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

NCT number: NCT04153409

Document date: July 25, 2019

Clinical study title	**A proof of concept study of the efficacy and safety of oral LAT8881 in acute migraine**
Protocol number	LAT-MIG-001
Drug name	LAT8881
Clinical phase	IIa
Sponsor	Lateral Pharma Pty Ltd 14/114 William St Melbourne, Vic 3000 Australia Phone: +61 (0)400 151 490 Email: dk@lateral-pharma.com
Principal investigator	[redacted]
Version	1.0
Date	25 July 2019

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

Confidentiality statement

Protocol signatures

Investigator's statement

The undersigned Investigator(s) agree:

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

Investigator name (Print)	Investigational site
Investigator signature	Date
Investigator name (Print)	Investigational site
Investigator signature	Date
Sponsor name (Print)	
Sponsor signature	Date

[redacted]

Table of contents

List of tables

List of figures

List of abbreviations

Abbreviation	Definition
µg	microgram
µl	microlitre
ADL	Activities of daily living
ADR	adverse drug reaction
AE	adverse event
cGMP	Current Good Manufacturing Practice
CGRP	calcitonin gene-related peptide
CI	confidence interval
(e)CRF	(electronic) case report form
CTN	Clinical Trial Notification (scheme)
DHE	Dihydroergotamine
EC	ethics committee
ECG	electrocardiogram
FAS	Full analysis set
FOCBP	female of child bearing potential
g	gram
GCP	Good clinical practice
hCG	human chorionic gonadotropin
hGH	human growth hormone
ICF	Informed consent form
ICH	International Conference on Harmonisation
IHS	International Headache Society
IUD	intrauterine device
im	intramuscular
IMP	Investigational medicinal product
iv	intravenous
kg	kilogram
m	metre
m^2	square metre
MAO-A	monoamine oxidase A
MedDRA	Medical Dictionary for Regulatory Activities
mg	milligram
mL	millilitre

Abbreviation	Definition
mOhm	milliohm
mV	millivolt
n	number (of subjects)
NRS	Numeric rating scale
NSAID	nonsteroidal antiinflammatory drug
PCI	PCI Pharma Services
PIC/S	Pharmaceutical Inspection Cooperation Scheme
PIS	Participant information sheet
PP	per protocol
PT	Preferred term
SAE	serious adverse event
SAP	statistical analysis plan
SOC	system organ class
SOP	standard operating procedure
Subject ID	unique number given to each subject on screening
t	time
SUSAR	suspected unexpected serious adverse reaction
TCA	tricyclic antidepressant
TEAE	Treatment emergent adverse event
TGA	Therapeutic Goods Administration
TIA	transient ischaemic attack
TYR	tyrosine

1. Protocol synopsis

Title:	A Proof of concept study of the efficacy and safety of oral LAT8881 in acute migraine
Protocol number	LAT-MIG-001
Clinical phase	IIa
Principal investigator	[redacted]
Study site	Emeritus Research Level 2/1180 Toorak Rd Camberwell VIC 3124, Australia
Investigational medicinal product (IMP)	LAT8881 [redacted] 30 mg capsules and matching placebo. Two capsules to be taken at the onset (within one hour from the onset of pain) of a migraine headache of moderate to severe intensity. Total daily dose of IMP: 0 or 60 mg LAT8881
Indication	Treatment of acute migraine with or without aura
Study description	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 with or without aura. Subjects enrolled in 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 a single dose of IMP, to treat one migraine headache. 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. After treatment of one migraine headache in the second treatment period or a maximum of 28 days from commencement of the second treatment period, the subject will return to the clinic for re-evaluation. An End of study visit (telephone) will occur 7 days after the end of the second treatment period. Subjects will complete diaries to record menstrual cycle, onset, and nature of migraine and non-migraine headaches, pain scores at time of IMP dosing and various time points post dose, associated symptoms, episodes of vomiting and rescue medication. Adverse events will be monitored.
Number of subjects planned	It is planned to have 20 subjects complete the study, defined as taking one dose of IMP in each treatment period and attending the followup (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 noncompletion rate is higher than anticipated, additional subjects may be enrolled to ensure 20 subjects complete the study.

Study objectives

Primary

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)

Secondary

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 for a migraine headache 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

Exploratory

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

Endpoints

Primary endpoint

Change in migraine headache pain score, using an 11-point NRS, (0 = none, 10 = worst imaginable), from the time of dosing (t = 0 min) 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.

Secondary efficacy endpoints

1. Change in migraine-associated symptoms of nausea, photophobia and phonophobia. Symptoms are assessed on an 11- point Likert scale (0 = no symptoms, 10 = 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 (0 = no symptoms, 10 = 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.

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

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.

