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

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Statistical Analysis Plan

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[redacted]

1 Definitions

Abbreviation	Definition
AE	Adverse event
ANCOVA	Analysis of covariance
ATC	Anatomical Therapeutic Chemical Classification System
$AUC_{0\text{-}inf}$	Area under LAT8881 concentration time curve from dosing to the last observed concentration value above the limit of quantification, extrapolated to infinity
$AUC_{0\text{-}t}$	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
BMI	Body mass index
BPI	Brief Pain Inventory
CI	Confidence interval
C_{max}	Maximum plasma drug concentration
CV	Co-efficient of variation
CS	Clinically Significant
eCRF	Electronic Case report form
DPN	Diabetic peripheral neuropathy
ECG	Electrocardiogram
FAS	Full analysis set
HbA1c	Glycosylated haemoglobin
hCG	Human chorionic gonadotropin
[redacted]	[redacted]
IASP	International Association for the Study of Pain
ICH	International Conference on Harmonisation
IMP	Investigational medicinal product
LLOQ	Lower limit of quantification
LS	Least square
m	Number of events / mentions
MedDRA	Medical Dictionary for Regulatory Activities
[redacted]	[redacted]
Min	Minimum
Max	Maximum
n	Number of subjects
NCS	Not clinically significant
NeuPSIG	Neuropathic Pain Special Interest Group

NPRS	Numeric pain rating scale
NPSI	Neuropathic Pain Symptom Inventory
PC	Plasma concentration
PD-Q	painDETECT questionnaire
PGIC	Patient Global Impression of Change
PHN	Postherpetic neuralgia
PK	Pharmacokinetics
PP	Per protocol
PT	Preferred term
[redacted]	[redacted]
[redacted]	[redacted]
SAS	Statistical Analysis System
SAE	Serious adverse event
SD	Standard deviation
SF-MPQ-2	Short-form McGill Pain Questionnaire 2
SOC	System organ class
Subject ID	Subject identifier
SUSAR	Suspected unexpected serious adverse reaction
$T_{1/2}$	Terminal elimination half life
TEAE	Treatment-emergent adverse event
T_{max}	Time to maximum plasma LAT8881 concentration
[redacted]	[redacted]
WHODD	World Health Organization's Drug-Dictionary

2 Introduction

2.1 Background

Neuropathic pain (NP) is defined as pain caused by a lesion or disease of the somatosensory nervous system.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%. 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.[i] 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. 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.

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.

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2.2 Rationale

Six clinical studies with LAT8881 have been completed, with over 700 subjects treated with LAT8881. These studies were designed to investigate the safety and tolerability of LAT8881 and subsequently its efficacy in the treatment of obesity [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 [redacted]. *This trend was not observed in subsequent studies* [redacted] *which evaluated lower daily doses.*

3 Study Objectives

3.1 Primary Objective

1. *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)*

3.2 Secondary Objectives

1. *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)*

2. *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*

3. *To determine the proportion of responders to oral LAT8881 in NP compared with placebo*

4. *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*

5. *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*

6. *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)*

7. *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)*

8. *To evaluate the effect of oral LAT8881, compared with placebo, on emotional functioning when measured by the Beck Depression Inventory-II (BDI-II)*

9. *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*

10. *To determine the change from baseline in rescue medication use during oral LAT8881 administration, compared with placebo*

11. *To evaluate the safety and tolerability of oral LAT8881 in NP after a single dose and after four weeks treatment*

12. *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*

3.3 Exploratory Objectives

1. *To investigate the relationship between baseline subject characteristics, such as clinical diagnosis (PHN or DPN) and [redacted], and the change in NPRS after oral LAT8881 treatment, compared with placebo*

2. *To investigate the change from baseline on [redacted] after four weeks treatment with oral LAT8881, compared with placebo*

3. *To investigate the relationship between plasma LAT8881 concentrations and the change in mean pain score in subjects with NP*

4. *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*

4 Study Design

4.1 Overview

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 below.

The pharmacokinetics (PK) of LAT8881 will be investigated on Days 1, 28, 50 and 77 in 15 subjects (PK subjects) at Australian sites. [redacted] will be performed in at least 20 subjects [redacted] before the first dose on Days 1 and 50 and after the morning dose on Days 28 and 77. PK subjects will not participate [redacted] will not participate in PK analyses.

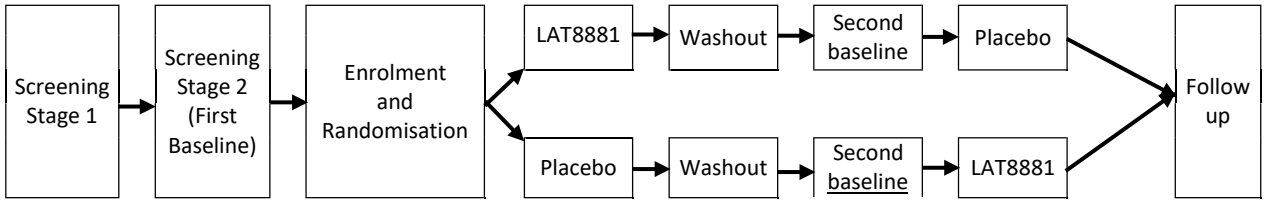

Figure 1: Overall study design for LAT-NP-001

4.2 Sample Size Justification

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.

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.

4.3 Randomization 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.

Details regarding Randomization is provided in [redacted]), and unblinding plan is provided in [redacted]).

4.4 Inclusion/Exclusion Criteria

4.4.1 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*

4.4.2 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 selfevaluation 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*

4.5 Treatment allocation

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. Each capsule contains 30 mg LAT8881 plus [redacted] excipients. Placebo capsules contain the excipients [redacted] only (without LAT8881).

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 2949 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.

