Official title: A proof of concept study of the efficacy and safety of oral LAT8881 in acute migraine

NCT number: NCT04153409

Document date: February 27, 2020

Statistical Analysis Plan

Sponsor Name	Lateral Pharma Pty Ltd
Protocol ID	LAT-MIG-001
Protocol Version	1.0 (dated 25 July 2019)
Study Name	LAT-MIG-001
Study Title	A proof of concept study of the efficacy and safety of oral LAT8881 in acute migraine
CRF Version	Metadata version 1.1
Document ID	LAT-MIG-001_Statistical Analysis Plan
Document Version	1.00

[redacted]

	Signature	Date
Author:	[redacted]	

Reviewer:

[redacted]

Approver:	[redacted]

Table of Contents

1 Definitions 6

2 Introduction 7

2.1 Background 7

2.2 Rationale 7

3 Study Objectives 8

3.1 Primary Objective 8

3.2 Secondary Objectives 8

3.3 Exploratory Objectives 8

4 Study Design 8

4.1 Overview 8

4.2 Sample Size Justification 9

4.3 Randomisation and Blinding 9

4.4 Inclusion/Exclusion Criteria 10

4.4.1 Inclusion Criteria: 10

4.4.2 Exclusion Criteria: 11

4.5 Treatment allocation 12

5 Assessment Schedule 13

6 Interim Analysis 15

7 Efficacy and Safety Endpoints 15

7.1 Primary Efficacy Endpoints 15

7.2 Secondary Efficacy Endpoints 15

7.3 Safety Endpoints 15

7.4 Exploratory Endpoints 15

8 Statistical Methods 16
8.1 Changes to Planned Analyses 16
8.2 Handling Missing/Incomplete Data 17
8.3 Handling Outliers 17
8.4 Multiplicity Adjustment 17
9 Analysis Populations 17
9.1 Full Analysis Set (FAS) 17
9.2 Per Protocol (PP) Population 17
9.3 Safety Population 18
10 Analysis Variables 18
10.1 Population Flags 18
10.2 Treatment groups 18
10.3 Visits 18
10.4 Study Periods 19
10.5 Completion Flags 19
10.6 Study Duration 20
10.7 Migraine History 20
10.8 Medical History and Concurrent Diseases 20
10.9 Prior and Concomitant Medications 20
10.10 Adverse Event Flags 21
10.11 Laboratory Assessments 22
10.12 Baseline 22
10.12.1 Safety Endpoints 22
10.12.2 Efficacy Endpoints 22
10.13 Change from Baseline 22
10.14 Extent of Exposure 22
10.15 Analysis Flags 22

10.15.1 Difference between Treatments 22
10.15.2 Sustained Pain-Free 23
10.15.3 Time Deviated from Scheduled Timepoints 23
10.15.4 Responder 23
10.15.5 Time to First Pain-Free Timepoint 23
10.16 Paired Difference in Pain-Free Subjects 23
10.17 Preferred Treatment 24
10.18 Subgroups for exploratory analysis 24
11 Statistical Analyses 25
11.1 Subject Disposition 25
11.2 Protocol Deviations 26
11.3 Demographic and Baseline Characteristics 26
11.4 Migraine History 27
11.5 Medical/Surgical History 27
11.6 Prior and Concomitant Medications 27
11.7 Extent of Exposure 28
11.8 Efficacy Analyses 29
11.8.1 Primary Efficacy analyses – NRS Pain Scores 29
11.8.1.1 Descriptive summary 29
11.8.1.2 Time-Trend Plots 29
11.8.1.3 Mixed Effect Regression Model for repeated measurements (MMRM) 30
11.8.2 Secondary Efficacy Analyses 31
11.8.2.1 NRS Symptom Scores 31
11.8.2.2 Time-Trend Plots 31
11.8.2.3 Most Troublesome Symptom 31
11.8.2.4 Time-Trend Plots 32
11.8.2.5 No Headache Pain 32
11.8.2.6 Migraine and Headache Diary 33
11.8.3 Exploratory Analysis 33

11.8.3.1 Sustained Pain-free at 24 Hours 33
11.8.3.2 Time to First Pain-free Timepoint 33
11.8.3.3 Subject Satisfaction Survey 33
11.8.3.4 Association between Change in NRS Pain Score and Baseline Characteristics 34
11.9 Safety Analyses 35
11.9.1 Adverse Events 35
11.9.1.1 Overall Adverse Events 35
11.9.1.2 Summary of Adverse Events by SOC and PT 36
11.9.1.3 Summary of Treatment emergent Adverse Events by SOC, PT, Relationship and Severity 36
11.9.2 Laboratory Assessments 36
11.9.2.1 Continuous Summary 36
11.9.2.2 Listings 36
11.9.3 Other Safety Analyses 37
11.9.3.1 Vital Signs 37
11.9.3.2 Physical Examination 38
11.9.3.3 Electrocardiogram Assessments 38
11.9.3.4 Telephone Visits 38
12 Index of Tables, Listings and Graphs 38
13 References 38
14 Appendices 38
15 Change Log 39

1 Definitions

Abbreviation	Definition
ADR	Adverse Drug Reaction
ATC	Anatomical Therapeutic Chemical Classification
BMI	Body Mass Index
CI	Confidence Interval
CS	Clinically Significant
DDP	Data Display Plan
AE	Adverse Event
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
EOS	End of Study
FAS	Full Analysis Set
ICH	International Conference on Harmonisation
IMP	Investigational Medicinal Product
LSMeans	Least Square Means
Max	Maximum
MedDRA	Medical Dictionary for Regulatory Activities
Min	Minimum
MMRM	Mixed Model for Repeated Measures
NRS	Numeric Rating Scale
NTF	Note-to-File
PP	Per Protocol
PT	Preferred Term
SAE	Serious Adverse Event

SAP	Statistical Analysis Plan
SD	Standard Deviation
SOC	System Organ Class
SUSAR	Suspected Unexpected Serious Adverse Reaction
TEAE	Treatment Emergent Adverse Event
WHODD	World Health Organization Drug Dictionary

2 Introduction

2.1 Background

Migraine is a disabling neurovascular disorder, characterised by moderate to severe headaches which are usually throbbing, affect one side of the head and are accompanied by nausea and sensitivity to light and/or sound. It is one of the most common chronic conditions worldwide.

The most common migraine types are migraine without aura (common migraine) and migraine with aura (classic migraine).

Migraine without aura is identified by headache symptoms lasting 4–72 hours, commonly with a unilateral location, pulsating quality of moderate or severe intensity, aggravated by routine physical activity and associated with nausea and/or light and sound sensitivity. Diagnosis is based on at least five attacks.

Migraine with aura is identified by recurrent attacks, lasting minutes, of unilateral fully reversible visual, sensory or other central nervous system symptoms that usually develop gradually and are commonly followed by headache and associated migraine symptoms. Diagnosis of migraine with aura requires at least two such attacks.

