13]	
Adverse event assessment	X[14]	X[14]	X	X	X	
Blood sampling for PK analysis[15]			X[16]		X[16]	
Daily NPRS ratings[17]		X	X[18]	X	X[18]	X
Short form BPI assessment			X		X	
Short form McGill questionnaire 2			X		X	
Neuropathic Pain Symptom Inventory			X		X	
Beck Depression Index-II			X		X	
PGIC					X	

1 Height measured only at screening
2 Pre-dose
3 Pre-dose and 0.5 hours post-dose
4 Includes assessment of area of pain
5 Targeted physical examination
6 Haematology, clinical chemistry, urinalysis
7 Results of clinical laboratory tests not required prior to dosing
8 Females of child bearing potential only
9 Blood pregnancy test
10 Urine pregnancy test
11 QST subjects only
12 QST to be assessed pre-dose, within 7 days of the first dose
13 Supervised administration
14 SAEs only (UK subjects only)
15 PK subjects only
16 Pre-dose and up to 6 hours post-dose
17 Each evening, throughout baseline, treatment and washout periods
18 Additional ratings pre-dose and up to 6 hours post-dose in PK subjects

2.2 Second Baseline Period, Second Treatment Period and Follow Up

	Second Baseline Period	Second Treatment Period			End of Study
Visit No		**5**	**6**	**7**	**8**
Study Day	**43 to 49**	**50 ± 1**	**63 ± 1**	**77 ± 1**	**91 ± 2**
Weight		X	X	X	X
12 lead ECG		X[19]		X[19]	
Vital signs		X[20]	X	X	X
Physical examination[21]		X[22]	X[22]	X[22]	X[22]
Concomitant medications		X	X	X	X
Clinical laboratory safety testing[23]		X[19,24]		X[19]	X
QST sensory phenotype assessment[25]		X[26]		X	
IMP administration		X[27]	X	X[27]	
Adverse event assessment		X	X	X	X
Blood sampling for PK analysis[28]		X[29]		X[29]	
Daily NPRS ratings[30]	X	X[31]	X	X[31]	
Short form BPI assessment		X		X	
Short form McGill questionnaire 2		X		X	
Neuropathic Pain Symptom Inventory		X		X	
Beck Depression Index-II		X		X	
PGIC				X	

19 Pre-dose
20 Pre-dose and 0.5 hours post-dose
21 Includes assessment of area of pain
22 Targeted physical examination
23 Haematology, clinical chemistry, urinalysis
24 Results of clinical laboratory tests not required prior to dosing
25 QST subjects only
26 QST to be assessed pre-dose, within 7 days of the first dose of this treatment period
27 Supervised administration
28 PK subjects only
29 Pre-dose and up to 6 hours post-dose
30 Each evening throughout baseline and treatment periods
31 Additional ratings pre-dose and up to 6 hours post-dose in PK subjects

3. Introduction and background information

3.1 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 preclinical and clinical safety record. This is the first clinical study to investigate this compound in neuropathic pain.

3.2 LAT8881

LAT8881 is a 16 amino acid peptide fragment based on human-growth hormone (hGH). [redacted]

LAT8881 was initially developed for the treatment of obesity (known during these studies as AOD9604). Six clinical trials involving 936 subjects were completed, with over 700 subjects treated with oral LAT8881 (Section 3.2.2). There were no significant safety issues but the most recent efficacy study (METAOD006) did not meet the primary endpoint and development was discontinued for this indication in 2007.

3.2.1 Nonclinical studies

3.2.1.1 Preclinical pain studies

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[redacted]

[redacted]

[redacted]

[redacted]

3.2.1.2 Nonclinical safety studies

Studies in rats and monkeys at doses up to 10 mg/kg LAT8881 intravenously for up to periods of 28 days had no clinically significant toxic effect in either species. Fourteen-day treatment with oral doses of LAT8881 up to 100 mg/kg/day was well tolerated in both rats and monkeys and without any overt systemic toxicity.

Chronic toxicity testing was conducted in both rodent and non-rodent species. Doses of 0 (control), 0.5, 20 and 100 mg/kg/day LAT8881 (0, 3.5, 140, 700 mg/m^2/day) were administered orally to rats once per day for six months (26 weeks). There were no unscheduled deaths and no treatment-related clinical signs. No marked effects on body weight were observed and there were no treatment-related effects on food consumption, food conversion efficiency ratios, ophthalmic examination, organ weights, macropathology, histopathology or clinical laboratory parameters. There was no effect of LAT8881 on bone densitometry.

LAT8881 0.5, 10 and 50 mg/kg/day (6, 120 and 600 mg/m^2/day) or vehicle control was administered to cynomolgus monkeys once per day for nine months. In this study there were no unscheduled deaths and no clinical signs attributable to treatment with LAT8881. There were no treatment-related changes in body weight, ophthalmology, haematology, biochemistry, urinalysis, organ weights, necropsy or histology. There was no effect of LAT8881 on bone densitometry.

No antibodies to LAT8881 were detected in the serum of rats and monkeys at the end of the toxicological studies, indicating that LAT8881 was not neutralised by an antibody reaction, and thus LAT8881 is considered unlikely to be immunogenic.

Extensive genotoxicity testing has been conducted. It is considered unlikely that LAT8881 is a potential genotoxic hazard to humans.

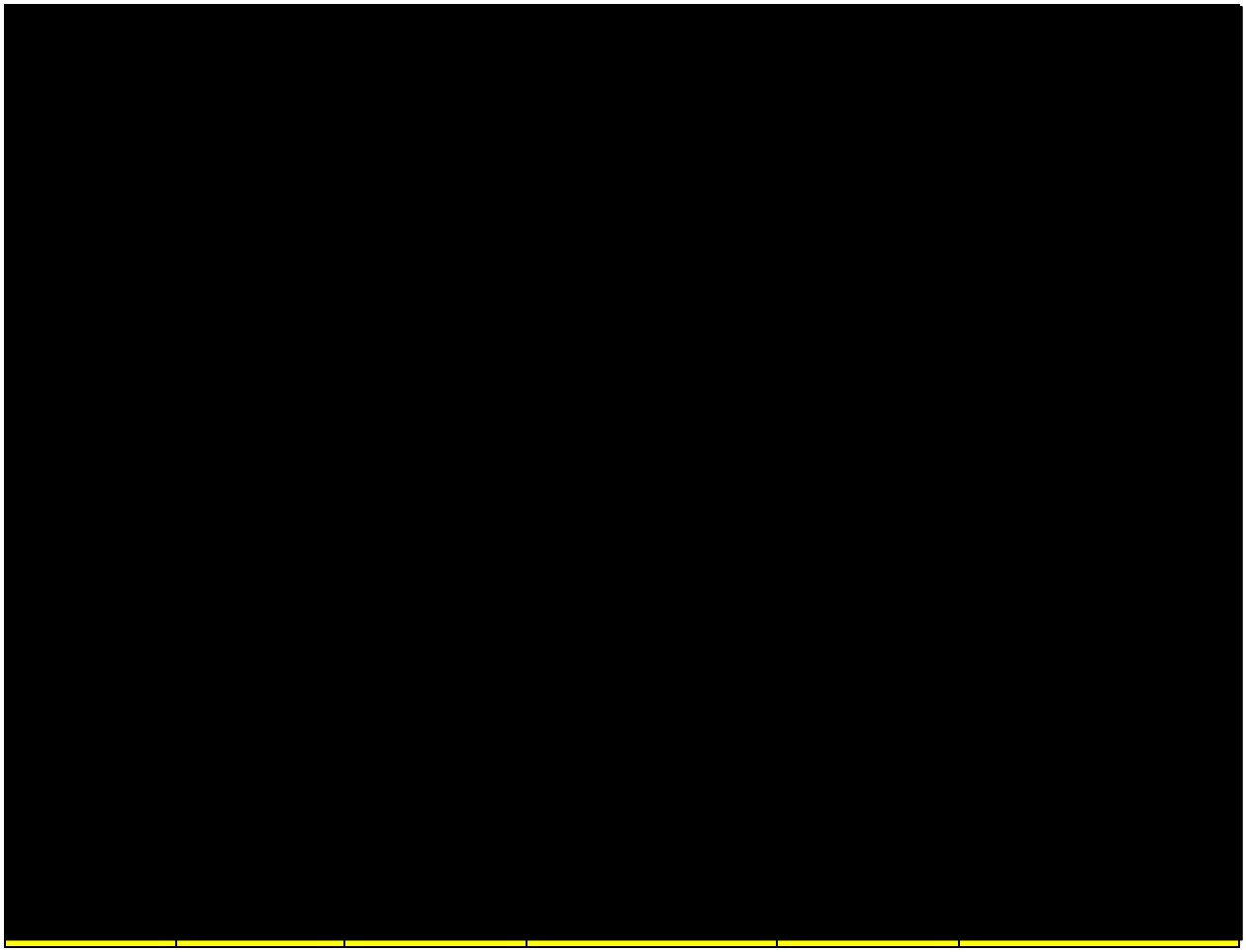
Reproductive studies have been undertaken in rats and rabbits at doses up to 50 mg/kg/day (rabbit) and 100 mg/kg/day (rat). The rabbit studies found no evidence of an effect on foetal development when administered from Days 6-18 of gestation. The rat studies involved dosing from 2 weeks pre-mating (males and females) up to Day 6 of lactation (females) or 2 weeks after pup delivery (males). No effect on reproduction was observed in these studies.