5 Assessment Schedule

5.1 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]			
[redacted]			[redacted]		[redacted]	
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, biochemistry, 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
[redacted]
[redacted]
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

5.2 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
[redacted]		[redacted]		[redacted]	
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, biochemistry, urinalysis
24 Results of clinical laboratory tests not required prior to dosing
[redacted]
[redacted]
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

6 Interim Analysis

There is no interim analysis planned for this study.

6.1 Unblinding and Dissemination of Results

There is no interim analysis planned for this study, so this section is not applicable.

7 Efficacy and Safety Endpoints

7.1 Primary Efficacy Endpoints

1. *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.

7.2 Secondary Efficacy Endpoints

1. *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)*
2. *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)*
3. *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*
4. *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*
5. *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*
6. *Maximum change in mean NPRS from baseline after 1, 2, 3 or 4 weeks treatment in each treatment period*
7. *Change in functioning from baseline to the end of 4 weeks treatment in each treatment period, as measured by the BPI interference scale*
8. *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*
9. *Change in neuropathic pain symptoms from baseline to the end of 4 weeks treatment in each treatment period, as assessed by NPSI*

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

7.3 Safety Endpoints

1. *Physical examinations and vital signs*
2. *ECG*
3. *Clinical chemistry and haematology analyses*
4. *Urinalysis*
5. *Number and type of Treatment Emergent Adverse Events (TEAEs), including serious adverse events (SAEs), and suspected unexpected serious adverse reactions (SUSARs)*
6. *Concomitant medications*

7.4 Pharmacokinetic endpoints

1. *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*

7.5 Exploratory endpoints

1. *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* [redacted]
2. *Change from baseline in* [redacted] *to the end of 4 weeks treatment, in each treatment period*
3. *Correlation between plasma LAT8881 concentration and the change in mean NPRS from baseline to the end of four weeks treatment in PK subjects*
4. *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*

8 Statistical Methods

Efficacy endpoints will be summarized in a descriptive manner and analyzed using statistical methods described in section 11.7. The level of significance for statistical tests will be 0.05 and all tests will be two-sided. All p-values will be displayed to four decimal places, with p-values less than 0.0001 presented as '<0.0001' and p-values greater than 0.9999 presented as '>0.9999'. All analyses will be done using SAS [redacted]

Safety endpoints will be summarised in a descriptive manner.

Continuous data will be reported using the following descriptive statistics:

1. Number of observations (n)

2. Mean and standard deviation (SD)
3. Minimum (min) and maximum (max)
4. Median

Minimum and maximum values will be reported to the precision of the endpoint reported with maximum of three decimal places; the mean will be presented with one decimal place more and the standard deviation two decimal places more than the precision of the endpoint reported. Categorical data will be presented using frequency (n = number of subjects; m = number of events) and percentage (%).

Listings will be provided for all data recorded in eCRF to study subject profiles. All listings will be sorted by treatment sequence, subject ID, study period and date (if applicable). Unscheduled visit data will only be listed and not included in summaries.

8.1 Handling Missing/Incomplete Data

For medications / adverse events, if start date is partial then the first day/first month will be imputed. If end date is partial then the last day/last month will be imputed. Medications/Adverse Events with missing year will be considered as concomitant/TEAE respectively (assuming worst case). If an AE started during the same month/year as first dose of IMP in period 1, then the date will be imputed as first IMP date and considered as TEAE (assuming worst case).

Flags identifying the study period for the start/stop dates for prior/ concomitant medications and adverse events will be generated (see Sections 10.6, 10.9). Imputed dates will be used for analyses and collected dates recorded in database will be listed.

The method for missing data imputation for the primary endpoint will be discussed during the blinded review meeting prior to database lock.

8.2 Handling Outliers

Laboratory results with modifiers will be analyzed with the maximum or minimum value defined without the modifiers. For example, a value of “<5” will be considered as “5” for summaries.

8.3 Multiplicity Adjustment

Since there is only one primary endpoint defined in the study as per the protocol, multiplicity adjustment is not required. Although, hypothesis tests for secondary and efficacy endpoints will be performed and caution must be taken when interpreting these results. Adjusted p-values using Bonferroni method may be derived for post-hoc analyses if deemed necessary.

9 Analysis Populations

Membership of the analysis populations will be reviewed and finalized during the blind review of the data conducted prior to database lock.

9.1 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.

9.2 Per protocol population

The Per Protocol (PP) population will include all subjects who received at least one dose of IMP and excludes subjects with <80% treatment compliance or who have other major protocol deviations impacting the study endpoints. Deviations for exclusion from the PP population due to inadequate exposure to IMP or completeness of primary efficacy endpoint will be determined during blinded review meeting. Per-protocol population will be defined for each study period separately.

The PP population is the primary population to analyse efficacy endpoints. Demographic and baseline characteristics of the PP population will also be presented.

9.3 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.

9.4 [redacted]

[redacted]

10 Analysis Variables

10.1 Population Flags

Population flags will be finalized and authorized by the Study Statistician and Sponsor during the blind review meeting prior to database lock as per definitions provided in Section 9. These flags will be included in the analysis datasets.