This is the first clinical study with LAT8881 in migraine and will assess its potential for treating acute migraine in a proof of concept trial.

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 (previously known as AOD9604) and subsequently its efficacy in the treatment of obesity [redacted].

A seventh study (LAT-NP-001) to investigate the safety and efficacy of LAT8881 in neuropathic pain at a dose of 60 mg per day (30 mg twice daily) has recently commenced and is recruiting subjects. No results from this study are yet available.

In all development studies for obesity, 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.

3 Study Objectives

3.1 Primary Objective

To evaluate the effect of oral LAT8881 on migraine headache compared with placebo, when assessed by the headache severity on an 11-point Numeric Rating Scale (NRS)

3.2 Secondary Objectives

1. *To evaluate the effect of oral LAT8881 on migraine-associated symptoms compared with placebo, when assessed by the change in symptoms based on a 11- point Likert scale*
2. *To investigate the percentage of subjects achieving "no headache pain" following treatment with oral LAT8881 compared with placebo at any timepoint to 8 hours post dose, with no use of rescue medication*
3. *To evaluate the safety and tolerability of single doses of oral LAT8881 in subjects with migraine headache*

3.3 Exploratory Objectives

1. *To investigate the percentage of subjects who are "sustained pain-free," defined as having no headache pain following treatment with oral LAT8881 for a migraine headache compared with placebo, with no use of rescue medication and no relapse of headache pain within 24 hours (24-hour sustained pain-free) after administration*
2. *To investigate the time to first pain-free timepoint following treatment with oral LAT8881 for a migraine headache compared with placebo to 24 hours post dose, with no use of rescue medication*
3. *To determine the need for extra analgesic (rescue) medication after treatment with oral LAT8881 administration for a migraine headache, compared with placebo*
4. *To investigate subject satisfaction with treatment of a migraine headache*
5. *To investigate other factors influencing the extent of change in pain score and symptom scores in subjects with migraine headaches*

4 Study Design

4.1 Overview

This is a randomised, placebo-controlled, double-blind, crossover, Phase IIa proof of concept study to investigate the efficacy and safety of oral LAT8881 in acute migraine headache with or without aura.

During the screening period, potential subjects will keep a diary to record onset and duration of headaches, including pain and symptom scores and concomitant medications over a 4-5 week period.

Females of childbearing potential will also record menstrual cycles. Subject will nominate their most troublesome symptom.

Subjects entered into the study will be randomised to receive IMP (LAT8881 60 mg or placebo), to be taken at the onset (within one hour from the onset of pain) of a migraine headache of moderate to severe intensity [Numeric rating scale (NRS) ≥4]. Rescue medication should not be taken until at least 2 hours post dose. Subjects will be given one dose of IMP (2 capsules), to treat one migraine headache.

Subjects will complete diaries to record menstrual cycle (in menstruating females), onset and nature of migraine and non-migraine headaches, pain scores at time of IMP dosing and various time points post dose, associated symptoms and rescue medication. Adverse events will be monitored.

After treatment of one migraine headache (or a maximum 28 days) the subject will return to the clinic for re-evaluation and crossover to the second treatment. In the second treatment period, they will take IMP in the same manner as in treatment period 1.

A followup (End of study) visit will occur within 7 days after treatment of one migraine headache in the second treatment period or a maximum 8 weeks from randomisation.

Subjects will complete diaries to record menstrual cycle (in menstruating females), onset and nature of migraine and non-migraine headaches, pain scores at time of IMP dosing and various time points post dose, associated symptoms and rescue medication. Adverse events will be monitored.

4.2 Sample Size Justification

It is planned to have 20 subjects complete the study, defined as taking one dose of IMP in each treatment period and attending the follow-up (End of study) visit.

Assuming up to 20% of subjects do not treat one migraine headache in each treatment period or dropout of the study, 26 subjects will be enrolled in the study.

If the dropout rate or non-completion rate is higher than anticipated, additional subjects may be enrolled to ensure 20 subjects complete the study.

4.3 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.

Details regarding randomisation are provided in the [redacted] and instructions for unblinding are 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. *Males or females aged 18 to 75 years at the time of consent*
2. *Diagnosis of episodic migraine headache at least 12 months ago with or without aura as defined in ICHD-3-beta*
3. *Onset of migraine headache before age 50*
4. *Medical history of 2 - 8 migraine headache attacks per month for the previous 12 months; ≥ 75% of attacks progress to moderate or severe pain within 2 hours (i.e., rapidly-escalating)*
5. *Minimum 48 hours on average between migraine headache attacks*
6. *Acute headache medication on ≤ 14 days/month in the 3 months prior to screening*
7. *Willing and able to comply with all study procedures including completion of a headache diary and a migraine diary on the day of a migraine headache*

8. *Female subjects must be:*

    a) *of non-child-bearing potential [surgically sterilised or postmenopausal (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*

9. *Male subjects with female partners of childbearing potential must use adequate and highly effective methods of contraception, from screening until 28 days after their last IMP administration.*

10. *Subjects must be sufficiently competent in English to understand the purposes and risks of the study and to provide written informed consent*

4.4.2 Exclusion Criteria:

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

1. *Unable to distinguish migraine from other primary headache conditions*

2. *Average of 15 or more headache (migraine or non migraine) days per month or history of more than 25% of headaches occurring at time of wakening (wake up headaches)*

3. *History of aura lasting more than 60 minutes*

4. *History of vomiting within 2 hours of onset of a migraine headache in more than 25% of migraine headaches*

5. *Medication overuse headache, defined as:*

    a. *use of opioids, triptans or ergot alkaloids or any combination of these medications for treatment of headaches 10 or more days per month during the 90 days prior to screening OR*

    b. *Non-steroidal anti-inflammatory drugs (NSAIDs) or simple analgesics for treatment of headaches on more than 14 days per month during the 90 days prior to screening*

6. *Recent (3 years) history of frequent or chronic hemiplegic/ basilar migraine, tension headache, retinal migraine, ophthalmoplegic migraine as per ICHD classification, or treatment resistant atypical migraine*

7. *Hospital admission for status migrainosis or medication overuse headache within 6 months of screening*

8. *Current clinically significant systemic disease or neurological or psychiatric condition which in the opinion of the investigator or sponsor could jeopardise the safety of the subject or the validity of the study results*

9. *Cerebrovascular disease, including but not limited to a history of stroke or recent (3 years) transient ischaemic attack (TIA)*

10. *Major surgery within 6 weeks of screening or planned during the study period*

11. *Clinically significant abnormality as assessed by the investigator or sponsor's medical monitor on haematology, biochemistry, vital signs, physical examination or 12-lead electrocardiogram (ECG)*

12. *Malignancy within 5 years of screening, with the exception of carcinoma in situ, nonmelanoma skin cancers and prostate cancer not requiring treatment or on stable (> 6 months) treatment with hormone therapy*

13. *History of alcohol abuse, illicit or illegal drug use in the last 2 years*

14. *Use of Prohibited medications or treatments within the specified time period before Screening or planned during the study*

15. *Participation in another clinical trial or administration of any investigational product or experimental product within 60 days or 5 half-lives (whichever is longer)*

16. *History of significant hypersensitivity to LAT8881 (formerly known as AOD9604), excipients in the drug product formulation or drugs of a similar chemical or pharmacological class.*

17. *Surgical or medical conditions which could significantly alter drug absorption, distribution, metabolism or excretion*

18. *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*

4.5 Treatment allocation

Subjects entered into the study will be randomised to receive IMP (LAT8881 60 mg or placebo), to be taken at the onset (within one hour from the onset of pain) of a migraine headache of moderate to severe intensity.