More detailed results from the preclinical studies with LAT8881 are provided in the Investigator's Brochure.

3.2.2 Clinical studies

Six clinical studies with LAT8881 have been completed, with over 700 subjects treated with LAT8881 ([redacted]). These studies were designed to investigate the safety and tolerability of LAT8881 and subsequently its efficacy in the treatment of obesity (METAOD005, METAOD006).

[redacted]



In all studies it was noted that the study drug was well tolerated. The only dose-related adverse event (AE) trend was an increased incidence of gastrointestinal effects and general body symptoms of abdominal pain and headache in Study METAOD004 at 54 mg. This trend was not observed in subsequent studies.

More detailed results from these clinical studies with LAT8881 are available in the Investigator's Brochure.

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4. Study objectives

4.1 Primary objective

- To evaluate the efficacy of oral LAT8881 in NP compared with placebo, when assessed by change in mean pain intensity scores from baseline to the end of four weeks treatment, based on an 11 point numeric pain rating scale (NPRS)

4.2 Secondary objectives

- To investigate the effect of oral LAT8881 in NP compared with placebo at different timepoints (up to 6 hours) following a single dose and after 4 weeks treatment, as measured by the NPRS (PK subjects only)
- To investigate the effect of oral LAT8881 on mean pain scores in NP compared with placebo after 1, 2 and 3 weeks of dosing, as measured by the NPRS
- To determine the proportion of responders to oral LAT8881 in NP compared with placebo
- To investigate the maximum effect of oral LAT8881 in NP compared with placebo, as determined by the maximum change from mean NPRS baseline after 1, 2, 3 or 4 weeks treatment
- To evaluate the effect of oral LAT8881, compared with placebo, on functioning in subjects with NP when measured by the 7-item short form Brief Pain Inventory (BPI) Interference Scale
- To evaluate the effect of oral LAT8881, compared with placebo, on pain symptoms in subjects with NP when measured by the short-form McGill Pain Questionnaire 2 (SF-MPQ-2)
- To evaluate the effect of oral LAT8881, compared with placebo, on symptoms in subjects with NP, when measured by the Neuropathic Pain Symptom Inventory (NPSI)
- To evaluate the effect of oral LAT8881, compared with placebo, on emotional functioning when measured by the Beck Depression Inventory-II (BDI-II)
- To evaluate the effect of oral LAT8881, compared with placebo, on overall health and quality of life in subjects with NP, when measured by the Patient Global Impression of Change (PGIC) scale
- To determine the change from baseline in rescue medication use during oral LAT8881 administration, compared with placebo
- To evaluate the safety and tolerability of oral LAT8881 in NP after a single dose and after four weeks treatment
- To investigate the pharmacokinetics of twice daily oral LAT8881 in 15 subjects with NP after a single dose and after 4 weeks treatment with oral LAT8881

4.3 Exploratory objectives

- To investigate the relationship between baseline subject characteristics, such as clinical diagnosis (PHN or DPN) [redacted], and the change in NPRS after oral LAT8881 treatment, compared with placebo
- To investigate the change from baseline on specified QST parameters [redacted] after four weeks treatment with oral LAT8881, compared with placebo
- To investigate the relationship between plasma LAT8881 concentrations and the change in mean pain score in subjects with NP
- To investigate the impact of variability in NPRS scores during the first baseline period on the difference between baseline and 4 week NPRS scores after LAT8881 or placebo

5. Study design

5.1 Overall study design

This is a randomised, placebo-controlled, double-blind, crossover, multi-site, Phase IIa study to investigate the efficacy and safety of oral LAT8881 in neuropathic pain. The overall study design is shown in Figure 4. Details of the procedures during each phase are described in Section 8.

The pharmacokinetics (PK) of LAT8881 will be investigated on Days 1, 28, 50 and 77 in 15 subjects (PK subjects) at Australian sites. Quantitative sensory testing (QST) will be performed in up to 20 subjects (QST subjects) before the first dose on Days 1 and 50 and after the morning dose on Days 28 and 77. PK subjects will not participate in QST measurements and QST subjects will not participate in PK analyses.

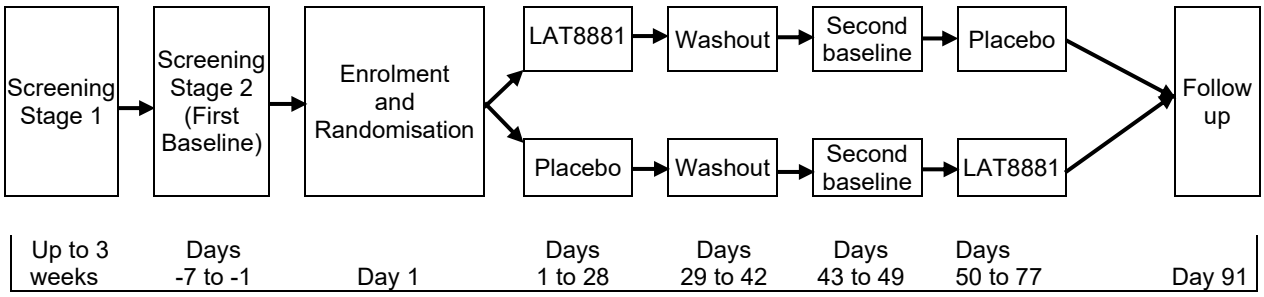

Figure 4: Overall study design for LAT-NP-001

Potential subjects will be required to provide written informed consent prior to any study-specific screening procedures being performed. Screening assessments will be performed from Day -28 to Day -1. Subjects deemed likely to be eligible for the trial will be given access to a diary during Screening Stage 1 and training on how to complete it from Days -7 to -1 inclusive (Screening Stage 2, first baseline period). These diary results will be reviewed on Day 1 to confirm that the subject is eligible for the study.

On Day 1, after the first baseline period, eligible subjects will be enrolled and randomised to LAT8881 or placebo. They will receive the investigational medicinal product (IMP) twice daily for four weeks (Days 1 to 28). On the morning of Day 28 they will return to the clinic for their end of first treatment visit and will take an IMP capsule in the morning during their clinic visit. They will take their final IMP dose for this treatment period in the evening.

The first treatment period will be followed by a washout period of two weeks (Days 29 to 42 inclusive) and then a second baseline period of one week (Days 43 to 49 inclusive). Over these days (i.e. Days 29-49 inclusive) subjects will not take any IMP.

On Day 50, subjects will return to the clinic and cross over to receive the second treatment (either LAT8881 or placebo, whichever treatment was not received in the first treatment period) twice daily for four weeks (Days 50 to 77). On the morning of Day 77, they will return to the clinic for their end of second treatment visit and will take an IMP capsule in the morning during their clinic visit. They will take their final IMP dose for this treatment period in the evening.

Subjects will return to the clinic on Day 91, two weeks after their last treatment visit, for an end of study visit.

5.2 Justification of study design

This is the first study with LAT8881 in subjects with neuropathic pain. As such, it has been designed to evaluate, in a well-defined patient group, the concept that LAT8881 is safe and effective in this indication. Subsequent studies will evaluate other development issues, such as the optimal dosing strategy, and the

applicability of these results to related pain conditions.

Subjects enrolled into this study have been diagnosed with PHN or DPN, both conditions being well accepted examples of neuropathic pain. Because the pain is chronic, without a period effect, and treatment is symptomatic rather than curative, a crossover study is considered appropriate. Indeed, studies with other agents have successfully demonstrated analgesic effects in PHN and DPN with a crossover study design.[7]

A major advantage of a crossover design is the smaller number of subjects required to demonstrate efficacy, compared with a parallel design. In this study, 44 evaluable subjects are required to show the same statistical outcomes, compared with over 100 subjects had a parallel group design been utilised. The main disadvantage is the longer duration of the study for each subject and a higher risk of dropouts. It is anticipated that approximately 20% of subjects will not complete the study, based on analysis of Phase III studies with duloxetine, pregabalin and gabapentin in DPN and PHN[8] and taking into account the good tolerability of LAT8881 in previous clinical studies. In an attempt to minimise dropouts in this study, subjects are allowed to continue on their current stable medications and will have access to rescue paracetamol. Should these measures not be adequate and the dropout rate is higher than anticipated, enrolment will continue until the required number of completing subjects is reached.

A four week treatment period is considered to be an appropriate balance between reducing the potential for dropouts and ensuring that there is adequate time to observe a treatment effect. This duration has been accepted as usually suitable for proof of concept studies in chronic pain conditions.[7] The washout period of two weeks was based on preclinical pharmacodynamic data, as the pharmacokinetics of LAT8881 does not show a temporal association with its effect in pain models.