10.2 Treatment

The following treatment variables along with corresponding numeric equivalents will be included as core variables in all analysis datasets:

- Planned / Actual Treatment Sequence : LAT8881 60 mg-Placebo, Placebo-LAT8881 60 mg •

Planned / Actual Treatment: LAT8881 60 mg, Placebo

10.3 Visits

Analysis visits will be defined as follows within each study period:

Visit as per Protocol	Study Period	Analysis Visit
Visit 1 (Days -28 to -1)	Pre-Treatment	Screening

Day 1, Visit 2	Period 1	Visit 2/Visit 5
Day 14, Visit 3	Period 1	Visit 3/Visit 6
Day 28, Visit 4	Period 1	Visit 4/Visit 7
Day 50, Visit 5	Period 2	Visit 2/Visit 5
Day 63, Visit 6	Period 2	Visit 3/Visit 6
Day 77, Visit 7	Period 2	Visit 4/Visit 7
Day 91, Visit 8 or Early Termination	-	EOS / Early Termination

For NPRS scores, post-baseline summaries will be based on weeks within study:

- Week 1 (Days 1-7 and 50-56)
- Week 2 (Days 8-14 and 57-62)
- Week 3 (Days 15-21 and 63-69)
- Week 4 (Days 22-28 and 70-76)

Timepoints will be included for NPRS data as 'Pre-dose' and 'X hours post-dose' for subjects with measurements taken at timepoints. NPRS will be derived using diary scores as detailed in Section 10.15.

10.4 Study Periods

Duration between initial screening and end of first treatment (Days -28 to 28) is considered as study period 1; washout (Days 29 to 42) is considered as washout period; duration between second baseline period up to end of study visit (Days 43 to 91) is considered as study period 2. Study periods will be considered to set analysis visits.

10.5 Completion Flags

- Subjects are considered to have completed period 1 when Day 28 visit is completed. •

  Subjects are considered to have completed period 2 when Day 77 visit is completed.
- Subjects are considered to have completed study when EOS at Day 91 visit is completed.

10.6 Prior and Concomitant Medications

Medications that ended before first dose of IMP (LAT8881 or placebo) in the first treatment period are considered as prior medications. If medications are ongoing or they start on or after first dose of IMP (LAT8881 or placebo) they are considered concomitant.

Medications that started on or after first dose of IMP in treatment period 1 or during wash-out will be counted in the first treatment period and allocated to the treatment received in treatment period 1.

Medications that started on or after first dose of IMP in treatment period 2 will be counted in the second treatment period and assigned to the treatment received in treatment period 2. If medication occurred in first study period and continued to second, it will be counted in both study periods (as 'New' in period 1 and 'Ongoing' in period 2).

Programming note for concomitant medications:

- Period 1, Ongoing - if CM start date is prior to first dose of IMP in period 1 and end date is on or after first dose of IMP in period 1.
- Period 1, New - if CM start date is on or after first dose of IMP and before first IMP date in period 2.
- Period 2, Ongoing - medications that were new or ongoing in period 1, with end date on or after first IMP date in period 2.
- Period 2, New - if CM start date is on or after first dose of IMP in period 2.

Concomitant medications will either be flagged as "Ongoing" or "New" within a study period, but not in both.

10.7 Rescue Medications

Rescue medications will be flagged for analysis. Additionally, cumulative dose in milligrams (mg) will be calculated within each study period. If a subject has ongoing rescue medication in both study periods, then the cumulative dose within each study period will be calculated.

10.8 Medical History and Concurrent Diseases

Medical history with an end date prior to first dose of IMP in the first treatment period is considered as medical history, and those that are ongoing on and after first dose of IMP are considered as concurrent diseases.

10.9 Adverse Event Flags

Treatment emergent adverse event (TEAE) flags will be marked for adverse events if they occurred or worsened on or after the first administration of IMP in the first study period. Adverse events occurring during screening and first baseline period will not be considered as TEAEs.

If the events cannot be determined as TEAE due to partial dates, then the worst case will be considered and they will be flagged as TEAE in the respective study period based on AE start date.

Related Adverse Events will be flagged for Possibly, Probably and Definitely Related adverse events. Adverse events that started on or after first dose of IMP in treatment period 1 or during wash-out will be counted in the first treatment period and allocated to the treatment received in treatment period 1. AEs that commenced on or after first dose of IMP in treatment period 2 will be counted in the second treatment period and assigned to the treatment received in treatment period 2. If an adverse event occurred in first period and continued to second period, it will be counted in both study periods (as 'New' in period 1 and 'Ongoing' in period 2). If AEs have same month/year as IMP date, then the

decision regarding whether to consider them as 'Ongoing' or 'New' within the period will be decided in the blinded review meeting.

Suspected unexpected serious adverse events (SUSARs) will be flagged by the Sponsor and included in analyses datasets.

Programming note for adverse events:

- Period 1, Ongoing - if AE start date is prior to first dose of IMP in period 1 and end date is on or after first dose of IMP in period 1.
- Period 1, New - if AE start date is on or after first dose of IMP and before first IMP date in period 2.
- Period 2, Ongoing - AEs that were new or ongoing in period 1, with end date on or after first IMP date in period 2.
- Period 2, New - if AE start date is on or after first dose of IMP in period 2.

Adverse events will either be flagged in "Ongoing" or "New" within a study period, but not in both.

10.10 Laboratory Assessments

Laboratory results marked as clinically significant will be categorized as, "Abnormal, CS" and results marked as not clinically significant will be categorized as, "Abnormal, NCS". Results within normal range will be marked as "Normal". Not done results will be categorized as, "Not Done".

If repeat assessments are taken within the same scheduled visit/date, then the latest assessment will be considered for analysis. All laboratory parameters will be reported in SI units.

10.11 painDETECT Questionnaire

The PD-Q total scores (range -1 to 38) indicating a neuropathic pain component will be categorized as follows: $\leq$12 = Unlikely, 13-18 = Uncertain, $\geq$19 = Likely

10.12 Baseline

10.12.1 Safety Endpoints

For safety endpoints, latest measurement taken prior to Day 1 dosing in the first study period will be considered as baseline for both study periods.

10.12.2 Efficacy Endpoints

Baseline will be derived for efficacy endpoints within each study period:

- Period 1 baseline:
- NPRS score: Mean of the last five available ratings of daily pain recorded in baseline period 1.

- NPRS score with timepoints: For subjects with NPRS collected at timepoints in baseline and week 4 visits, baseline will be defined as the pre-dose assessment at the respective visit.