After treatment of one migraine headache (or a maximum 28 days) the subject will return to the clinic for re-evaluation and crossover to the second treatment.

5 Assessment Schedule

	Screening	Treatment period 1			End of period 1	Treatment period 2			End of period 2, early withdrawal	End of study
Visit no	1	2			3				4	5 (phone)
Study day	-28 to -1 (+7days)	1	Telephone (if required)	Headache episode	29 ± 2[1]		Telephone (if required)	Headache episode	57 ± 2[1]	64 ± 2[2]
Written informed consent	X									
Eligibility assessment	X									
Confirmation of eligibility		X								
Enrolment and randomisation		X								
Medical history, demographics	X									
Height and weight	X									
12 lead ECG	X	X			X				X	
Pregnancy test[3]	X	X				X				
Vital signs	X	X			X				X	
Physical examination	X[4]	X[5]			X[5]				X[5]	
Clinical laboratory safety testing[6]	X	X			X				X	
Concomitant medications	X	X	X	X	X		X	X	X	X
IMP issued		X				X				
IMP administration[7]				X				X		
Adverse event assessment			X		X		X		X	X
Headache diary[8]	X			X				X	X	
Migraine diary[9]	X			X				X		
Patient satisfaction survey					X				X	

1 Or maximum 5 business days after dose of IMP
2 Or 7 days after Visit 4
3 Females of childbearing potential only, blood test at screening, urine other occasions

[redacted]

4 Full physical examination
5 Targeted physical examination
6 Haematology, biochemistry, urinalysis
7 Migraine episode only
8 Headache diary during both non-migraine and migraine headaches
9 Migraine diary, during migraine headaches

[redacted]

[redacted]

6 Interim Analysis

No interim analysis planned for this study.

7 Efficacy and Safety Endpoints

7.1 Primary Efficacy Endpoints

Change in migraine headache pain score, using an 11-point NRS, (0 = none, 10 = worst imaginable), from the time of dosing to 0.5, 1.0, 1.5, 2, 4, 8 and 24 hours post dose. Pain is recorded in a subject diary and should reflect the subject's pain at the time of recording.

7.2 Secondary Efficacy Endpoints

1. *Change in migraine-associated symptoms of nausea, photophobia and phonophobia. Symptoms are assessed on an 11- point Likert scale with 0 = no symptoms and 10 being severe symptoms at time of dosing and at 0.5, 1.0, 1.5, 2, 4, 8 and 24 hours post dose.*
2. *Change in each subject's most troublesome symptom that may include nausea, photophobia and phonophobia cognitive impairment, dizziness and functional disability. Symptoms are assessed on an 11- point Likert scale with 0 = no symptoms and 10 being severe symptoms at time of dosing and at 0.5, 1.0, 1.5, 2, 4, 8 and 24 hours post dose.*
3. *The percentage of subjects achieving "no headache pain" at 0.5, 1.0, 1.5, 2, 4 and 8 hours post dose.*

7.3 Safety Endpoints

1. *Changes in physical examinations and vital signs*
2. *Changes in clinical laboratory tests*
3. *Percentage of Treatment emergent adverse events (TEAEs), including serious adverse events (SAEs), and suspected unexpected serious adverse reactions (SUSARs)*
4. *Changes in concomitant medications*

7.4 Exploratory Endpoints

1. *The percentage of subjects who are "sustained pain-free," defined as having no migraine headache pain at 24 hours, with no use of rescue medication and no relapse of headache pain within 24 hours (24-hour sustained pain-free) after administration*
2. *The time to first pain-free timepoint following treatment with oral LAT8881 compared with placebo to 24 hours post dose, with no use of rescue medication*
3. *Supplemental analgesic medication use in the 24 hour post treatment period*
4. *Subject satisfaction with each treatment based on a 7-point Likert Scale, overall preference for Treatment 1 or Treatment 2, and historical comparison with usual treatment*

5. *Association between change in headache pain and symptom scores and selected subject baseline characteristics, including for example, migraine with/without aura, relationship to menstrual cycle*

8 Statistical Methods

Efficacy endpoints will be summarised in a descriptive manner and analysed using statistical methods described in section 11.8. Changes over time for the primary and secondary efficacy outcomes will be explored using a statistical model as defined in Section 11.8. The level of significance for any statistical tests undertaken will be 0.05 and all tests will be two-sided. Any 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 (version 9.4, SAS Institute Inc., Cary, NC, USA).

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 the 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 Changes to Planned Analyses

The protocol states that, as this study is a Phase IIa proof of concept study, no formal statistical hypotheses are planned to be tested although some may be investigated as part of the data presentation. It was expected that treatment effects would be assessed using descriptive statistics only and hypothesis tests used minimally.

However, by allowing subjects to be included in the Per Protocol population with a minimum of one dose of IMP, there is a possibility that subjects will be included with efficacy results for only one treatment period and unable to have an estimate of the difference between treatments. Hence, fewer subjects will be included in the summary results and any analyses for the difference between treatments.

In order to include the results for all subjects regardless of whether they took IMP in only one or both treatment periods a mixed effects model with repeated measurements (MMRM) analysis can be undertaken. This approach will be taken for the change from baseline NRS pain score to each postbaseline timepoint for each treatment only.

The remaining endpoints of a continuous nature (change from baseline NRS symptom score, change from baseline NRS symptom score for the most troublesome symptom, subject satisfaction with IMP, subject satisfaction with IMP compared with usual medication for an acute migraine attack) may be analysed using the MMRM approach depending on the number of subjects who complete both treatment periods. The decision will be made at the blind review meeting prior to database lock.

8.2 Handling Missing/Incomplete Data

Partial dates will not be imputed.

Flags identifying the study period for the start/stop dates for prior/ concomitant medications and adverse events will be generated (see Sections 10.9 and 10.10).

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

8.3 Handling Outliers

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

8.4 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 will be performed 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 finalised during the blind review of the data conducted prior to database lock.