The power of the study was set at 90% to lessen the potential for a false negative outcome. To obtain this statistical power with a pragmatic sample size, the study was designed with two arms only (LAT8881 60 mg/day or placebo). Standard randomisation and double-blinding procedures are applied to ensure the validity of the study.

[redacted]

The efficacy outcome measures in this trial are based on those recommended by international consensus[16] and are described in Section 10.5.

5.3 Justification of dose

The dose of 60 mg/day is based on both preclinical efficacy studies and clinical data from previous studies with LAT8881. [redacted]

Subsequent studies will investigate a dose response to LAT8881 in patients with neuropathic pain at doses below 60 mg/day to determine a minimum effective and optimal therapeutic dose.

5.4 Number of planned subjects

It is planned to have 44 subjects complete the study. Assuming a 20% dropout, 55 subjects will be recruited. If the dropout rate is higher than 20%, additional subjects (up to 60 in total) may be recruited at the sponsor's discretion to ensure 44 subjects complete the study.

5.5 Duration of study

The duration of recruitment for this study is anticipated to be approximately 9 months. The duration of the

study will be approximately 13 months.

5.6 Duration of subject participation

Maximum participation duration is 17 weeks: screening and first baseline (up to 4 weeks), first treatment (4 weeks), washout (2 weeks) second baseline (1 week), second treatment (4 weeks), follow up (2 weeks).

5.7 Withdrawal of subjects from study

Subjects can terminate their participation in the study at any time, without giving a reason and without prejudice to further treatment. Subjects may also be withdrawn at any time at the discretion of the investigator(s) or sponsor for safety, behavioral or administrative reasons.

Subjects who discontinue from the study should always be asked about the reason(s) for their discontinuation and about the presence of any Adverse Events. The reason(s) for withdrawal will be documented in the case report form (CRF).

Possible reasons for discontinuation of a subject may include:

- Withdrawal of consent by the subject
- Serious or significant AE or laboratory abnormality
- Non-compliance with the protocol
- The need to take medication which may interfere with study measurements or is contraindicated
- New inter-current diseases, which may affect the safety of the IMP
- Subject is lost to follow-up
- Withdrawal for other reasons
- Lateral terminating the study for administrative, financial, or other reasons

Subjects withdrawing from the study will be requested to attend an End of Study Visit. If the subject withdraws during the treatment period, the subject should attend the End of Study visit within 14 days of the last dose of LAT8881 where possible.

Any new AEs occurring during that period must also be reported in the CRF and must be followed up until resolved, unless, in the investigator's opinion, the condition is unlikely to resolve. This visit is primarily for the purposes of monitoring subject safety.

Any AEs that are continuing at the time of withdrawal from the study, should, wherever possible, be followed to resolution or stabilisation, whichever is earlier.

Reasonable efforts will be made to contact subjects who are lost to follow-up. These must be documented in the subject's source documents.

5.8 Replacement of subjects

Subjects who withdraw after randomisation will not be replaced.

6. Study population

6.1 Inclusion criteria

Subjects must meet the following criteria to be entered into the study:

1. Clinical diagnosis of post herpetic neuralgia, with pain persisting for at least 3 months after the onset of herpes zoster rash

OR

2. Clinical diagnosis of distal painful polyneuropathy due to Type I or Type II diabetes mellitus with:
    a) symmetrical, bilateral pain in the lower extremities for at least 3 months and
    b) diabetes under control for at least 3 months prior to randomisation, as indicated by a glycated haemoglobin level (HbA1c) of ≤ 11% (97 mmol/mol) and on a stable dose of insulin or oral diabetic medication for 3 months prior to screening, and
    c) no change in diabetic medication planned for the duration of the study
3. Positive sensory symptoms (mechanical or thermal) associated with neuropathic pain, confirmed by:
    a) painDETECT Questionnaire (PD-Q) and
    b) Clinical assessment, showing signs of neuropathic pain in either a dermatomal (PHN) or distal symmetrical distribution (DPN)
4. Aged 18 to 75 years
5. Subjects must be sufficiently competent in English to understand the purposes and risks of the study and able to give voluntary written informed consent to participate in the study
6. Willing and able to comply with all study procedures
7. Completion of at least five NPRS scores during the week preceding randomisation
8. An average daily pain score on the NPRS of at least 4 and no more than 8 in the last five diary entries before randomisation
9. No more than one score on the NPRS of 9 or more, and no more than one score of 2 or less, in the last five diary entries before randomisation
10. Females of child bearing potential must have a negative pregnancy test at Visit 1 (Screening) and at Visit 2 (Day 1) prior to administration of IMP
11. Female subjects must be:
    a) of non child-bearing potential [surgically sterilised or post–menopausal (12 months with no menses without alternative medical cause)] OR
    b) not pregnant, breast feeding or planning to become pregnant AND willing to comply with the medically acceptable contraceptive requirements of the study from Screening to at least 28 days after the last IMP administration

6.2 Exclusion criteria

Subjects who meet any of the following criteria will be excluded from the study:

1. Presence of moderate to severe pain from other causes that may confound assessment or self-evaluation of NP
2. Subjects with both DPN and PHN
3. Skin conditions in the affected area that could alter sensation or assessments

4. History of or current clinically significant gastrointestinal, hepatic, renal, cardiovascular, respiratory, endocrine, oncological, immunological, neurological, ophthalmological, haematological or psychiatric disorder or any other condition, which in the opinion of the investigator or sponsor would jeopardise the safety of the subject or the validity of the study results
5. Medical history of, or currently active, human immunodeficiency virus, hepatitis B or hepatitis C virus
6. Clinically significant abnormal 12-lead ECG
7. Immunocompromised state, or conditions known to be associated with an immunocompromised state
8. Clinically significant or unstable medical or psychological condition that would compromise participation in the study
9. Recent history of malignancy within 5 years preceding screening (except resected cervical or skin cancer [except melanoma]). Subjects who have had no evidence of disease in the last 5 years are eligible
10. Active herpes zoster infection on screening
11. Current alcohol abuse, illicit or illegal drug use
12. Use of prohibited medication (see study medications)
13. Previous treatment with LAT8881 (formerly identified as AOD9604) within the last 5 years
14. Participation in an investigational trial within 60 days or 5 half-lives (whichever is longer) prior to screening
15. History of significant hypersensitivity to LAT8881 or drugs of a similar pharmacological class (e.g. somatropin)
16. Surgical or medical conditions which could significantly alter drug absorption, distribution, metabolism or excretion
17. An employee of the sponsor or research site personnel directly affiliated with this study, whether biological or legally adopted, or their immediate family members, defined as a spouse, parent, sibling, or child
18. Previous neurolytic or neurosurgical therapy for PHN or DPN
19. PK subjects:
    a. Blood or plasma donation of more than 500 mL during the 3 months prior to randomisation
    b) History of fainting during phlebotomy

6.3 Contraception requirements

Subjects must be willing to comply with the contraceptive requirements of the study.

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 28 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.

6.4 Dietary, lifestyle and other restrictions

Subjects should refrain from use of alcohol within 8 hours prior to all visits and during visits.

Regular smokers who are unable to refrain from smoking cigarettes or tobacco during study visits will be excluded from the study. Replacement nicotine is permitted.

7. Study Treatments

7.1 Description

The IMP is supplied as opaque, size 0 capsules, in a high-density polyethylene bottle containing 60 capsules. One bottle will contain sufficient capsules for one treatment period.

7.2 Formulation

7.2.1 LAT8881 capsules

Each capsule contains 30 mg LAT8881 plus [redacted] as excipients.

7.2.2 Placebo capsules

Placebo capsules contain the excipients [redacted] only (without LAT8881).

7.3 Manufacturer

LAT8881 is is manufactured by [redacted] in accordance with current Good Manufacturing Practice (cGMP).

The active and placebo blends for encapsulation will be formulated and the capsules will be filled by [redacted] under cGMP conditions.

[redacted] will be responsible for quality control and stability testing.

7.4 Storage

At the study site, the IMP must be stored refrigerated (2-8^{0}C) in a secure area, with access limited to authorised personnel.

Subjects will also be asked to store their treatment at home under refrigeration.

7.5 Packaging and labelling

IMP capsules will be packaged in bottles by [redacted]. Each bottle will contain 60 IMP capsules (60 capsules of formulated LAT8881 or 60 placebo capsules). The two bottles for treatment of each subject (active/placebo) will be packaged together in a clear plastic bag, according to the randomisation schedule prepared by the unblinded study statistician. Each bottle will appear identical to the other bottle in the bag, except for the treatment period number (1/2 or 2/2) on the label.

Bottles containing the IMP capsules and the bag in which they are packed will be labelled according to Annex 13 of the PIC/S Guide to Good Manufacturing Practice.[11]

Each bottle will have both a permanently attached label and a tear-off drug accountability label. The tear-off accountability label must be removed and attached to the Drug Accountability log when the product is dispensed. On dispensing, a dispensing label will be attached permanently to the bottle.

Details of labelling and dispensing will be provided in the Study Procedures Manual.