- Secondary Efficacy endpoints: Latest measurement taken prior to Day 1 dosing.

- Period 2 baseline:

- NPRS score: Mean of the last five available ratings of daily pain recorded in baseline period 2. If there are less than 5 ratings in baseline period 2, then baseline from period 1 will be considered.

- NPRS score with timepoints: For subjects with NPRS collected at timepoints in baseline and week 4 visits, baseline will be defined as the pre-dose assessment at the respective visit. If pre-dose assessment is missing, then pre-dose assessment from the respective visit in period 1 will be considered.

- Secondary Efficacy endpoints: Latest measurement taken on/after Day 43 and prior to Day 50 dosing. If baseline measurement is missing in period 2, then baseline from period 1 will be considered.

10.13 Change from Baseline

Change and % Change between Baseline and post-baseline result will be calculated for all efficacy and safety endpoints within each study period as below:

- Change = Result at Day x – Baseline Result

- % Change = $\frac{\text{Result at Day x} - \text{Baseline Result}}{\text{Baseline Result}} \times 100$

When baseline NPRS score = 0, % change from baseline will be calculated using an imputed value of 0.1 at baseline. The range of the NPRS score is 0-10; an imputed value of 0.1 is deemed small enough to be close to zero for percentage change calculations. This imputation will not be included in absolute or change from baseline results.

For subjects with NPRS collected at timepoints in baseline and week 4 visits, change and % change from baseline will be calculated using pre-dose values for timepoints 0.5, 1, 2, 4, 6 hours at each visit.

10.14 Treatment Compliance

The following parameters will be derived within each study period for treatment compliance summaries:

- Total dose administered = number of dose administered days * 60 mg

- Total dose assigned = 28 days * 60 mg

Total dose administered & assigned will only be calculated for LAT8881 group, and will be identified as '-' for Placebo group.

- Treatment compliance (%) = _____ *100

*Total number of capsules = number of dose administered days * 2 (2 capsules per day, 30 mg each)*

- Treatment Duration (days) = (Date of Last Dose – Date of First Dose) + 1

10.15 Efficacy Endpoints

10.15.1 NPRS Mean Scores

NPRS mean daily score ranging from 0 (no pain) to 10 (worst imaginable pain) will be derived at baseline and weeks 1 to 4 for each treatment period. Baseline mean score is defined in Section 10.12.2. The mean daily pain score each week during treatment is the arithmetic mean of the last 5 available ratings of daily pain recorded in each 7 day period within each treatment period. Standard deviations (SD) of the mean scores will be included in analyses datasets. If a subject has <5 non-missing ratings, the mean score will be set to missing for the respective week.

10.15.2 Short form BPI

Short form BPI total mean score ranging from 0 (does not interfere) to 10 (completely interferes) is the arithmetic mean of seven items. No correction will be done for missing data if the subject has omitted a few items. Mean scores will be calculated on the available items.

10.15.3 SF-MPQ-2

SF-MPQ-2 total mean score is the arithmetic mean of available scores ranging from 0 (no pain) to 10 (worst imaginable pain). No correction will be done for missing data if the subject has omitted a few items. Mean scores will be calculated on the available items.

10.15.4 NPSI

NPSI total score is the sum of the scores of the 10 descriptors ranging from 0 (no pain) to 100 (worst imaginable pain). The total score will not be calculated if data is missing in at least one of the subscales.

10.15.5 BDI-II

BDI-II total score is the sum of the scores of the 21 items ranging from 0-63. The total score will not be calculated if data is missing in at least one of the subscales. Total score of 0–13 is considered minimal range, 14–19 is mild, 20–28 is moderate, and 29–63 is severe.

10.16 Analysis Flags

10.16.1 Responder

Subjects achieving $\geq$ 30% and $\geq$ 50% reduction in mean NPRS score from baseline to the end of 4 weeks treatment in each study period will be separately flagged for analysis. Subjects who achieved the reduction will be flagged as '1' and who did not will be flagged as '2'.

10.16.2 Maximum Reduction

For NPRS scores, maximum reduction from baseline (that is, maximum negative change from baseline) for a subject within each study period will be flagged. Time to maximum change in days and week at which maximum reduction was attained will be included.

10.16.3 Baseline NPRS Variability

Baseline NPRS mean score will be recorded along with the respective standard deviations for each subject. Subjects will be sorted by SD (highest to lowest) for the first baseline results. Subjects having variability in quartiles 1 to 3 (i.e., 75%), will be flagged for analysis (i.e. subjects with the 25% most variable baseline results for treatment period 1 will be excluded).

11 Statistical Analyses

Summaries will be based on treatment sequence for the following:

- Subject Disposition
- Demographic and Baseline Characteristics
- Prior Medications
- Medical / Surgical History

"Total" columns will be included in these summaries. For all other analyses, summaries will be based on treatment overall and within study periods.

Following conventions will be used for the choice of treatment sequence / group in summaries:

- FAS Population – Planned treatment sequence / group
- Safety Population – Actual treatment sequence / group
- Per-protocol Population – Actual treatment sequence / group
- [redacted] Actual treatment sequence / group

Analysis of Plasma concentration and Pharmacokinetic data will be done separately, and not included in this Statistical Analysis Plan.

11.1 Subject Disposition

Following categories will be summarized in subject disposition table:

- Subjects enrolled (who met all the inclusion criteria and none of the exclusion criteria) – frequency (n)
- Subjects in FAS population – frequency (n)
- Subjects in Safety Population – frequency (n) and percentage (%) based on FAS
- Subjects in Per-Protocol Population – frequency (n) and percentage (%) based on FAS

- Subjects in [redacted] – frequency (n) and percentage (%) based on FAS
- Subjects completed the study, subjects who attended each visit within each study period frequency (n) and percentage (%) based on FAS
- Subjects who terminated the study along with reasons - frequency (n) and percentage (%) based on FAS
- Study duration in days – n, mean and standard deviation, median, minimum, maximum

Note that FAS population will be displayed by planned treatment sequence and all other categories will be displayed by actual treatment sequence. Reasons for discontinuation will be sorted by descending order of frequency within the "Total" column.