9.1 Full Analysis Set (FAS)

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 (PP) Population

The Per Protocol (PP) population will include all subjects who received at least one dose of IMP and excludes subjects who have any major protocol deviation 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 the blinded review meeting prior to database lock.

A per-protocol (PP) population will be used for efficacy analyses and to analyse exploratory endpoints.

9.3 Safety Population

The safety population consists of all randomised subjects who receive at least one dose of IMP.

The safety population will be used for the analysis of safety and tolerability data. Subjects will be analysed as treated, regardless of the randomised treatment assigned, if this differs from that to which the subject was randomised.

10 Analysis Variables

10.1 Population Flags

Population flags will be finalised and authorised 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 groups

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:

Visit as per CRF	Study Period	Analysis Visit
Visit 1 (Days -28 to -1)	-	Visit 1 (Screening)
Day 1, Visit 2	Period 1	Visit 2
Day 15, Telephone Visit 1	Period 1	-
Day 29, Visit 3	Period 1	Visit 3
Day 44, Telephone Visit 2	Period 2	-
Day 57, Visit 4	Period 2	Visit 4
Day 64, Visit 5 or Early Termination	Period 2	Visit 5 (End of Study)

Analysis timepoints for efficacy endpoints within each study period will be defined as follows:

Timepoint as per CRF	Analysis Timepoint
Before IMP was taken (Pre-dose)	Pre-dose
30 minutes after IMP taken (t=0.5 hrs)	30 minutes
1 hour after IMP taken (t=1 hr)	1 hour
1.5 hours after IMP taken (t=1.5 hrs)	1.5 hours
2 hours after IMP taken (t=2 hrs)	2 hours
4 hours after IMP taken (t=4 hrs)	4 hours
8 hours after IMP taken (t=8 hrs)	8 hours
24 hours after IMP taken (t=24 hrs)	24 hours

10.4 Study Periods

- Screening: Day -28 to Day -1
- Period 1: Visit 2 to Visit 3
- Period 2: Day after Visit 3 to Visit 5*

*Subjects who had a migraine event and took period 2 dose of IMP on the same day as Visit 3 will be identified and study periods for such subjects will be defined in the blinded review meeting.

Study periods for adverse events and concomitant medications will be assigned as below. •

Pre-IMP: Screening to first dose of IMP (irrespective of study period)

- Period 1: IMP date at period 1 to IMP date at period 2.
- Period 2: On and after IMP date at period 2.

Study periods will be considered to set analysis visits.

10.5 Completion Flags

- Subjects are considered to have completed period 1 when Visit 3 is completed.
- Subjects are considered to have completed period 2 when Visit 4 is completed.
- Subjects are considered to have completed study when EOS at Visit 5 is completed.

10.6 Study Duration

Study duration will be calculated as,

Study Duration (days) = (Date of EOS / Early Termination visit – Date of Informed Consent) + 1.

10.7 Migraine History

Time since migraine diagnosis (years) = (Informed consent date – date of migraine diagnosis)+1/365.25.

10.8 Medical History and Concurrent Diseases

Medical history with an end date prior to Visit 2 will be considered as medical history.

Medical history with missing end date or ongoing during Visit 2 will be considered as concurrent diseases. Adverse events occurring after Visit 2 and before IMP (Period 1) will also be flagged in the analysis datasets and summarised as concurrent diseases.

10.9 Prior and Concomitant Medications

Medications will be summarised by the study periods below: •

Prior: Pre-Day 1

- Concomitant:
  - Pre-IMP
  - Post-IMP: LAT8881 60 mg and Placebo

Study Period	**Rule**
Prior	Medications that started and ended before Visit 2.
Pre-IMP	Medications that are ongoing on or after Visit 2 but before any dose of IMP (LAT8881 or placebo) irrespective of study periods.
Post-IMP: LAT8881 60 mg and Placebo	Period 1: Medications that are ongoing on or after dose of IMP (LAT8881 or placebo) in period 1 but before IMP in period 2. Period 2: Medications that are ongoing on or after dose of IMP (LAT8881 or placebo) in period 2.

If a subject has ongoing medication in more than one study period, then the use of that medication will be counted in all applicable study periods. New medications added in the corresponding study period and medications that are ongoing from the previous study period will be flagged and summarised separately within each study treatment.

If the medication is started on the same day of IMP dosing, but timing of onset of event in relation to IMP dosing is not clear, then, the worst case will be considered (Post-IMP). This will also be raised to

the site and if this is confirmed to be before dose then a note to file (NTF) will be created stating the same. This will be incorporated into the analysis datasets for analysis purposes.

10.10 Adverse Event Flags

Adverse events will be summarised by the study periods below and flags generated:

- Pre-IMP
- Post-IMP: LAT8881 60 mg
- Post-IMP: Placebo

Study Period	**Rule**
Pre-IMP	AEs started before any dose of IMP (LAT8881 or placebo) irrespective of periods.
Post-IMP: LAT8881 60 mg and Placebo	Period 1: AEs that started on or after dose of IMP (LAT8881 or placebo) in period 1 but before IMP in period 2. Period 2: AEs that started on or after dose of IMP (LAT8881 or placebo) in period 2.

An additional flag will be generated for treatment emergent adverse events (TEAE) if they occurred or worsened on or after the first administration of IMP (LAT8881 or placebo) irrespective of the study period. Adverse events occurring prior to first dose of IMP (LAT8881 or placebo) will not be considered as TEAEs. For example, for subjects who had taken the IMP in period 1, any AE post that dose will be considered as a TEAE regardless of whether it is before or after the dose of IMP in period 2. For subjects who had taken their first dose of IMP in period 2, i.e. did not take IMP during period 1, any AEs post IMP in period 2 will be considered as TEAEs.

If an adverse event occurred in a study period and continues to other study periods, it will be counted in all the applicable study periods. New events occurred in the corresponding study period and events that are ongoing from the previous study period will be flagged and summarised separately within each study treatment.

AEs that are ongoing from the previous period but just change in severity will still be considered as an ongoing AE. This will be identified and manually flagged during the blinded review meeting. AEs that are resolved and restart will be considered as a new event.

If the event occurs on the same day of IMP dosing, but timing of onset of event in relation to IMP dosing is not clear, then, worst case will be considered (Post-IMP). This will also be raised to the site and if this is confirmed to be before dose then a note to file (NTF) will be created stating the same. This will be incorporated into the analysis datasets for analysis purposes.

Related Adverse Events will be flagged for Possibly, Probably and Definitely Related adverse events.

All related SAEs will be considered Suspected unexpected serious adverse events (SUSARs) and included in analyses datasets.

10.11 Laboratory Assessments

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

10.12 Baseline

All analysis datasets containing measurements taken at more than one visit/time point will have baseline flags.

10.12.1 Safety Endpoints

For safety endpoints, measurement taken at Visit 2 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:

In both study periods, for NRS Pain Score and 11 point Likert scale for Symptoms (Nausea, Photophobia and Phonophobia) scores, ‘Pre-dose’ measurement will be considered as baseline.