7.6 Randomisation and blinding

A computer-generated randomisation schedule and treatment allocation will be prepared by an unblinded statistician prior to the start of the study.

The treatment sequence each subject will receive will not be disclosed to the investigator, study site personnel, subjects, or sponsor personnel. The randomisation codes will be available to the Investigator if required for emergency unblinding purposes (see Section 7.13).

7.7 Dispensing of investigational product

The investigator is responsible for ensuring that IMP is dispensed in accordance with the protocol and only to subjects enrolled in the study.

On the morning of Day 1, after receipt of a prescription/authorisation from the investigator (or delegate), the study nurse (or Investigator) will obtain the allocated treatment. The subject's study number, initials, date and treatment number will be recorded in the Drug Accountability Log. The log will be countersigned by the investigator and must be available for inspection at any time.

7.8 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 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.

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

7.9 Accountability of study supplies

All supplies of IMP are provided for use only in this clinical study and must not be used for any other purpose.

The investigator or designee is responsible for accountability of IMP, reconciliation and record maintenance. The investigator or designated site staff must maintain accountability records throughout the course of the study including records of the amount of IMP dispensed, the identification of the subject to whom the IMP was dispensed, the date and the amount dispensed.

Subjects must bring their medication bottles with them to clinic visits during the treatment periods and the number of remaining capsules will be entered onto the CRF. The product, including used bottles and records, must be available for inspection by a study monitor during the study.

Following completion of the study, remaining unused supplies will be returned to Lateral or destroyed as directed by the sponsor.

7.10 Doses and treatment regimens

Subjects will be instructed to take one capsule with water at approximately 12 hour intervals (morning and evening) at least 30 minutes before food. Once the dosing times are established, the subject should attempt to take the capsule at the same times throughout the treatment periods. If more than 16 hours has elapsed since the last dose, the dose should be missed and the next dose taken at the regular scheduled time.

Subjects will be instructed to return to the clinic on Days 28 and 77 without taking their morning dose.

7.11 Dose reduction/dose adjustments

No within-subject dose reductions or adjustments are permitted. If a subject experiences an adverse event requiring (in the investigator's opinion) temporary or permanent suspension of the IMP, the subject should be withdrawn from the study (refer to Section 5.7). The maximum allowed temporary suspension of IMP before withdrawal is 3 doses in the last 10 days or 8 doses in the 28 day treatment period.

7.12 Treatment compliance

Subjects will be asked to return their IMP bottles for a capsule count at each treatment visit.

Study drug accountability forms will be kept by pharmacy during the study and will be reviewed by the study monitor. Treatment compliance will be recorded in the subject's source documents and the CRF.

7.13 Unblinding

7.13.1 Medical Emergency

In a medical emergency, when management of a subject's condition requires knowledge of the study drug, the code may be broken by the investigator to determine the treatment allocation of the subject. Details will be provided in the Study Manual.

Such emergencies and code break should be notified to the study Medical Monitor and/or sponsor as soon as possible. The date, reason for and name of the individual breaking the code will be documented along with a list of unblinded persons.

7.13.2 End of study

The randomisation schedule, allowing identification of the treatment sequence received by each subject, will be disclosed after approval and locking of the database.

7.14 Concomitant medications

7.14.1 Permitted medications

The following medications are permitted:

- Subjects may take their usual oral medications for PHN or DPN, providing the dose has been stable for at least 30 days before randomisation and is maintained for the duration of the study until the end of study visit
- Diabetics must be on stable diabetic medication for at least 3 months before randomisation, and the medication must be maintained at the same dose until the end of study visit
- Subjects may also take the following medications, provided the regimen is stable for 30 days before randomisation and remains steady from randomisation to the end of study visit
    - benzodiazepine
    - anxiolytic, such as buspirone
    - serotonin and noradrenaline (norepinephrine) reuptake inhibitor
    - oral aspirin (≤ 150 mg/day)
    - tricyclic antidepressant
- In addition, up to 4 g per day of paracetamol (rescue medication) may be taken except within 4 hours of the first and last clinic visit in each treatment period

7.14.2 Prohibited medications

The following medications are prohibited.

- Patch containing 8% capsaicin (Qutenza), if applied within the last six months before randomisation
- Current or recent (within 7 days of randomisation) use of any other topically applied pain medication
- Cryotherapy, intrathecal/epidural opioids, systemic corticosteroids or botulinum toxin if administered in the last 6 months. Topical or inhaled corticosteroids are permitted. A short course

(<7days) of oral prednisolone or equivalent for other conditions, up to 4 weeks preceding Day 1, is allowed

- Steroid or local anaesthetic nerve blocks within the last 12 months

Subjects who change concomitant medication during the study period should notify the investigator promptly and details of the medications used should be documented in the source documents and CRF. Concomitant medications will be recorded by their trade and/or generic name.

8. Study procedures

The Schedule of Assessments for the study are provided in Section 2.

8.1 Subject informed consent

Following identification of potential subjects, staff in the clinic will contact the subject, explain the nature of the study and confirm potential interest and eligibility. The Participant (Subject) Information Sheet (PIS) and Consent Forms (ICFs) may be provided. The subject will then be invited to attend the clinic for further information, signing of the ICF and conduct of screening procedures.

The investigator must provide adequate information regarding the study, including its purpose, possible risks and potential benefits. Subjects must also be advised that they are free to discontinue from the study at any time. Subjects must be given time to review the study information and ask any questions.

Written informed consent must be provided by the subject before any tests or investigations outlined in the study protocol are carried out.

The ICF must be personally signed and dated by both the investigator and the subject. The investigator must store the original, signed ICF with the subject's medical notes/source documents. A copy of the signed and dated ICF will be given to the subject.

Screening procedures may commence immediately following signing of the ICF.

8.2 Screening visit (Day -28 to Day -1), Visit 1

After written informed consent has been obtained, a unique Screening Number (Subject ID) will be assigned and screening assessments may commence. Screening assessments may be performed on different days if required.

Screening assessments will be conducted in two stages: Stage 1 (initial screening) and Stage 2 (first baseline period).

8.2.1 Screening Stage 1 (initial screening)

During Stage 1 of the screening period (Days -28 to Day -8), subjects will undergo the following screening assessments:

- Medical history
- Demographics
- Height, weight and BMI
- PD-Q assessment
- 12-lead ECG
- Vital signs
- Physical examination, including clinical assessment of pain
- Concomitant medications
- Blood sample for routine haematology and clinical chemistry screening and, in female subjects of child-bearing potential, to test for pregnancy
- Urine sample for urinalysis

Subjects deemed likely to be eligible for the trial after initial screening will be given access to a diary and training on how to record daily pain assessments each evening. They will be instructed to complete the diary from Days -7 to -1 inclusive and to return on Day 1, for confirmation of study eligibility. They will also be reminded not to take paracetamol within 4 hours of the next clinic visit.

Up to 20 subjects deemed likely to be eligible for inclusion in the study after initial screening will also have a QST scheduled within seven days of the first dose.

8.2.2 Screening Stage 2 (first baseline)

Subjects deemed likely to be eligible for the trial will record their pain assessments each evening in their diary.

8.3 First treatment period (Days 1 to 28), Visits 2 to 4

8.3.1 Day 1, Visit 2

Subjects will return to the unit on Day 1 (Visit 2) with their diary completed from Days -7 to -1 inclusive.

The following assessments will be undertaken on Day 1:

- Review of the subject's pain diary
- Weight
- PD-Q
- ECG
- Vital signs
- Targeted physical examination, including assessment of painful regions
- Concomitant medications
- Blood sample for routine haematology and clinical chemistry assessments
- Urine sample for urinalysis (dipstick) and, in female subjects of child-bearing potential, a urine sample for pregnancy testing

Results from safety monitoring tests are not required prior to dosing. Eligible subjects will be enrolled, assigned a unique Randomisation Number and randomised to LAT8881 or placebo.

Subjects will complete baseline assessments for Patient Reported Outcomes:

- Interference scale of the short form BPI
- SF-MPQ-2
- NPSI
- BDI-II

In PK subjects, a pre-dose NPRS will be completed (maximum one hour before dosing) and a pre-dose blood sample taken for PK analysis. QST subjects will have a pre-dose QST assessment, if not completed within the previous 7 days.

Subjects (except for PK subjects) will take their first dose of IMP and remain in the clinic for up to one hour to check for any adverse events. Vital signs will be measured 30 (+/-10) minutes after IMP dosing.

PK subjects will take their first dose of IMP and remain in the clinic for at least 6 hours. At scheduled times (2, 5, 15, 30, 60 minutes, 2, 4 and 6 hours after IMP dosing), blood samples will be taken for PK analysis. NPRS will be monitored at 0.5, 1, 2, 4 and 6 hours. Vital signs will be measured 30 (+/-10) minutes after IMP dosing.

Before leaving the clinic, each subject will be reminded to take a dose of IMP twice daily and to continue recording pain scores in their diary each evening.

All subjects will leave the unit with sufficient IMP for the first treatment period.