In DDP: Table 14.1.1.1

Subject disposition, analysis populations, status of inclusion/exclusion criteria, subjects excluded from analysis population along with reasons and unblinding details will be listed by subject. In DDP: Listing 16.2.1.1, Listing 16.2.1.2, Listing 16.2.1.3 and Listing 16.2.3.1

11.2 Protocol Deviations

Number and percentage of subjects with any deviation and number of deviation events will be summarized by treatment within each study period. The same will be sub-classified by category (major/minor) and description as follows:

- Inclusion / Exclusion
- Investigational Product
- CCMeds
- Lab
- Visit Schedule
- Procedures / Tests
- Randomisation
- Safety Reporting
- Protocol Specific Discontinuation Criteria
- Other

Deviation categories will be displayed in the descending order of frequency of total number of deviations in LAT8881 group (both study periods). Percentages will be based on Safety population. Protocol deviations occurring between screening and washout periods will be counted in Period 1, and those occurring between second baseline period until follow-up will be counted in Period 2.

In DDP: Table 14.1.2.1

Protocol deviations will be listed by subject.

In DDP: Listing 16.2.2.1

11.3 Demographic and Baseline Characteristics

Demographic and baseline characteristics will be summarized by treatment sequence. Categorical and continuous variables will be provided in the same table. The following variables will be presented: age (years), sex, ethnicity, race, childbearing potential, neuropathic pain history (PHN or DPN), PD-Q (scores and categories). The latest non-missing PD-Q results will be included in this summary.

Percentages for childbearing potential will be based only on the female population. The summary will be repeated for FAS, safety, per protocol and [redacted] (as per ICH E3 Guidelines). In DDP: Table 14.1.3.1 to Table 14.1.3.4

Subject demographics, neuropathic pain history and PD-Q scores and categories will be listed by subject.

In DDP: Listing 16.2.4.1, 16.2.4.3, 16.2.4.4

11.4 Medical History and Concurrent Diseases

The number and percentage of subjects with any medical history and number of mentions will be summarized by treatment sequence. The summaries will be provided by body system class. Body system class will be displayed in the descending order of frequency of number of mentions in "Total" column. Percentages will be based on the safety population. The summary will be repeated for concurrent diseases.

In DDP: Table 14.1.4.1, Table 14.1.4.2

Medical history and concurrent diseases will be listed by subject and body system. In

DDP: Listing 16.2.4.2

11.5 Prior and Concomitant Medications

The number and percentage of subjects who have taken any prior medication and number of mentions will be summarized by treatment sequence. Medications will be classified by Therapeutic Main group (ATC Level 2) and Chemical Subgroup (ATC Level 4). The therapeutic main group and chemical substance group will be displayed in the descending order of frequency of total number of mentions in LAT8881 group (both study periods). Medications will be coded using the World Health Organization's Drug-Dictionary (WHODD) version March 2019 or later. The summary will also be presented for concomitant medications by treatment overall and within each study period separately. The summary by treatment overall will only include both 'Ongoing' and 'New' medications within each treatment and counted once in 'Total' column. Percentages will be based on the safety population.

In DDP: Table 14.1.5.1, Table 14.1.5.2.1, Table 14.1.5.2.2

Prior and Concomitant medications will be listed by subject and therapeutic subgroup. Use of prohibited medications will be recorded as protocol deviations and will be listed in 16.2.2.1.

In DDP: Listing 16.2.4.5

11.5.1 Rescue Medications

Number and percentage of subjects who have taken any rescue medication will be summarized along with cumulative dose (mg) taken by treatment overall and within each study period. Extent of further analyses of rescue medications will be decided during the blinded review meeting.

Rescue medication will be listed by subject. In

DDP: Table 14.1.5.3, Listing 16.2.4.6

11.6 Efficacy Analyses

All Efficacy summaries will be based on the Per-Protocol population and repeated for the FAS population.

11.6.1 Primary Efficacy analyses – Mean daily NPRS scores

11.6.1.1 Descriptive summary

Descriptive summaries of NPRS mean scores, absolute change and % change from baseline results will be presented by treatment overall and within each study period. Visits to be included in this table are: Visit 2/5 (Baseline), Weeks within Study period: Week 1, Week 2, Week 3, Week 4. The summary will be repeated for Per-Protocol and FAS populations.

Daily NPRS scores, mean scores and standard deviation, absolute change and percentage change for each week will be listed for all enrolled subjects.

In DDP: Table 14.2.1.1 to 14.2.1.2, Listing 16.2.6.1.1, Listing 16.2.6.1.2

11.6.1.1.1 NPRS at timepoints

For per-protocol subjects with NPRS collected at timepoints in baseline and week 4 visits, descriptive summaries of NPRS mean scores, absolute change and % change from baseline results will be presented by study period and total including timepoints 0.5, 1, 2, 4 and 6 hours after the dose of IMP at Visit 2/Visit 5 and Visit 4/Visit 7.

In DDP: Table 14.2.1.3

11.6.1.2 Mixed Effect Regression Model

A mixed effects regression model using a covariance pattern will be fitted to the absolute change from baseline mean NPRS scores at weeks 1, 2, 3 and 4 within each treatment period for the PP population. This analysis will provide the results for the primary efficacy endpoint (change from baseline to week 4) and for the secondary endpoint (change from baseline to weeks 1, 2 and 3).

The model will have fixed effects for period, week, treatment and the interaction between week 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.