Patients who reported migraine with missing pre-dose result for NRS or symptom scores will be flagged and discussed during blinded review meeting to define the baseline measurement.

10.13 Change from Baseline

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 Period X, Timepoint Y) – (Period X, Baseline Result)

10.14 Extent of Exposure

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

Total dose administered (mg) = number of capsules consumed by the subject * dose level consumed in mg
Number of capsules consumed will be determined by number of capsules returned at Visit 3 or Visit 4. Each bottle contains 2 capsules, and number of capsules returned will be subtracted to confirm the number of capsules consumed.

10.15 Analysis Flags

10.15.1 Difference between Treatments

For subjects who took IMP in both visits, difference between their scores at each timepoint will be calculated as below.

Difference at timepoint X = Score (LAT8881 60 mg) at Timepoint X – Score (Placebo) at timepoint X.

10.15.2 Sustained Pain-Free

Subjects having no use of rescue medication and no relapse of headache pain within 24 hours after administration of IMP in each period will be separately flagged as 'Sustained Pain-free' for analysis.

10.15.3 Time Deviated from Scheduled Timepoints

Actual time difference from 'Time IMP was taken' to each of the timepoints will be calculated and discussed during blinded review meeting and any analysis flags may be created to exclude the same.

Time deviated (hours) = (Time the corresponding timepoint recorded - Time IMP was taken) / 60.

Time difference between pre-dose measurement and IMP dosing should not be more than 30 mins. This difference will also be highlighted in the blinded review meeting.

10.15.4 Responder

Subjects achieving no migraine headache pain at each time point in each study period will be separately flagged for analysis. Presence or absence of pain will be determined as follows:

- Absence: NRS Pain score 0 or 1 at the corresponding timepoint.
- Presence: NRS Pain score more than 1 at the corresponding timepoint.

10.15.5 Time to First Pain-Free Timepoint

For NRS scores for pain, subjects achieving no migraine headache pain timepoints will be flagged for each subject within each study period. The first pain-free timepoint in which the no migraine (score 0 or 1) achieved will be considered as the time to first pain-free timepoint. Time to first pain-free timepoint will be calculated based on the actual time difference as below.

Time (hours) = (Time the corresponding timepoint recorded - Time IMP was taken) / 60.

Subjects who did not achieve no migraine at 24 hours will be censored at 24 hours.

10.16 Paired Difference in Pain-Free Subjects

Difference between treatments (LAT8881 – Placebo) for No Headache Pain at each timepoint, Sustained Pain-Free at 24 hours and First Pain-Free Timepoint will be calculated as below for the percentage difference; the numerator represents the difference in the number of subjects.

	Placebo		
LAT8881	Pain free	Pain	Total
Pain free	a	b	**a + b**
Pain	c	d	c + d

Total	**a + c**	B + d	a + b + c + d

$$\textbf{\textit{Pain free for placebo}}\ (\%) = \frac{a+c}{a+b+c+d}$$

$$\textbf{\textit{Pain free for LAT8881}}\ (\%) = \frac{a+b}{a+b+c+d}$$

$$\textbf{\textit{Pain free}}\ (\textbf{\textit{LAT8881}} - \textbf{\textit{Placebo}}\ )(\%) = \frac{a+b}{a+c+b+d} \quad \frac{a+c}{a+b+c+d} \quad \frac{b-c}{a+b+c+d} - =$$

10.17 Preferred Treatment

For subject satisfaction score, the preferred treatment will be flagged based on the treatment period and assigned treatment. I.e., If a subject has chosen 'Treatment period 1' as their preferred treatment, then the corresponding treatment group at period 1 will be flagged as their preferred treatment.

10.18 Subgroups for exploratory analysis

Below subgroups will be defined in the analysis datasets and used for the additional exploratory analyses.

- Age at onset: before 15 years and at 15 years or older.

  Age at onset to be calculated as: (Date of episodic migraine diagnosis - Date of birth + 1)/ 365.25.

- Sex group: Male, Female (menstruating), Female (non-menstruating) and Female (postmenopausal)

  For Female subjects, menstruating and non-menstruating will be determined using the start and end dates of the menstrual cycle and the migraine start date. If the migraine start date is between start and end date of menstruation, then the subject will be considered as 'menstruating' and 'non-menstruating' otherwise.
  Post-menopausal status can be determined by the reasons collected on the diary
  Any ambiguity in determining the category will be discussed and clarified in the blinded review meeting.

- Nature of migraine: with aura and without aura.

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

Number of analysis to be done on the primary and secondary endpoints will be confirmed based on subjects exposed to IMP at blinded review meeting.

11.1 Subject Disposition

Following categories will be summarised in subject disposition table:

- 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 completed the study, subjects who attended each visit within each study period - frequency (n) and percentage (%) based on FAS; Early Termination will be summarised in period 2 irrespective of when the subject discontinued from the study.
- 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

Subject disposition, status of inclusion/exclusion criteria, status of unblinding, subjects excluded from analysis population along with reasons 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

11.2 Protocol Deviations

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

- Inclusion / Exclusion
- Investigational Product
- Concomitant medications
- Laboratory tests
- 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 combined). Percentages will be based on FAS population. Protocol deviations occurring between Visit 2 and Visit 3 will be counted in Period 1, and those occurring after Visit 3 will be counted in Period 2.

In DDP: Table 14.1.2

Protocol deviations will be listed by subject.

In DDP: Listing 16.2.2

11.3 Demographic and Baseline Characteristics

Demographic and baseline characteristics will be summarised 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, height (cm), weight (kg) and BMI (kg/m^2). Height, weight and BMI are as reported in screening.

Percentages for childbearing potential will be based only on the female population.

The summary will be repeated for FAS, safety and per protocol populations (as per ICH E3 Guidelines).

In DDP: Table 14.1.3.1 to Table 14.1.3.3

Subject demographics will be listed by subject.

In DDP: Listing 16.2.4.1

11.4 Migraine History

Migraine history will be summarised by treatment sequence. Categorical and continuous variables will be provided in the same table. The following variables will be presented: Time (years) since migraine diagnosis, Average frequency of migraine headaches per month (in last 12 months), Average frequency of migraine headaches per month (in last 12 months) categories (≤1, 2-3, 4-5 and >5), Average duration of a migraine headache (hours), Number of subjects experiencing non-migraine headaches, Average frequency of non-migraine headaches per month (in last 12 months), Average frequency of non-migraine headaches per month (in last 12 months) categories (<1, 2-3, 4-5 and >5), Nature of migraines experienced, Average duration of aura (minutes) and Associated symptoms experienced. Number and percentage of subjects with each most troublesome symptom will be summarised by treatment sequence. Symptoms to be included are: nausea, photophobia, phonophobia and other.

Summary will be based on safety population.