8.3.2 Day 14 (± 1), Visit 3

On Day 14 (Visit 3), subjects will take their morning IMP dose and return to the clinic with their medication bottle. The following assessments will be undertaken:

- Weight
- Vital signs
- Targeted physical examination
- Concomitant medications
- Adverse events
- Compliance with medication
- Compliance with diary entries

Subjects will be reminded to continue their medication and to continue to record daily NPRS entries into their diary. They will be asked to return on Day 28 with their medication bottle, but without taking their morning dose of IMP. They will also be reminded not to take paracetamol within 4 hours of the next clinic visit.

8.3.3 Day 28 (± 1), Visit 4

On the morning of Day 28 (Visit 4, Last Day of First Treatment Period), subjects will not take their morning dose of IMP. They will return to the clinic with their medication bottle.

The following assessments will be undertaken:

- Weight
- ECG
- Vital signs
- Targeted physical examination
- Concomitant medications
- Blood and urine samples for safety analysis (haematology, clinical chemistry, urinalysis)
- Adverse events
- Compliance with medication
- Compliance with diary entries

Subjects will also complete assessments for Patient Reported Outcomes:

- Interference scale of the short form BPI
- SF-MPQ-2
- NPSI
- BDI-II
- PGIC

Subjects (except PK and QST subjects) will take their morning dose of IMP and leave the clinic. They will take their Day 28 evening dose and then discontinue treatment until their next visit on Day 50. They will be asked to continue daily NPRS diary entries, and to return to the unit on Day 50 with their medication bottle. They will also be reminded not to take paracetamol within 4 hours of the next clinic visit.

In PK subjects, a pre-dose NPRS will be completed (maximum one hour before dosing) and a pre-dose blood sample will be taken for PK analysis. PK subjects will take their morning dose of IMP and remain in

the clinic for at least 6 hours. At scheduled times (2, 5, 15, 30, 60 minutes, 2, 4 and 6 hours after IMP dosing), blood samples will be taken for PK analysis. NPRS will be monitored at 0.5, 1, 2, 4 and 6 hours. Subjects will then leave the clinic. They will take their Day 28 evening dose and then discontinue treatment until their next visit on Day 50. They will be asked to continue daily diary entries, and to return to the unit on Day 50 with their medication bottle. They will also be reminded not to take paracetamol within 4 hours of the next clinic visit.

QST subjects will take their morning dose of IMP and will have QST parameters [redacted] assessed 2 hours after this dose. An appointment for a QST assessment will be scheduled within seven days of the start of the next treatment period. They will then leave the clinic. They will take their Day 28 evening dose and then discontinue treatment until their visit on Day 50. They will be asked to continue daily diary entries, and to return to the unit on Day 50 with their medication bottle. They will also be reminded not to take paracetamol within 4 hours of the next clinic visit.

8.4 Washout (Days 29-42)

The first treatment period will be followed by a washout period of two weeks (Days 29 to 42 inclusive). Subjects will continue their NPRS diary entries each evening, but will not take any IMP.

8.5 Second baseline period (Days 43-49)

During the second baseline period (Days 43 to 49 inclusive), subjects will continue their diary entries and will not take any IMP. They will record their NPRS rating each evening.

8.6 Second treatment period (Days 50-77), Visits 5 to 7

Subjects will return to the unit on Day 50 (± 1) with their diary completed from Days 29 to 49 inclusive and with their medication bottle.

8.6.1 Day 50 (± 1), Visit 5

Subjects will return on Day 50, and the following assessments will be undertaken:

- Review of the subject's pain diary (Days 43-49 inclusive)
- Weight
- ECG
- Vital signs
- Targeted physical examination, including assessment of area of pain
- Concomitant medications
- Blood and urine samples for safety analysis (haematology, clinical chemistry, urinalysis)

Results from safety monitoring tests are not required prior to dosing. Subjects will also complete their second baseline assessments for Patient Reported Outcomes:

- Interference scale of short form BPI
- SF-MPQ-2
- NPSI
- BDI-II

In PK subjects, a pre-dose NPRS will be completed (maximum one hour before dosing) and a pre-dose blood sample taken for PK analysis. QST subjects will have a pre-dose QST assessment, if not completed within the previous 7 days.

Subjects (except for PK subjects) will take their allocated IMP and will remain in the clinic for up to one

hour to check for adverse events. Vital signs will be measured 30 (+/-10) minutes after IMP dosing.

PK subjects will take their allocated IMP and will remain in the clinic for at least 6 hours. At scheduled times (2, 5, 15, 30, 60 minutes, 2, 4 and 6 hours after IMP dosing), blood samples will be taken for PK analysis. NPRS will be monitored at 0.5, 1, 2, 4 and 6 hours. Vital signs will be measured 30 (+/-10) minutes after IMP dosing.

All subjects will leave the unit with sufficient IMP for the second treatment period. They will be reminded to complete their NPRS diary each evening.

8.6.2 Day 63 (± 1), Visit 6

On Day 63 (Visit 6), subjects will take their morning IMP dose and return to the clinic with their medication bottle. The following assessments will be undertaken:

- Weight
- Vital signs
- Targeted physical examination
- Concomitant medications
- Adverse events
- Compliance with medication
- Compliance with diary entries

Subjects will be reminded to continue their medication and to record daily entries into their diary. They will be asked to return on Day 77 with their medication bottle, but without taking their morning dose of IMP. They will also be reminded not to take paracetamol within 4 hours of the next clinic visit.

8.6.3 Day 77 (± 1), Visit 7

On the morning of Day 77 (Visit 7, Last Day of Second Treatment Period), subjects will not take their morning dose of IMP. They will return to the clinic with their medication bottle and the following assessments will be undertaken:

- Weight
- ECG
- Vital signs
- Targeted physical examination
- Concomitant medications
- Blood and urine samples for safety analysis (haematology, clinical chemistry, urinalysis)
- Adverse events
- Compliance with medication
- Compliance with diary entries

Subjects will also complete assessments for Patient Reported Outcomes:

- Interference scale of the short form BPI
- SF-MPQ-2
- NPSI
- BDI-II

- PGIC

Subjects (except PK and QST subjects) will take their morning dose of IMP and leave the clinic. They will take their second Day 77 IMP dose in the evening and then discontinue treatment.

In PK subjects, a pre-dose NPRS will be completed (maximum one hour before dosing) and a pre-dose blood sample will be taken for PK analysis.

PK subjects will take their first dose of IMP and remain in the clinic for at least 6 hours. At scheduled times (2, 5, 15, 30, 60 minutes, 2, 4 and 6 hours after IMP dosing), blood samples will be taken for PK analysis. NPRS will be monitored at 0.5, 1, 2, 4 and 6 hours. They will leave the clinic and take their second Day 77 IMP dose in the evening. They will then discontinue treatment.

QST subjects will take their morning dose of IMP and will have QST parameters [redacted] assessed 2 hours after this dose. They will leave the clinic and will take their second Day 77 dose in the evening. They will then discontinue treatment.

All subjects will be asked to bring their medication bottle to the End of Study visit.

8.7 End of Study visit

8.7.1 Day 91 (± 2) Visit 8

At the end of study visit, subjects will return with their medication bottle. The following assessments will be undertaken:

- Weight
- Vital signs
- Targeted physical examination
- Concomitant medications
- Blood and urine samples for safety analysis (haematology, clinical chemistry, urinalysis)
- Adverse events

8.8 Early withdrawal visit

Subjects who do not complete the study will be asked to return for an End of Study visit (Section 8.7.1). This visit should be scheduled approximately two weeks after the last dose was taken.

9. Study Endpoints

9.1 Primary endpoint

- Absolute change in mean pain score, using an 11 point NPRS, from baseline to the last week of each treatment period. Pain is recorded once daily in a subject diary in the evening, and should reflect the subject's average pain over the last 24 hours

Baseline mean pain for each subject is defined as the mean of the last five available ratings of daily pain, recorded in each baseline period.

End of treatment mean pain for each subject is defined as the mean of the last five available ratings of daily pain, recorded in the last 7 days of each 4 week treatment period.