Least squares means and corresponding 95% confidence intervals (CI) will be presented for the mean change from baseline for LAT8881, Placebo and difference between LAT8881 vs. placebo at each visit.

P-values for testing the null hypothesis that the difference in least squares means between LAT8881 and placebo at each visit is 0 will be declared statistically significant if the p-value < 0.05.

The covariance pattern will take into account the covariance between observations in different treatment periods and the covariance between observations within the same period (i.e between weeks).

[redacted]

```
proc mixed data=<input>;
   class <subject> <study period> <treatment> <week>; model
   <change> = <baseline> <study period> <week> <treatment>;
   random <subject> <subject>*<period>; lsmeans <treatment>
   <week> / pdiff;
run;
```

The model will also be fitted to the absolute change from baseline in mean NPRS ratings for the FAS population. Extent of senstivity analyses of missing data patterns to be undertaken will be decided during the blinded review meeting. In DDP: Tables 14.2.2.1 to 14.2.2.2

11.6.1.2.1 NPRS at timepoints

A mixed effects regression model using a covariance pattern will be fitted to the absolute change from pre-dose NPRS scores at timepoints 0.5, 1, 2, 4 and 6 hours post-dose at baseline and week 4 visits within each study period for the per-protocol subjects with NPRS collected at timepoints in baseline and week 4 visits.

The model will have fixed effects for period, week, timepoint and the interaction between week and timepoint. Pre-dose pain score within each week will be included as a covariate. A random effect for subject will be included to capture the repeated measures nature of the design.

Least squares means and corresponding 95% confidence intervals (CI) will be presented for the mean change from pre-dose for each timepoint at each visit. P-values for testing the null hypothesis that the difference in least squares means across timepoints at each visit will be declared statistically significantd if the p-value < 0.05.

The covariance pattern will take into account the covariance between observations in different treatment periods and the covariance between observations within the same period (i.e between weeks).

[redacted]

```
proc mixed data=<input>;
   class <subject> <timepoint> <week>; model
<change> = <baseline> <week> <timepoint>; random
<subject> <subject>*<week>; lsmeans <timepoint>
<week> / pdiff;  run;
```

In DDP: Tables 14.2.2.3

11.6.2 Secondary Efficacy analyses

11.6.2.1 Percentage change from baseline in mean NPRS scores

The mixed effects regression model fitted to the absolute change from baseline in mean NPRS scores will be fitted to the percentage change from baseline in mean NPRS scores for both the PP and FAS populations. No sensitivity analyses of missing data patterns will be undertaken.

In DDP: Tables 14.2.2.1 to 14.2.2.2

11.6.2.2 Responder analysis

Number and percentage of subjects achieving ≥30% and ≥50% reduction in NPRS mean scores at the end of each treatment period (week 4) will be summarized. Proportions of responders will be compared between LAT8881 vs. Placebo across study periods using McNemar's test. P-values for testing the null hypothesis that there is no difference between LAT8881 and placebo will be reported.

[redacted]
```
proc freq data = <input>;
   table
   <responder>*<treatment>;
   exact mcnem; weight
   <subject>;
run;
```

All analyses mentioned above will be repeated for Per-Protocol and FAS Populations.

In DDP: Table 14.2.3.1 to 14.2.3.2

11.6.2.2.1 Mixed Effects Logistic Regression

A mixed effects logistic regression model, including fixed effect terms study period and treatment and random effect term subject ID will be used to assess the odds of achieving a ≥30% and ≥50% reduction in NPRS mean scores at the end of each treatment period (week 4) with LAT8881 compared to placebo. This will be repeated for Per-Protocol and FAS Populations.

[redacted]
```
proc glimmix data=<input>;
   class <subject> <study period> <treatment> ; model
   <response> (event='1') = <study period> <treatment>
                          / dist=binary link=logit oddsratio;
   random / subject=<subject> ;
run;
```

In DDP: Table 14.2.3.3, 14.2.3.4

11.6.2.3 Maximum change from baseline

Maximum reduction from baseline in NPRS mean scores will be summarized. Number and percentage of subjects will be summarized for the week at which maximum reduction from baseline in NPRS mean scores was reached by treatment overall and within each study period. This will be repeated for Per Protocol and FAS populations.

In DDP: Table 14.2.4.1 to 14.2.4.2

11.6.2.3.1 Mixed Effects Regression Model

Mixed effects regression models will be used to compare the maximum reduction from baseline in NPRS mean scores. The model will have fixed effects for period and treatment. Baseline score within each period by treatment combination and time taken to reach maximum reduction will be included as covariates. A random effect for subject will be included to capture the repeated measures nature of the design. Least squares mean changes from baseline and corresponding 95% CI will be presented for LAT8881, Placebo and the difference between LAT8881 vs. placebo overall. The null hypothesis that the difference in least square mean changes from baseline between LAT8881 and placebo across study periods is 0 will be tested. Statistical significance will be declared if the p-value for the difference between treatments < 0.05. In DDP: Table 14.2.4.3, 14.2.4.4

[redacted]

```
proc mixed data=<input>;
   class <subject> <study period> <treatment>;
   model <maximum reduction> = <baseline> <study period> <treatment> <time
                                                    to maximum reduction>;
   random <subject> <subject>*<period>;
   lsmeans <treatment>/ pdiff;
run;
```

11.6.2.4 Patient reported outcomes

Patient Reported outomes: BPI, SF-MPQ-2, NPSI, BDI-II, PGIC will be considered for secondary efficacy analyses. All analyses will be repeated for Per-protocol and FAS populations.

11.6.2.4.1 Descriptive Summaries

Descriptive summaries of patient reported outcomes (BPI, SF-MPQ-2, NPSI, BDI-II) and absolute change from baseline results will be presented by treatment overall and within each study period. Visits to be included in this table are: Baseline, Week 4.