In DDP: Table 14.1.4

Migraine history will be listed by subject.

In DDP: Listing 16.2.4.2

11.5 Medical/Surgical History

The number and percentage of subjects with any medical history and number of mentions will be summarised by treatment sequence. The summaries will be provided by system organ class (SOC) and preferred term (PT). System organ class will be displayed in the descending order of frequency of number of mentions in the "Total" column and preferred terms will be displayed in the descending order of frequency within the SOC. Percentages will be based on the safety population. The summary will be repeated for concurrent diseases.

Medical history and concurrent diseases will be classified as mentioned in section 10.8.

In DDP: Table 14.1.5.1, Table 14.1.5.2

Medical history and concurrent diseases will be listed by subject, system organ class and preferred term.

In DDP: Listing 16.2.4.3

11.6 Prior and Concomitant Medications

Medications will be summarised by the study periods below:

- Prior or Pre-Day 1 (Visit 2)
- Pre-IMP: irrespective of the study periods
- Post IMP: LAT8881 60 mg and Placebo

The number and percentage of subjects who have taken any prior medication and number of mentions will be summarised 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. Medications will be coded using the World Health Organisation's Drug-Dictionary (WHODD) version September 2019 or later.

Percentages will be based on the safety population.

The summary will also be presented for concomitant medications by treatment overall and within each study period separately.

Treatment overall: Medications reported before any IMP, irrespective of the study periods will be summarised as 'Pre-IMP'. Medications reported after IMP in period 1 and before IMP in period 2 will be summarised under the treatment assigned at period 1. Medications reported after IMP in period 2 will be summarised under the treatment assigned at period 2. Medications that are ongoing from the previous period and new events will be summarised separately within each treatment period and treatment.

By Study Period: Medications reported post-IMP within each period and treatment will be summarised under the corresponding treatment for that period. Medications that are ongoing from the previous period and new events will be summarised separately within each treatment period and treatment. If a subject has ongoing medication in more than one study period, then the use of that medication is counted in all applicable study periods as 'ongoing'.

Rescue medications and other non-rescue medications will be presented separately. Rescue medications will be presented first followed by other non-rescue medications within the same table.

Percentages will be based on the safety population.

In DDP: Table 14.1.6.1, Table 14.1.6.2 and 14.1.6.3

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.

Rescue medication use over the treatment periods will be listed for each subject separately.

In DDP: Listing 16.2.4.4 and Listing 16.2.4.5

11.7 Extent of Exposure

Number and percentage of subjects exposed to IMP and number of subjects not exposed to IMP will be summarised by study period and treatment. Continuous summary statistics will be displayed for

total IMP administered in mg by treatment overall and within each study period. Number and percentage of subjects exposed and not exposed to IMP in any one of the periods or both will also be summarised by study period. The summary will be based on the FAS population.

The same will be repeated for Safety and Per Protocol populations.

In DDP: Table 14.1.7.1, Table 14.1.7.2 and Table 14.1.7.3

IMP administration and compliance data will be listed by treatment sequence, subject and treatment period for FAS population to include the IMP dispensing information.

In DDP: Listing 16.2.5

11.8 Efficacy Analyses

All Efficacy summaries will be based on the Per-Protocol population. The presentation of descriptive summaries for the FAS population will be determined at the blind review meeting prior to database lock based on the difference between the numbers of subjects in each population.

11.8.1 Primary Efficacy analyses – NRS Pain Scores

Migraine pain intensity will be recorded using the NRS in a subject migraine diary at the pre-dose and at 0.5, 1.0, 1.5, 2, 4, 8 and 24 hours post dose. The NRS is an 11-point scale which grades pain from 0 (no pain) to 10 (worst pain imaginable). Pain should reflect the subject's pain at the time of recording.

11.8.1.1 Descriptive summary

A descriptive summary of NRS pain scores and absolute change from baseline results will be presented by treatment overall and within each study period. Timepoints to be included in this table are: Before IMP was taken (Pre-dose), 30 minutes after IMP taken (t=0.5 hrs), 1 hour after IMP taken (t=1 hr), 1.5 hours after IMP taken (t=1.5 hrs), 2 hours after IMP taken (t=2 hrs), 4 hours after IMP taken (t=4 hrs), 8 hours after IMP taken (t=8 hrs) and 24 hours after IMP taken (t=24 hrs).

Difference between treatments:

The difference in absolute NRS pain scores and change from baseline between both treatments will be summarised by timepoint. Timepoints to be included in this table are: Before IMP was taken (Predose), 30 minutes after IMP taken (t=0.5 hrs), 1 hour after IMP taken (t=1 hr), 1.5 hours after IMP taken (t=1.5 hrs), 2 hours after IMP taken (t=2 hrs), 4 hours after IMP taken (t=4 hrs), 8 hours after IMP taken (t=8 hrs) and 24 hours after IMP taken (t=24 hrs). 95% Confidence interval for the difference between treatments will also be provided.

Difference between treatments will be calculated as mentioned in section 10.15.1.

In DDP: Table 14.2.1.1

11.8.1.2 Time-Trend Plots

Time-trend plots may be created for NRS over time by subject. Each subject will be presented in a separate plot. X-axis will be the timepoint (hours) and Y-axis will be the NRS pain score. Plots will be

grouped by treatment. There may be one or two trend lines per subject based on the number of periods the subject took IMP.

Time trend plots will be created to visualise and compare changes over timepoints in the NRS pain score for subjects in the Per-Protocol population. Mean values of change from baseline within each treatment group along with standard error bars will be plotted on y-axis, and timepoints will be plotted on the x-axis. Treatment groups will be displayed side-by-side in a single page.

Difference in NRS pain scores between both treatments for each subject will also be plotted using time trend plots. Difference between LAT8881 60 mg and Placebo will be plotted in y-axis and timepoints will be plotted in x-axis.

Difference between treatments will be calculated as mentioned in section 10.15.1.

In DDP: Figure 14.2.1.2, Figure 14.2.1.3 and Figure 14.2.1.4

NRS Migraine Pain Scores will be listed by subject.

In DDP: Listing 16.2.6.3

11.8.1.3 Mixed Effect Regression Model for repeated measurements (MMRM)

A mixed effects regression model using a covariance pattern will be fitted to the absolute change from baseline in NRS pain scores at each post-IMP timepoint within each treatment period for the PP population.

The model will have fixed effects for treatment period, timepoint, treatment and the interaction between timepoint and treatment. Baseline pain score within each period 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 changes from baseline for LAT8881, Placebo and the difference between LAT8881 vs. placebo at each timepoint. P-values for testing the null hypothesis that the difference in least squares means between LAT8881 and placebo at each timepoint 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 timepoints).