9.2 Secondary endpoints

- Change in NPRS score at 0.5, 1, 2, 4 and 6 hours after the first dose of IMP in each treatment period, compared with the score recorded no more than 60 minutes before the first dose of IMP in that treatment period (PK subjects only)
- Change in NPRS score at 0.5, 1, 2, 4 and 6 hours after a single dose of IMP, following four weeks treatment with IMP in each treatment period, compared with the score recorded no more than 60 minutes before this dose (PK subjects only)
- Change in mean pain scores from baseline after 1, 2 and 3 weeks of dosing with IMP in each treatment period, using an 11 point NPRS. Pain scores at weeks 1, 2 and 3 are defined as the mean of the last five available ratings of daily pain in the subject diary, recorded in the previous 7 days of treatment
- 30% responder rate, based on the proportion of subjects achieving ≥ 30% reduction in mean NPRS from baseline to the end of 4 weeks treatment in each treatment period
- 50% responder rate, based on the proportion of subjects achieving ≥ 50% reduction in mean NPRS from baseline to the end of 4 weeks treatment in each treatment period
- Maximum change in mean NPRS from baseline after 1, 2, 3 or 4 weeks treatment in each treatment period
- Change in functioning from baseline to the end of 4 weeks treatment in each treatment period, as measured by the BPI interference scale
- Change in pain characteristics and intensity from baseline to the end of 4 weeks treatment in each treatment period, as assessed by the SF-MPQ-2
- Change in neuropathic pain symptoms from baseline to the end of 4 weeks treatment in each treatment period, as assessed by NPSI
- Change in emotional functioning from baseline to the end of 4 weeks treatment in each treatment period, as assessed by the BDI-II
- PGIC at the end of each four week treatment period
- Paracetamol (rescue medication) use per week over each treatment period compared with the preceding baseline

9.3 Safety endpoints

- Physical examinations and vital signs
- ECG
- Clinical chemistry and haematology analyses

- Urinalysis
- Number and type of Treatment Emergent Adverse Events (TEAEs), including serious adverse events (SAEs), and suspected unexpected serious adverse reactions (SUSARs)
- Concomitant medications

9.4 Pharmacokinetic endpoints

- Pharmacokinetic parameters: C_{max}, T_{max}, $AUC_{0\text{-}inf}$ in each treatment period, after a single dose and at the end of four weeks treatment in PK subjects

9.5 Exploratory endpoints

- Association between change in mean NPRS from baseline to the end of four weeks treatment and selected subject baseline characteristics, including clinical diagnosis and pre-treatment QST parameters
- Change from baseline in specified QST parameters [redacted] to the end of 4 weeks treatment, in each treatment period
- Correlation between plasma LAT8881 concentration and the change in mean NPRS from baseline to the end of four weeks treatment in PK subjects
- Change in mean NPRS score from baseline to the last week of each treatment period, after omission of subjects with the 25% most variable first baseline NPRS scores

10. Study measurements

10.1 Clinical assessments

10.1.1 Medical history

The medical history will include any conditions reported by the subject or noted by the investigator in each body system, including allergies or drug sensitivities, past surgeries and any history of substance abuse (drug or alcohol) and will be recorded at screening. A review of the subject's medication use will also occur.

A diagnosis of shingles or diabetes and the date (month/year) at which PHN or DPN was first reported should be confirmed by an independent source (e.g. general practitioner, hospital records).

10.1.2 Demographics

Demographic information will include the subject's age, gender and ethnic affiliation.

10.1.3 painDETECT questionnaire

The PD-Q consists of seven pain sensory symptom items (burning, tingling/prickling, light touching, sudden pain attacks/electric shock-type pain, cold/heat, numbness, slight pressure), one pain course pattern item, and one pain radiation item. From this questionnaire, a PD-Q total score, ranging from -1 to 38 is calculated. A total score ≥19 indicates a neuropathic component is likely, ≤12 indicates a neuropathic component is unlikely and scores 13-18 are considered uncertain i.e. a neuropathic pain component can be present.[12] The English version of the PD-Q is widely used and is reported to be reliable as a screening tool for neuropathic pain, although it has yet to be fully validated.[13,14]

The PD-Q will be used in conjunction with clinical assessment to facilitate diagnosis of neuropathic pain.

10.1.4 Electrocardiogram

12-lead ECGs will be performed with subjects lying in a supine or semi-supine position for at least 5 minutes prior to measurement. All ECG tracings will be reviewed by the Investigator or an appropriately medically qualified reviewer designated this responsibility by the Investigator.

10.1.5 Vital signs

Resting supine or semi-supine blood pressure (systolic and diastolic), heart rate, and respiratory rate will be evaluated. The same arm should be used throughout the study. Body temperature (tympanic), will also be evaluated as part of vital signs.

Subjects should be resting in a supine position for at least 5 minutes prior to and during vital signs measurement.

10.1.6 Physical examination

Physical examinations are to be performed by a medically qualified physician according to their standard medical practice. Any new or worsening abnormality, clinical sign or finding must be documented.

A full physical examination is to be performed at the first screening visit. At other scheduled time points, a targeted (symptom directed) physical examination, as clinically indicated, is to be performed. All physical examinations will include assessment of the area of pain.

A full physical examination will include assessments of the head (eyes, ears, nose, mouth, throat), skin, neurological system, respiratory system, cardiovascular system, musculoskeletal system, abdomen (liver and spleen), lymph nodes and extremities, general appearance, and any additional assessments needed to establish baseline status or change from baseline or evaluate symptoms or adverse events.

Neuropathies other than PHN and DPN will be excluded by clinical assessment at screening. Nerve conduction studies are not required for this assessment.

10.1.7 Height and weight

Height (centimetres) and weight (kilogram), without shoes, will be measured at the screening visit and BMI calculated. Weight (without shoes) will be measured at all other visits.

10.1.8 QST phenotype

QST measurements will be undertaken by a researcher specifically trained in this procedure at sites which have experience in the technique. [redacted] Tests will be undertaken at a painful dermatome in PHN subjects or at a painful peripheral site in DPN subjects.

[redacted]

Full details of the QST procedures will be provided in the QST manual.

10.2 Laboratory assessments

10.2.1 Clinical safety testing

Blood and urine samples will be taken at screening, on Days 1, 28, 50, 77 and at the end of study visit. Blood samples will be tested at one nominated laboratory per study site. Urinalysis (dipstick) will be performed at the investigational site.

Details of the volume of blood and type of tubes required for the following tests will be provided in the Study Manual. At the investigator's discretion, sample collection may be repeated if an abnormal result occurs due to technical or other reasons.

The following tests will be performed.

10.2.1.1 Haematology

Haemoglobin, haematocrit, red blood cell count, white blood cell count with differential (neutrophils, lymphocytes, monocytes, basophils, eosinophils), platelet count, mean corpuscular haemoglobin, mean corpuscular volume, mean corpuscular haemoglobin concentration

10.2.1.2 Clinical chemistry

Glucose, sodium, potassium, chloride, bicarbonate, calcium (corrected), creatinine, urea, uric acid, amylase, lipase, triglyceride, HDL-cholesterol, LDL-cholesterol, total cholesterol, total protein, lactate dehydrogenase, creatine kinase, C-reactive protein, albumin, phosphate. HbA1c will be measured in DPN subjects only and only at screening.

Aspartate aminotransferase, alanine aminotransferase, gamma-glutamyl transferase, alkaline phosphatase, conjugated bilirubin, total bilirubin

Activated partial thromboplastin time, international normalised ratio

10.2.1.3 Urinalysis

Specific gravity, pH, glucose, protein, blood, ketones, urobilinogen, bilirubin, nitrite, leukocytes.

If urinalysis on dipstick is positive for leukocytes and/or blood/haemoglobin, a microscopic examination including erythrocytes, leucocytes, bacteria, casts, epithelial cells and crystals will be performed.

10.2.1.4 Pregnancy

Human chorionic gonadotropin levels (hCG) will be measured in blood samples from females of child-bearing potential at screening. Urine hCG will be measured on Day 1.

10.2.2 Pharmacokinetics

Blood samples (4 mL) will be taken pre-dose (within 30 minutes of dosing) and 2, 5, 15, 30, 60 minutes, 2, 4 and 6 hours after IMP ingestion. Blood samples will be obtained by direct venepuncture or via an indwelling cannula. Samples taken 2, 5 and 15 minutes after dosing should be within +/- 1 minute of the stated time, samples at later time points within +/- 5 minutes of the stated time.

[redacted] Blood samples will be kept on ice immediately after collection to minimise degradation and centrifuged within 60 minutes post-collection in a pre-cooled (refrigerated) centrifuge. The resulting PK plasma samples will be transferred to clean, pre-labelled polypropylene tubes and stored frozen prior to analysis. Pre-dose samples will be centrifuged separately prior to dosing.

Further details will be provided in the Laboratory Manual.

Samples will be analysed under GLP conditions by [redacted] An initial batch of 25% of the total number of samples will be tested. If all samples tested are below the limit of quantification of the assay, further analyses will not be undertaken until the sensitivity of the assay is significantly increased.

10.3 Adverse event monitoring

Subjects will be asked by direct questioning at each visit whether they have experienced any AEs. Aes will be assessed as described in Section 12.2.

10.4 Concomitant medications

Changes in use or new medications used during course of study will be documented and reviewed at each study visit.

10.5 Efficacy assessments

10.5.1 Pain intensity

10.5.1.1 NPRS

The NPRS is an 11 point scale which grades pain from 0 (no pain) to 10 (worst pain imaginable). It is a recommended core outcome for the assessment of pain intensity in clinical trials of chronic pain treatments.[16]

Subjects will be asked to rate the intensity of their average pain over the previous 24 hours in a diary. Entries should be made at the same time each evening.

10.5.2 Patient reported outcomes

10.5.2.1 Short form BPI

The interference scale of the short form BPI[15] has been recommended by international consensus[16] as a core outcome measure of physical functioning in chronic pain clinical trials. It measures the interference of pain on seven items (general activity, mood, walking ability, work, relations with other people, sleep, enjoyment of life). Each scale is graded from 0 (does not interfere) to 10 (completely interferes). The result is the mean of the scores from the seven items.