Descriptive summaries as well as number and percentage of subjects reporting each of the categories in PGIC scale (1 - Substantially worse, 2 - Moderately worse, 3 - Slightly worse, 4 - No change, 5 - Slightly improved, 6 - Moderately improved, 7 - Substantially improved) will be summarized by treatment overall and within each study treatment period.

The summaries will be repeated for Per-Protocol and FAS populations.

In DDP: Tables 14.2.5.1, 14.2.5.2, 14.2.6.1, 14.2.6.2, 14.2.7.1, 14.2.7.2, 14.2.8.1, 14.2.8.2, 14.2.9.1, 14.2.9.2

All patient reported outcomes will be listed.

In DDP: Listing 16.2.6.2 to 16.2.6.6

11.6.2.4.2 Mixed Effects Regression Model

Mixed effects regression models will be used to compare the absolute change from baseline to week 4 for the patient reported outcomes (BPI, SF-MPQ-2, NPSI, BDI-II, PGIC). The models will have fixed effects for period and treatment. Baseline score within each period by treatment combination will be included as a covariate for all endpoints except PGIC. A random effect for subject will be included to capture the repeated measures nature of the design. Least squares mean changes from baseline and corresponding 95% CI will be presented for LAT8881, Placebo and the difference between LAT8881 vs. placebo overall. The null hypothesis that the difference in least square mean changes from baseline between LAT8881 and placebo across study periods is 0 will be tested. Statistical significance will be declared if the p-value for the difference between treatments < 0.05.

In DDP: Tables 14.2.5.3, 14.2.5.4, 14.2.6.3, 14.2.6.4, 14.2.7.3, 14.2.7.4, 14.2.8.3, 14.2.8.4, 14.2.9.3, 14.2.9.4

[redacted]

```
proc mixed data=<input>;
   class <subject> <study period> <treatment>; model
   <change> = <baseline> <study period> <treatment>;
   random <subject> <subject>*<period>; lsmeans
   <treatment>/ pdiff;
run;
Note that, PGIC will not have <baseline> in the model statement.
```

11.6.2.5 NPRS and baseline covariates

The mixed effects linear regression model will be repeated for the change from baseline in NPRS scores by including additional covariate: clinical diagnosis (PHN, DPN). Further analyses will be decided and performed in a post-hoc manner post database lock.

In DDP: Table 14.2.10.1

11.6.3 Exploratory Analyses

11.6.3.1 [redacted]

Descriptive summaries of average [redacted] will be presented by study period at Baseline and week 4 visits for test and control areas. This summary will be based [redacted]

[redacted] will be listed by subject.

In DDP: Table 14.2.11.1, Listing 16.2.6.7

11.6.3.1.1 Mixed Effects Regression Model

Mixed effects regression models will be used to compare the absolute change from baseline to week [redacted] The models will have fixed effects for period and treatment. Baseline 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. Least squares mean changes from baseline and corresponding 95% CI will be presented for LAT8881, Placebo and the difference between LAT8881 vs. placebo overall. The null hypothesis that the difference in least square mean changes from baseline between LAT8881 and placebo across study periods is 0 will be tested. Statistical significance will be declared if the p-value for the difference between treatments < 0.05. [redacted]. See Section 11.6.2.4.2 for SAS program.

In DDP: Table 14.2.11.2

11.6.3.2 NPRS and baseline variability

The model fitted to the change from baseline mean NPRS scores will be repeated by excluding subjects with highly variable baseline NPRS mean scores in first study period for Per-Protocol and FAS populations.

In DDP: Table 14.2.12.1 to 14.2.12.2

11.7 Safety Analyses

All safety summaries will be based on the Safety population Screening visits will not be included in summaries, and will only be listed. Baseline measurements will be summarized under 'PreTreatment' for all safety summaries. EOS / Early Termination visits will be summarized in 'Total' within last treatment taken.

11.7.1 Adverse Events

All adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) version 20.0 or later.

11.7.1.1 Overall Adverse Events

The number and percentage of subjects and number of events will be summarized by treatment overall and within each study period for the following categories:

1. All adverse events reported
2. Treatment emergent adverse events (TEAEs)
3. Serious adverse events
4. Serious treatment-emergent adverse events
5. Related treatment-emergent adverse events
6. Related treatment-emergent serious adverse events
7. Suspected unexpected serious adverse events (SUSARs)

8. Treatment-emergent adverse events led to death

9. Treatment-emergent adverse events led to study discontinuation

In DDP: Table 14.3.1.1.1, Table 14.3.1.1.2

The summary by treatment overall will only include 'New' events within each treatment. All adverse events will be listed by subject, system organ class and preferred term sorted by event start dates.

In DDP: Listing 16.2.7.1 to 16.2.7.5

11.7.1.2 Summary of Adverse Events by SOC and PT

The number and percentage of subjects and number of events will be summarized by treatment overall and within each study period, system organ class and preferred terms. The summary by treatment overall will only include both 'Ongoing' and 'New' AEs within each treatment and counted once in 'Total' column. Percentages will be based on the safety population. System organ class and preferred term will be displayed in the descending order of frequency of total number of events in LAT8881 group (both study periods).

The same will be for treatment-emergent AEs, treatment-emergent related AEs, treatment-emergent serious AEs and treatment-emergent related serious AEs. In DDP: Table 14.3.1.2.1 to Table 14.3.1.5.2

11.7.1.3 Summary of Adverse Events by SOC, PT and Severity

The number and percentage of subjects and number of events in each system organ class, preferred term and severity (Grades 1-5) will be summarized by treatment overall and within each study period for treatment-emergent adverse events. Adverse events that are possibly, probably, definitely related and unrelated will be displayed in columns. System organ class and preferred term will be displayed in the descending order of frequency of total number of events in LAT8881 group (both study periods). In DDP: Table 14.3.2.1.1, Table 14.3.2.1.2

11.7.2 Laboratory Assessments

11.7.2.1 Continuous Summary

Descriptive summaries of the absolute result and change from baseline in laboratory data will be presented by treatment overall and within each study period, parameter and visit for the safety population. Each laboratory category (haematology, clinical chemistry, liver function tests, coagulation, urinalysis) will be represented in separate tables. Both categorical and continuous results will be presented in the same table for urinalysis.