[redacted]

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

In DDP: Tables 14.2.1.5

11.8.2 Secondary Efficacy Analyses

11.8.2.1 NRS Symptom Scores

A descriptive summary of NRS symptom scores and absolute change from baseline results will be presented by treatment overall and within each study period. Timepoints to be included in this table are: Before IMP was taken (Pre-dose), 30 minutes after IMP taken (t=0.5 hrs), 1 hour after IMP taken (t=1 hr), 1.5 hours after IMP taken (t=1.5 hrs), 2 hours after IMP taken (t=2 hrs), 4 hours after IMP taken (t=4 hrs), 8 hours after IMP taken (t=8 hrs) and 24 hours after IMP taken (t=24 hrs). Symptoms to be presented: Nausea, Photophobia and Phonophobia.

Difference between treatments:

The difference in absolute NRS symptom scores and change from baseline between both treatments will be summarised by timepoint. Timepoints to be included in this table are: Before IMP was taken (Pre-dose), 30 minutes after IMP taken (t=0.5 hrs), 1 hour after IMP taken (t=1 hr), 1.5 hours after IMP taken (t=1.5 hrs), 2 hours after IMP taken (t=2 hrs), 4 hours after IMP taken (t=4 hrs), 8 hours after IMP taken (t=8 hrs) and 24 hours after IMP taken (t=24 hrs). 95% Confidence interval for the difference between treatments will also be provided.

Difference between treatments will be calculated as mentioned in section 10.15.1.

The summary will be based on Per-Protocol population.

In DDP: Table 14.2.2.1

11.8.2.2 Time-Trend Plots

Time-trend plots may be created for symptom scores over time by subject and symptom. Each subject and symptom will be presented in a separate plot. X-axis will be the timepoint (hours) and Y-axis will be the NRS pain score. Plots will be grouped by treatment. There may be one or two trend lines per subject based on the number of periods the subject took IMP.

Time trend plots will be created to visualise and compare changes over timepoints in the symptom score for subjects in the Per-Protocol population. Mean values of change from baseline within each treatment group along with standard error bars will be plotted on y-axis, and timepoints will be plotted on the x-axis. Treatment groups will be displayed side-by-side in a single page.

Difference in symptom scores between both treatments for each subject will also be plotted using time trend plots. Difference between LAT8881 60 mg and Placebo will be plotted in y-axis and timepoints will be plotted in x-axis.

Difference between treatments will be calculated as mentioned in section 10.15.1.

In DDP: Figure 14.2.2.2, Figure 14.2.2.3 and Figure 14.2.2.4

11.8.2.3 Most Troublesome Symptom

Descriptive summary of most troublesome symptom scores and absolute change from baseline results will also be presented by treatment overall and within each study period. Timepoints to be included

in this table are: Before IMP was taken (Pre-dose), 30 minutes after IMP taken (t=0.5 hrs), 1 hour after IMP taken (t=1 hr), 1.5 hours after IMP taken (t=1.5 hrs), 2 hours after IMP taken (t=2 hrs), 4 hours after IMP taken (t=4 hrs), 8 hours after IMP taken (t=8 hrs) and 24 hours after IMP taken (t=24 hrs). Both categorical and continuous summaries will be provided in a single table.

The summary will be based on Per-Protocol population.

Difference between treatments:

The difference in absolute most troublesome symptom scores and change from baseline between both treatments will be summarised by timepoint. Timepoints to be included in this table are: Before IMP was taken (Pre-dose), 30 minutes after IMP taken (t=0.5 hrs), 1 hour after IMP taken (t=1 hr), 1.5 hours after IMP taken (t=1.5 hrs), 2 hours after IMP taken (t=2 hrs), 4 hours after IMP taken (t=4 hrs), 8 hours after IMP taken (t=8 hrs) and 24 hours after IMP taken (t=24 hrs). 95% Confidence interval for the difference between treatments will also be provided.

Difference between treatments will be calculated as mentioned in section 10.15.1.

In DDP: Table 14.2.3.1

11 point Likert Migraine Symptom Scores will be listed by subject.

In DDP: Listing 16.2.6.4

11.8.2.4 Time-Trend Plots

Time-trend plots may be created for most troublesome symptom scores over time by subject and symptom. Each subject will be presented in a separate plot. X-axis will be the timepoint (hours) and Y-axis will be the NRS pain score. Plots will be grouped by treatment. There may be one or two trend lines per subject based on the number of periods the subject took IMP.

Time trend plots will be created to visualise and compare changes over timepoints in the most troublesome symptom score for subjects in the Per-Protocol population. Mean values of change from baseline within each treatment group along with standard error bars will be plotted on y-axis, and timepoints will be plotted on the x-axis. Treatment groups will be displayed side-by-side in a single page.

Difference in most troublesome symptom scores between both treatments for each subject will also be plotted using time trend plots. Difference between LAT8881 60 mg and Placebo will be plotted in y-axis and timepoints will be plotted in x-axis.

Difference between treatments will be calculated as mentioned in section 10.15.1.

In DDP: Figure 14.2.3.2, Figure 14.2.3.3 and Figure 14.2.3.4

11.8.2.5 No Headache Pain

Number and percentage of subjects who achieve ‘no headache pain’ (NRS pain score 0 or 1) at each timepoint will be presented by treatment overall. Presence or absence of pain will be determined as

mentioned in section 10.15.4. The paired difference in number of subjects with no headache pain (LAT8881 – Placebo) will be calculated as mentioned in section 10.16.

In DDP: Table 14.2.4

11.8.2.6 Migraine and Headache Diary

Migraine and headache diary details will be listed by subject. Menstrual cycle details will also be listed by subject.

In DDP: Listing 16.2.6.1, Listing 16.2.6.2 and Listing 16.2.6.5

11.8.3 Exploratory Analysis

11.8.3.1 Sustained Pain-free at 24 Hours

Number and percentage of subjects who are "sustained pain-free" at 24 hours (as defined in section 10.15.1) will be summarised treatment overall. The paired difference in number of subjects sustained pain-free (LAT8881 – Placebo) will be calculated as mentioned in section 10.16.

The summary will be based on Per-Protocol population.

In DDP: Table 14.2.5

11.8.3.2 Time to First Pain-free Timepoint

The number and percentage of subjects with their first pain free timepoint will be presented by timepoint. The paired difference in the number of subjects with their first pain free timepoint will be calculated as mentioned in section 10.16.

Time taken to first pain-free timepoint will also be analysed using Kaplan-Meier curve. Time to first pain-free timepoint will be calculated based on the actual time taken from IMP as mentioned in section 10.15.5.

In DDP: Table 14.2.6.1, Figure 14.2.6.2

11.8.3.3 Subject Satisfaction Survey

The subject's satisfaction score for each treatment and preference for LAT8881 or placebo recorded on a 7-point Likert scale will be summarised as a continuous endpoint with mean, SD, median, minimum and maximum. Within-subject difference in the satisfaction score between treatments will also be summarised. Within-subject difference will be compared using paired t-test and p-values will be presented.