10.5.2.2 SF-MPQ-2

The SF-MPQ-2[17] is a measure of both neuropathic and non-neuropathic pain, modified from the commonly used McGill Pain Questionnaire[18] and Short-form McGill Pain Questionnaire.[19] The SF-MPQ-2 adds seven symptoms characteristic of neuropathic pain to the SF-MPQ and has response scales from 0 to 10.

10.5.2.3 NPSI

The NPSI was designed specifically for the assessment of the different symptoms of neuropathic pain.[20] It contains ten items related to different pain descriptors (e.g. burning, squeezing, electric-shock, stabbing, tingling), allowing the assessment of the different dimensions of neuropathic pain, and two items on frequency and duration of pain. Each pain descriptor is rated on an 11-point numeric rating scale from 0 (no pain) to 10 (worst imaginable pain). Total pain intensity score is calculated by the sum of the 10 descriptors.

10.5.2.4 BDI-II

The BDI-II[21] consists of 21 items; each item is a list of four statements arranged in increasing severity about a particular symptom of depression. Each statement is scored from 0 to 3. Each of the 21 items is summed to give a single score for the BDI-II.

10.5.2.5 PGIC

The PGIC is a single-item rating by subjects of their improvement with treatment during a clinical trial.[22] It asks the subject to rate their improvement with therapy on a 7-point scale ranging from very much worse to very much improved, with no change as the mid-point.

11. Study Oversight

11.1 Within-subject stopping criteria

Administration of IMP will continue within an individual subject if, in the investigator's opinion, it is safe to do so.

The following criterion constitutes a contraindication to further administration of IMP to an individual subject:

- Any experience, which is considered, by the investigator and/or the sponsor to be serious, and severe and clinically significant, which would suggest significant hazard that may be associated with the use of the IMP

If the above criterion becomes applicable during the study, the subject must not receive further doses of IMP. Such subjects will be withdrawn and follow the withdrawal procedures as described in Section 5.7.

11.2 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 subjects 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:
  - Failure of investigator(s) to enrol eligible subjects into the study;
  - Failure of the investigator to comply with country-specific regulations;
  - Submission of false information from the research facility to the sponsor, the clinical monitor, or a regulatory authority;
  - Insufficient adherence to protocol requirements;
  - A conflict of interest of the investigator, his/her institution, or site personnel that could negatively impact the integrity of the clinical study;
  - 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 14.1.4. 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, subjects will be followed up for a minimum of two weeks following the last exposure to IMP, at which time an End of Study visit should be conducted. Refer to Section 8.7.1 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).

12. Adverse events

12.1 Definitions

12.1.1 Adverse event

An adverse event is any untoward medical occurrence in a patient or clinical investigation subject 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 Section 12.3). An adverse event is defined as 'serious' when it meets one of the pre-defined outcomes as described in Section 12.1.6.

12.1.2 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.

12.1.3 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 subject to expedited reporting to the applicable regulatory authorities.

For regulatory reporting purposes, SUSARS will be unblinded.

12.1.4 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.

12.1.5 Severity (Intensity) of adverse event

Grade refers to the intensity of an AE and should not be confused with seriousness (refer Section 12.1.6).

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 ADL**.
Grade 4	Life-threatening consequences; urgent intervention indicated.
Grade 5	Death related to AE.

Activities of Daily Living (ADL)

**Instrumental ADL – refers to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.*

***Self-Care ADL – refers to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden.*

12.1.6 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 subject 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 subject 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 subject 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.

12.2 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.

In the UK, all SAEs will be recorded from the time of the subject signing an informed consent. All non serious Aes 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 subject's source records. All spontaneously volunteered and enquired for, as well as observed AEs, will be recorded in the subject'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 Section 12.4. 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.

12.3 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.

12.4 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 subject 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 subject or in a female partner of a male study subject. 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 subject or in a female partner of a male study subject 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 subject'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 subjects, impact on the conduct of the study or alter the ethics approval/favourable opinion of the study.

12.5 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 subject is lost to follow up, whichever comes first. Follow-up investigations may be necessary according to the investigator's medical judgement.

13. Statistical analysis

13.1 General considerations

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, early withdrawals, and potential covariates. Any changes to the statistical analysis plan will be described and justified in the final report.

The descriptive summary for the categorical variables will include counts and percentages. The descriptive summary for the continuous variables will include number of subjects (n), means, medians, standard deviations, and minimum and maximum values. Pharmacokinetic measures will be analysed as for continuous variables. All data will be listed for all subjects. All confidence intervals (CIs) will be 95%, unless stated otherwise. All statistical analyses will be performed using SAS unless otherwise stated.

13.2 Sample size

The sample size estimation is based on the following assumptions:

- Power of 90%
- The mean change from baseline NPRS for the active treatment compared with placebo is at least 1 unit
- Standard deviation of the change from baseline in NPRS pain score is 2
- Correlation between active and placebo response is 0.5
- The test is two sided
- The dropout rate is 20%

The number of subjects within each treatment group is also sufficient to show a statistically significant change from baseline of 2 or more points on the NPRS.

13.3 Analysis populations

13.3.1 Full Analysis Set

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

13.3.2 Per protocol population

A per-protocol (PP) population will be based on duration of IMP treatment and protocol deviations. This population may exclude subjects 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.

13.3.3 Safety population

The safety population consists of all randomised subjects 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. Subjects will be analysed as treated, regardless of the randomised treatment assigned, if this differs from that to which the subject was randomised.

13.3.4 PK population

The PK population will include all subjects who received at least one dose of IMP, had at least one post-

dose sample collection for PK analysis and who did not have any clinically significant events or protocol deviations that may have compromised the integrity of the PK results.

13.4 Subject disposition

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

13.5 Analysis of efficacy data

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.

13.5.1 NPRS

The primary efficacy endpoint is the absolute change from baseline mean NPRS score to the end of treatment NPRS score after LAT8881, compared with the change from baseline after placebo treatment.

Daily NPRS scores for all enrolled subjects will be listed only. Mean and standard deviation of scores during the baseline period and weeks 1, 2, 3 and 4, and the absolute and percentage change from baseline in each period, will be listed for each subject and summarised for LAT8881 and placebo treatments overall and within treatment sequence for all randomised subjects and for the PP population. The maximum change in mean NPRS from baseline to weeks 1, 2, 3 and 4, determined for each subject after LAT8881and placebo, will be listed and summarised.

Mixed effects regression models will be used to compare the absolute and percentage changes from baseline to the end of each treatment for the mean NPRS scores. The models will have fixed effects for period and treatment. Baseline mean pain score within each period by treatment combination will be included as a covariate. A random effect for subject will be included to capture the repeated measures nature of the design.

The models for the primary endpoint will be expanded to compare the absolute and percentage changes from baseline for the mean NPRS scores after 1, 2 and 3 weeks of dosing with IMP in each treatment period. The model will also include a fixed effect for week (1, 2, 3 and 4), the interaction between treatment and week to assess whether the change from baseline for each treatment is different.

The mean score at each visit, change from baseline, difference between treatments in the change from baseline and corresponding 95% confidence intervals will be presented. Comparisons will be declared statistically significant if $p<0.05$.

In PK subjects, NPRS scores at specified times up to 6 hours on Days 1, 28, 50 and 77 will be listed and summarised. Change from pre-dose values will also be listed and summarised. Changes over time will be analysed using the same modelling approach as for the primary endpoint.

The proportion of subjects achieving at least 30% and 50% reduction in pain after four weeks treatment, as assessed by the mean NPRS score, will be summarised with the 95% confidence interval for the percentage reduction, estimated by Clopper Pearson Exact methodology. A mixed effects logistic regression model, including the same fixed and random effect terms as for the primary endpoint, will be used to assess the odds of achieving a reduction in pain at Day 28 and Day 77 with LAT8881 compared to placebo.

13.5.2 Patient reported outcomes

Baseline and end of treatment values for the BPI interference scale, SF-MPQ-2, NPSI and BDI will be listed for LAT8881 and placebo. Values at each timepoint and the change from baseline will be summarised. PGIC will be tabulated at the end of each treatment period and summarised. Differences

between the LAT8881 and placebo treatments in the change from baseline reported outcome will be analysed using the same model as for the primary endpoint.

13.5.3 Analgesic use

Paracetamol (rescue medication) use at baseline and weekly over the treatment period will be listed for each subject. The average weekly and cumulative dose of rescue paracetamol medication in each treatment period will be summarised by visit and treatment.

13.6 Analysis of safety data

13.6.1 Extent of exposure

The number of subjects exposed to study treatment, duration of exposure and total IMP administered, will be summarised.

13.6.2 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 subjects with the following adverse events will be prepared:

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

All summaries of adverse events will include only treatment emergent adverse events (TEAEs). Refer Section 12.1 for adverse event definitions.

13.6.3 Clinical laboratory evaluations

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 subjects with clinically significant abnormal results will be prepared.