Study population:

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[2]
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 (ie, 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

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 nonmigraine) 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*, non-melanoma 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) prior to screening
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

Study medications

Prohibited medications and treatments

Medications for migraine prophylaxis are prohibited:

- from 6 months prior to screening and throughout the study:
    - Calcitonin gene-related peptide pathway monoclonal antibodies CGRP antagonists, eg erenumab (Aimovig)
- from 3 months prior to screening and throughout the study
    - Antiepileptic drugs including valproate, topiramate
    - Betablockers
    - Triptans (eg naratriptan for premenstrual migraine)
    - Tricyclic antidepressants (TCAs)
    - Botulinum toxin
    - Calcium channel blockers
    - MAO-A inhibitors
    - Nerve blocks
    - Serotonin-norepinephrine (noradrenaline) reuptake inhibitor: eg venlafaxine, duloxetine
    - Selective serotonin reuptake inhibitors, eg fluoxetine, sertraline
- from Screening and throughout the study
    - NSAIDs

Investigational drugs for prophylaxis or treatment of migraine or other medical conditions

Any other medications which may impact on pain assessments are prohibited if taken within 24 hours prior to taking the dose of IMP.

The following treatments are prohibited during the study, including during the screening period:

- Neuromodulation devices, including TENS, eTENS, vagus nerve stimulation devices and acupuncture

Permitted medications

The following medications are permitted:

1 Rescue analgesics, 2 or more hours after dose of IMP: prescription and nonprescription drugs including Standard of Care medications for treatment of acute migraine headache

2 Other medications eg vitamins, herbal/dietary supplements (including Chinese medicines), oral and IUD contraceptives, hormone replacement therapy, not on the prohibited medications list which have been stable for 3 months prior to screening.

Study procedures

Screening (Visit 1)

Potential subjects will be required to provide written informed consent prior to any study-specific screening procedures being performed. A unique Screening number (Subject ID) will be assigned. During the screening procedure, subjects will undergo screening assessments including medical history, height, weight, 12-lead ECG, vital signs, and full physical examination. In addition to eligibility criteria, medical history will include details of history of migraine headaches: average duration (shortest and longest), description of nature (throbbing, aggravating factors, unilateral/bilateral, aura), severity and associated symptoms including most troublesome symptom and relationship to menstrual cycle.

Concomitant medications will be recorded. Blood will be collected for routine haematology and biochemistry screening and, in female subjects of child-bearing potential, to test for pregnancy. A urine sample will be collected for urinalysis.

Subjects deemed likely to be eligible for the trial will be given two diaries after completion of the above screening tests. The headache diary will be used to record menstrual cycles, and onset and nature of headaches (both migraine and non-migraine). In addition, they will be instructed to complete a migraine diary during a migraine headache to collect pain and symptom scores and concomitant medications. Scores will be recorded before taking their usual migraine medication and at 0.5, 1.0, 1.5, 2, 4, 8 and 24 hours after taking their usual migraine medication. The screening diaries will be completed for a minimum of 28 days. If the subject does not experience a migraine headache in this period or menstrual bleeding (menstruating females only), the screening diary period may be extended up to 35 days.

Note that diary entries completed prior to Day 1 will be used only to confirm compliance with diary completion requirements on the day of a migraine, to verify the nature of migraine headache and the subject's most troublesome symptom.

Visit 2

Treatment period 1

Subjects will return to the unit on Day 1 (Visit 2) with their diaries completed from Day -28 to Day -1 inclusive. If a subject has not experienced a migraine headache or menstrual bleeding (menstruating females only) during the 28-day period, the screening diary period may be extended by 7 days.

On Day 1, assessments including 12-lead ECG, vital signs, a targeted physical examination, recording of concomitant medications, review of the subject's diaries, blood and urine sampling for safety monitoring, and urine sampling for pregnancy

testing in FOCBP, will be conducted. Results from safety monitoring tests are not required prior to randomisation.

Eligibility will be confirmed and subjects will be randomised to LAT8881 60 mg or placebo.

Subjects will leave the unit with their two diaries, and one dose of IMP and instructions to take the dose within one hour of the onset of a migraine headache of moderate to severe intensity (NRS ≥4). The headache diary will be used to record menstrual cycles and onset and nature of headaches (both migraine and non-migraine). The migraine diary will be used during a migraine headache to collect pain and symptom scores and concomitant medications before taking the IMP and at 0.5, 1.0, 1.5, 2, 4, 8 and 24 hours after taking the dose. No analgesics or antimigraine medication other than medications for routine prophylaxis not on the Prohibited medicines list may be taken within 24 hours prior to taking the dose of IMP. Rescue medication is permitted a minimum of 2 hours post IMP dose. The subject's symptoms including nausea, photophobia and phonophobia plus the subject's most troublesome symptom if other than nausea, photophobia or phonophobia will be recorded at the time of dosing and at 0.5, 1.0, 1.5, 2, 4, 8 and 24 hours after taking the dose. Episodes of vomiting will also be recorded.

The subject will be instructed to phone the clinic within one business day of taking the dose.

On Day 15, if the subject has not phoned the clinic, the subject will be phoned to remind them to complete their diaries and to phone the clinic when the dose has been taken.

Subjects will return to the clinic for Visit 3 within 5 business days after taking the dose or a maximum of 28 days after Visit 2 if IMP has not been taken.