If the assumptions for normality are not met using Shapiro-Wilk test, the non-parametric equivalent Wilcoxon signed-rank test will be performed, and unadjusted p-values will be presented.

[redacted]

```
proc ttest data = <INDATA>;
paired <TESTVAR1>*<TESTVAR2>;
run;
```

The subject satisfaction score and preference for each treatment compared to their usual medication for an acute migraine attack will be presented in the same manner. Subjects preferred treatment will be derived as mentioned in section 10.16. The number and percent of subjects preferring LAT8881 60 mg or placebo treatment will be presented.

The difference between the proportions of subjects preferring LAT8881 60 mg compared to placebo will also be presented along with the 95% confidence interval for the difference.

In DDP: Table 14.2.7

Subject satisfaction survey will be listed by subject.

In DDP: Listing 16.2.6.6

11.8.3.4 Association between Change in NRS Pain Score and Baseline Characteristics

Descriptive Summary:

NRS pain scores, NRS symptom scores and most troublesome symptom scores will be summarised by visit and subgroup within treatment.

Descriptive summary of NRS Pain scores, NRS symptom scores and most troublesome symptom scores along with absolute change from baseline results will also be presented by treatment overall and subgroup. Timepoints to be included in this table are: Before IMP was taken (Pre-dose), 30 minutes after IMP taken (t=0.5 hrs), 1 hour after IMP taken (t=1 hr), 1.5 hours after IMP taken (t=1.5 hrs), 2 hours after IMP taken (t=2 hrs), 4 hours after IMP taken (t=4 hrs), 8 hours after IMP taken (t=8 hrs) and 24 hours after IMP taken (t=24 hrs).

The summary will be based on Per-Protocol population.

Difference between treatments:

The difference in absolute scores and change from baseline between both treatments will be summarised by timepoint. Timepoints to be included in this table are: Before IMP was taken (Predose), 30 minutes after IMP taken (t=0.5 hrs), 1 hour after IMP taken (t=1 hr), 1.5 hours after IMP taken (t=1.5 hrs), 2 hours after IMP taken (t=2 hrs), 4 hours after IMP taken (t=4 hrs), 8 hours after IMP taken (t=8 hrs) and 24 hours after IMP taken (t=24 hrs). 95% Confidence interval for the difference between treatments will also be provided.

Difference between treatments will be calculated as mentioned in section 10.15.1.

In DDP: Table 14.2.8.1 to Table 14.2.10.3

Time trend plots:

Time-trend plots will be created for the change from baseline NRS pain and symptom scores over time by treatment and subgroup. Each treatment group within a subgroup will be presented in a separate plot. Both treatments will be displayed side-by-side for comparison. X-axis will be the Timepoint (hours) and Y-axis will be the NRS pain score. Each subject will be presented by a line within the plots

and all subjects within a single group will be presented in the same color. Mean NRS pain score at each timepoint will also be plotted for reference.

Any change in the above analysis will be discussed and finalised in the blinded review meeting.

Subgroups are as defined in section 10.18.

In DDP: Figure 14.2.8

11.9 Safety Analyses

All safety summaries will be based on the Safety population and treatment groups as treated.

11.9.1 Adverse Events

All Adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) version 22.1 or higher.

11.9.1.1 Overall Adverse Events

The number and percentage of subjects and number of events will be summarised by AE status (new event or ongoing from the previous study period), 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 leading to death
9. Treatment-emergent adverse events leading to study discontinuation

The above categories and study periods will be classified as defined in section 10.10.

In DDP: Table 14.3.1.1 and Table 14.3.1.2

All adverse events will be listed by subject, system organ class and preferred term sorted by event start dates. Serious adverse events and deaths due to adverse events will be listed separately.

In DDP: Listing 16.2.7.1 to 16.2.7.3

11.9.1.2 Summary of Adverse Events by SOC and PT

The number and percentage of subjects and number of events will be summarised by treatment overall and within each study period, system organ class and preferred terms. 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 total LAT8881 60 mg group. All adverse events and all serious adverse events will be summarised by Pre-IMP and Post-IMP treatments. All treatment emergent and similar events will be summarised by study period, treatment and the event status (new event or ongoing from the previous study period).

The same will be repeated for all treatment-emergent AEs, treatment-emergent related AEs, serious AEs, treatment-emergent serious AEs, treatment-emergent related serious AEs, treatment-emergent AEs leading to discontinuation and treatment-emergent AEs leading to death.

In DDP: Table 14.3.1.2 to Table 14.3.1.4 and Table 14.3.2.1 to Table 14.3.2.5

11.9.1.3 Summary of Treatment emergent Adverse Events by SOC, PT, Relationship 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 summarised 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 60 mg group (all study periods).

In DDP: Table 14.3.1.5

11.9.2 Laboratory Assessments

11.9.2.1 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. 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

11.9.2.2 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, Visits 2 and Visit 3 will be listed separately.

In DDP: Listing 16.2.8.1 to 16.2.8.5 and Listing 16.2.8.8

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 and Listing 16.2.8.7

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
Liver Function Tests	Aspartate aminotransferase, alanine aminotransferase, gamma-glutamyl transferase, alkaline phosphatase, conjugated bilirubin, total bilirubin
Coagulation	Activated partial thromboplastin time, international normalised ratio
Urinalysis	Continuous: Specific gravity and pH
	Categorical: 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)

11.9.3 Other Safety Analyses

11.9.3.1 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 and visit for safety population. Vital signs parameters include: systolic blood pressure (mmHg), diastolic blood pressure (mmHg), respiratory rate (breaths/min), heart rate (beats/min) and body temperature (°C).

In DDP: Table 14.3.5.1

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

In DDP: Listing 16.2.9.1

11.9.3.2 Physical Examination

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

In DDP: Listing 16.2.9.2

11.9.3.3 Electrocardiogram Assessments

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

In DDP: Table 14.3.5.2

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

In DDP: Listing 16.2.9.3

11.9.3.4 Telephone Visits

Telephonic visits information will be listed by treatment sequence, subject ID, treatment period and visit.

In DDP: Listing 16.2.9.4

12 Index of Tables, Listings and Graphs

Refer LAT-MIG-001_Data Display Plan (Ver: 0.03) for the list of Tables, Listings and Graphs.

13 References

1. ICH. ICH Harmonized Tripartite Guideline: Statistical Principles for Clinical Trials E9. 1998.
2. ASA. Ethical Guidelines for Statistical Practice. Prepared by the Committee on Professional Ethics. 1999.
3. ICH. ICH Harmonized Tripartite Guideline: Structure and Content of Clinical Study Reports E3. 1995.

14 Appendices

Not applicable

15 Change Log

Version	Authored by	Change Date	Change Details	Reviewed by	Review Date
1.00	[redacted]	24-Feb-2020	Initial version	[redacted]	24-Feb-2020

[redacted]

Confidential

[redacted]