13.6.4 Other safety measures

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 subjects receiving concomitant medications will be tabulated overall and by medication received.

13.7 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-t}	Area under LAT8881 concentration time curve from dosing to the last observed concentration

	value above the limit of quantification
AUC_{0-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

AUC_{0-t} will only be calculated if there are at least three quantifiable data points.

$T_{1/2}$ will only be determined if there are at least three quantifiable elimination phase data points.

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

The change in PK parameters on the last day of treatment compared with those determined after the initial dose will be investigated using a paired t-test. The mean change after repeated dosing will be presented with the corresponding 95% confidence interval and p value.

13.8 Analysis of exploratory endpoints

Exploratory analyses will be undertaken to determine the relationship between change in mean NPRS from baseline to the end of four weeks treatment and baseline parameters, such as the clinical diagnosis (PHN or DPN) and baseline QST parameters. The effect of treatment on changes in QST parameters [redacted] from baseline to the end of four weeks treatment will also be analysed.

The effect of the variability in NPRS scores within the first baseline period on the ability to detect a treatment difference will be examined.

The relationship between plasma LAT8881 and NPRS in PK subjects will also be investigated.

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

14. Study management

14.1 Regulatory and ethical considerations

14.1.1 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 Helsinki[23] 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.

14.1.2 Ethics Committee review

Prior to the initiation of the study, the protocol and associated documentation (including all materials used to recruit subjects 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 subjects 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.

14.1.3 Informed consent process

The investigator will ensure that the subject is given full and adequate oral and written information about the nature, purpose, possible risks and potential benefits of the study. Subjects must also be notified that they are free to discontinue from the study at any time. The subject should be given the opportunity to ask questions and should be allowed time to consider the information provided.

The subject'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 subject's medical records. A copy of the signed and dated ICF must be given to the subject.

Subjects who are incompetent and unable to freely provide informed consent and subjects 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 subjects, the protocol and ICF will be amended as appropriate and submitted to the EC as outlined in Section 14.1.4. Following approval by the EC, subjects 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, subjects may be requested to re-consent to ongoing their participation in the study.

14.1.4 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 re-evaluation 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 subjects, 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.

14.1.5 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 subjects 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.

14.2 Quality control and quality assurance

14.2.1 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.

14.2.2 Study monitoring

The study will be independently monitored in accordance with ICH GCP[1], 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.

14.2.3 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 subjects.

The eCRFs should always reflect the latest observations on the subjects participating in the study; therefore, the eCRFs are to be completed as soon as possible during or after the subject'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 subject's medical record, that verify the existence of the subject, the inclusion and exclusion criteria and all records covering the subject's participation in the study. They include, but are not limited to, laboratory reports, hospital records, subject files, etc.

eCRFs will be completed for subjects who have signed the ICF, are eligible for this study and have been enrolled in the study.

14.2.4 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 subject 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.

14.3 Documentation, record access and archiving

14.3.1 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 sites. The investigator/institution is responsible for maintaining the study documents during the study as specified in the ICH GCP[1] 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.

14.3.2 Data protection

To protect the subject's identity, a unique subject identification code (Subject ID) will be assigned by the investigator to each study subject and used in lieu of the subject's name when the investigator reports SAEs and/or other study-related data. The subject's study number, rather than the subject's name, will appear on all documents and will be cross referenced by the subject'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 subject's consent to direct access to his/her original medical records for data verification purposes must be obtained prior to that subject's involvement in the study.

Subjects 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. Subjects 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, subjects will be identified in such reports only by study identification number (Subject ID), gender and age. All subject 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. Subject data in the database will be identified by Subject ID number only. Electronic CRFs will also identify subjects by Subject 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 subject's source documents and/or medical record.

14.3.3 Data retention & archiving

All study records (including the Investigator's Study File containing Essential Documents as defined in ICH GCP[1]) and source data must be available for retrospective review or audit.

Source documents are original documents, data, and records from which the subject's CRF data are

obtained. These include, but are not limited to: hospital records, subject'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.

14.4 Study administration

14.4.1 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 subjects 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 subjects 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 subject'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.

14.4.2 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 IHPT, subject 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 subject

only by the subject identification code (Subject ID). The investigator will maintain a current confidential Subject Identification List of full names of all subjects in this study. This list will allow the investigator to reveal the identity of the subjects 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.

14.4.3 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 subjects 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.

14.4.4 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].

14.4.5 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.

15. References

[1] International Conference on Harmonisation (ICH) Integrated Addendum to ICH E6(R1): Guideline for Good Clinical Practice E6(R2), 9 November 2016

[2] International Association for the Study of Pain. IASP taxonomy. 2017. Available from https://www.iasp-pain.org/Taxonomy#Neuropathicpain [Accessed 22 February 2018]

[3] van Hecke O, Austin SK, Khan RA, Smith BH, Torrance N. Neuropathic pain in the general population: a systematic review of epidemiological studies. Pain. 2014 Apr;155(4):654-62

[4] Colloca L, Ludman T, Bouhassira D, Baron R, Dickenson AH, Yarnitsky D et al. Neuropathic pain. Nat Rev Dis Primers. 2017 Feb; 3:17002

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Appendix 1: Protocol Amendments

Note that changes to the cover page, page footer and table of contents, which are self-explanatory, are not listed as amendments.

Section	Changed From	Changed To	Justification
V2, 29 March, 2019			
Doses and treatment regimens: Section 7.10		Added . If more than 16 hours has elapsed since the last dose, the dose should be missed and the next dose taken at the regular scheduled time.	Provides information about missing a dose
Prohibited Medications: Synopsis and Section 7.14.2		Added: A short course (<7days) of oral prednisolone or equivalent for other conditions, up to 4 weeks preceding Day 1, is allowed	Clarification of prohibited medications
Early withdrawal visit: Section 8.8		Added: This visit should be scheduled approximately two weeks after the last dose was taken.	Clarification of timing of the End of Study visit after Early Withdrawal
Medical History: Section 10.1.1.	will be recorded from screening until dosing with IMP on day 1	will be recorded at screening	Correction to timing of medical history
Exclusion criteria 6: Synopsis and Section 6.2	Clinically significant abnormal 12-lead electrocardiogram (ECG)	Clinically significant abnormal 12-lead electrocardiogram (ECG) at screening	It is only at screening that an abnormal clinically significant ECG mandates exclusion from the study.
Electrocardiogram: Section 10.1.4	Any subject with an abnormal ECG that is considered clinically significant will be excluded from the study	Any subject with an abnormal ECG at screening that is considered clinically significant will be excluded from the study	It is only at screening that an abnormal clinically significant ECG mandates exclusion from the study.
Clinical chemistry: Section 10.2.1.2	calcium (corrected) creatinine,	calcium (corrected), creatinine,	Comma added to separate tests
Clinical chemistry: Section 10.2.1.2		Added HbA1c will be measured in DPN subjects only and only at screening.	HbA1c is a screening test for DPN subjects
V3, 17 May, 2019			
Synopsis and Sections 5.1, 8.2.1, 8.2.2, 10.5.1.1	Electronic diary	diary	Diary is not electronic
Synopsis and Section 9.1	or since the last diary entry (whichever is shorter)	Deleted this text	Simplified diary instructions
Exclusion 6:	Clinically significant	Clinically significant abnormal 12-lead	Subjects may be

Section	Changed From	Changed To	Justification
Synopsis and Section 6.2	abnormal 12-lead electrocardiogram (ECG) at screening	electrocardiogram (ECG)	excluded if they have an abnormal ECG at screening or pre-dose on Day 1
Electrocardiogram: Section 10.1.4	Any subject with an abnormal ECG at screening that is considered clinically significant will be excluded from the study	Any subject with an abnormal ECG at screening or pre-dose on Day 1 that is considered clinically significant will be excluded from the study.	Subjects may be excluded with an abnormal ECG pre-dose on Day 1
V4, 15 July, 2019			
General Study Information			[redacted]
Synopsis	[redacted]		Updated current list of trial sites and addresses
Table 1	36 289	27 243	Subject numbers corrected
Section 7.2.1	Active Pharmaceutical Ingredient	LAT8881 capsules	Corrected terminology
Sections 7.3, 7.5	[redacted]	[redacted]	[redacted]
Section 10.1.4	Deleted: Any subject with an abnormal ECG at screening or pre-dose on Day 1 that is considered clinically significant will be excluded from the study.		Section 6.2 already covers this
V4, 27 August, 2019			
Section 7.13.1	Investigator asked to advise Sponsor/ Medical Monitor before breaking code	Investigator may break code without prior notification to Sponsor/Medical Monitor	Requested by MHRA
Section 12.2	SAEs which occur after signing of the informed consent to first IMP administration are recorded as medical history	In the UK, SAEs which occur after signing of informed consent will be recorded as an SAE on the database	Requested by MHRA

Section	Changed From	Changed To	Justification
V5, 9 October 2019			
Synopsis, Sections 5.1, 8.2.1	At least 20 QST subjects	Up to 20 QST subjects	Delay in QST recruitment