In DDP: Table 14.3.4.1 to Table 14.3.4.5

11.7.2.2 Shift Summary

Shift in laboratory result interpretations (Normal, Abnormal Not CS and Abnormal CS) will be summarized by treatment within each study period and overall, parameter and visit. Each category (haematology, clinical chemistry, liver function tests, coagulation) will be represented in separate tables. Percentages will be based on safety population.

In DDP: Table 14.3.4.6 to 14.3.4.9

11.7.2.3 Listings

All laboratory results will be listed for all subjects by treatment sequence, visit and parameter. Out of range results will be highlighted. Pregnancy results collected on Screening and Day 1 will be listed separately.

In DDP: Listing 16.2.8.1 to 16.2.8.5, Listing 16.2.8.7

Subjects with clinically significant laboratory results and subjects with out of range results will be separately listed by treatment sequence, category, visit and parameter. In DDP: Listing 16.2.8.6

Parameters collected in each laboratory category are listed below.

Category	Parameters
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
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.
Liver Function Tests	Aspartate aminotransferase, alanine aminotransferase, gammaglutamyl transferase, alkaline phosphatase, conjugated bilirubin, total bilirubin
Coagulation	Activated partial thromboplastin time, international normalised ratio
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.
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.

11.7.3 Other Safety Analyses

11.7.3.1 Extent of Exposure

Continuous summary statistics will be displayed for duration of exposure in days, total IMP administered in mg and % compliance by treatment overall and within each study period. The summary will be based on the Safety population. In DDP: Table 14.1.5.4

IMP administration and compliance data will be listed by treatment sequence, subject and treatment period for safety population. In DDP: Listing 16.2.5.1

11.7.3.2 Vital Signs

Descriptive summaries of absolute results and change from baseline in vital signs will be presented by treatment overall and within each study period, parameter, visit and timepoint (if applicable) for safety population. Vital signs parameters include: weight (kg), BMI (kg/m^2), systolic blood pressure (mmHg), diastolic blood pressure (mmHg), respiratory rate (breaths/min), heart rate (beats/min) and body temperature (^oC).

In DDP: Table 14.3.5.2

Vital signs will be listed by treatment sequence, subject ID, treatment period and visit for safety population.

In DDP: Listing 16.2.9.1

11.7.3.3 Physical Examination

Physical examination data will be listed by treatment sequence, subject, treatment period and visit only.

In DDP: Listing 16.2.9.2

11.7.3.4 Electrocardiogram Assessments

Number and percentage of subjects with overall findings (Normal, Abnormal Not CS and Abnormal CS) will be summarized by treatment overall and within each study period and visit. Percentages will be based on safety population.

In DDP: Table 14.3.6.1

ECG findings will be listed by treatment sequence, subject ID, treatment period and visit.

In DDP: Listing 16.2.9.3

12 Changes to Planned Analyses

- Mixed Effect Regression analyses for change from baseline in NPRS mean scores is combined for weeks 1-4 within the same model, instead of week 4 and weeks 1-3 separately as defined in study protocol.
- McNemar's test is included to compare proportion of subjects achieving $\geq$30% and $\geq$50% reduction in mean NPRS scores across study periods.
- Analysis of covariance is included to see the effect of treatment and placebo in maximum reduction from baseline adjusting for baseline NPRS mean scores and time taken to reach maximum reduction.
- Mixed Effect Regression analyses for change from baseline in NPRS mean scores including clinical diagnosis (PHN, DPN) and baseline [redacted] as additional covariates is

considered as secondary analyses instead of exploratory analyses since subgroups PHN and DPN were considered clinically relevant.

- PK Analyses is not included in this Statistical Analysis Plan, and will be done separately. PK Population is replaced with Per-Protocol population for subjects with NPRS assessments taken at timepoints in baseline and Week 4 visits.

13 Index of Tables, Listings and Graphs

Refer LAT-NP-001_Data Display Plan (Ver: 2.00) for the list of Tables, Listings and Graphs.

14 References

1. ICH. ICH Harmonized Tripartite Guideline: Statistical Principles for Clinical Trials E9. 1998.
2. ICH. ICH Harmonized Tripartite Guideline: Structure and Content of Clinical Study Reports E3. 1995.

15 Appendices

15.1 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. 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.

15.2 [redacted]

[redacted] *will be undertaken by a researcher specifically trained in this procedure at sites which have experience in the technique.* [redacted].

[redacted]

[redacted]

[redacted]

[redacted]

15.3 Pain intensity

15.3.1 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. 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.

15.4 Patient reported outcomes

15.4.1 Short form BPI

The interference scale of the short form BPI has been recommended by international consensus 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.

15.4.2 SF-MPQ-2

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

15.4.3 NPSI

The NPSI was designed specifically for the assessment of the different symptoms of neuropathic pain. 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.

15.4.4 BDI-II

The BDI-II 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.

15.4.5 PGIC

The PGIC is a single-item rating by subjects of their improvement with treatment during a clinical trial. 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.

16 Change Log

Version	Authored by	Change Date	Change Details	Reviewed by	Review Date
1.00	[redacted]	09-Mar-2019	Final draft for sponsor review	[redacted]	14-Nov-2019
2.00	[redacted]	24-May-2020	Amended to remove PK population and re-define analysis visits	[redacted]	27-May-2020