Visit 3

Assessments including 12-lead ECG, vital signs, a targeted physical examination and concomitant medications will be recorded and the subject's diaries will be reviewed. Blood and urine samples will be taken for safety monitoring and urine for pregnancy test (FOCBP only). Subject satisfaction with Treatment period 1 IMP will be recorded. Results from safety monitoring tests are not required prior to dosing.

Treatment period 2

Subjects will leave the clinic with their diaries and one dose of IMP (alternate treatment), instructions to take the dose within one hour of the onset of a migraine headache of moderate to severe intensity (NRS ≥4), but not less than 48 hours after last dose and instructions to complete the diaries as for Treatment period 1. No analgesics or antimigraine medication other than medications for routine prophylaxis not on the Prohibited medicines list may be taken within 24 hours prior to taking the dose of IMP. Rescue medication is permitted a minimum of 2 hours post dose.

The subject will be instructed to phone the clinic within one business day of taking the dose.

If the subject has not phoned the clinic, the subject will be phoned 14 days after Visit 3 to remind them to complete their diaries and to phone the clinic when the

dose has been taken.

Subjects will return to the clinic for Visit 4 within 5 business days, after taking the dose or a maximum of 28 days after Visit 3 if IMP has not been taken.

Visit 4

Subjects will return to the clinic with their diaries at completion of Treatment period 2.

Blood and urine samples will be taken for safety analysis. 12-lead ECG, vital signs, concomitant medications, targeted physical examination results and adverse events will be recorded. Subjects will be asked to complete assessments for Subject satisfaction of IMP Treatment period 2 and overall preference.

End of study, Visit 5

Subjects will be phoned 7 days after Visit 4 to review any new or changed adverse events or changes in concomitant medications.

Early withdrawal

An early withdrawal visit should be conducted within 7 days of the subject withdrawal, and/or a minimum 48 hours after last dose of IMP.

Subjects who are completing an early withdrawal visit will return with their diaries and IMP.

Blood and urine samples will be taken for safety analysis. 12-lead ECG, vital signs, concomitant medications, targeted physical examination results and adverse events will be recorded. Subjects will be asked to complete assessments for Subject satisfaction.

Statistical analysis

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

The safety population includes all subjects who receive at least one dose of IMP and will be the population used for the analysis of safety endpoints. The full analysis set (FAS) population will be used to present demographic and other baseline characteristics and summaries of efficacy endpoints. A per-protocol (PP) population will be used as the primary population for efficacy analyses and to analyse exploratory endpoints. The PP population will be based on IMP exposure, including the time of any episodes of vomiting and major protocol deviations.

The descriptive summaries for the categorical variables will include counts and percentages. The descriptive summaries for the continuous variables will include number of subjects (n), means, medians, standard deviations, and minimum and maximum values. All data will be listed for all subjects. As this is a Phase IIa proof of concept study, no formal statistical hypotheses are being specified although some may be investigated as part of the data presentation. A p-value of <0.05 will be declared statistically significant. Treatment period order will be ignored in any treatment comparisons. Results will be presented in a descriptive format by treatment within each treatment period and overall. Treatment comparisons will take into account the paired nature of the treatment responses where feasible.

Individual pain score-time profiles for each treatment within each subject will be presented graphically. The difference between the NRS pain scores at each

timepoint for LAT8881 60 mg compared with placebo within each subject will be estimated and presented graphically. The number of subjects, mean, standard deviation, minimum and maximum NRS pain score at each timepoint, change from baseline, difference between treatments at each timepoint and change from baseline difference between treatments will be presented for each treatment overall and within each treatment period.

Nausea, photophobia and phonophobia symptom scores will be summarised and presented in the same way as the pain scores. The number and percent of headaches with each most troublesome symptom of migraine including nausea, cognitive impairment, dizziness, functional disability, photophobia phonophobia and vomiting will be summarised for each treatment. The most troublesome symptom scores will be summarised and presented in the same way as the pain scores.

The number and percent of subjects with 'no headache pain' at each time point will be presented for each treatment. Two-way tables will present the presence/absence of pain classified for each treatment at each timepoint. Absence of pain will be defined as a pain NRS score of 0 or 1.

The number and percent of subjects who are “sustained pain-free” at 24 hours after dose of IMP will be presented by treatment. A two-way table will present the “sustained pain-free” status for subjects on each treatment.

The number and percent of subjects will be summarised by their first pain-free timepoint. A two-way table will present the classification of each subject’s first pain-free timepoint by treatment. Kaplan-Meier curves will present the time to first pain-free timepoint.

Patient Satisfaction for each treatment recorded on a 7-point Likert scale and the within-subject difference between treatments will be summarised. The mean difference between treatments will be compared with a paired t-test and the 95% confidence interval for the mean difference will be presented. The number and percent of subjects from the overall satisfaction score will be presented for each treatment.

Additional exploratory analyses to investigate the association between change in headache pain and symptom scores and selected subject baseline characteristics will be undertaken in a similar fashion with descriptive statistics.

Adverse event data will be coded to system organ class and preferred term using the Medical Dictionary for Regulatory Activities (MedDRA). A by-subject AE data listing, including verbatim term, preferred term, system organ class, severity and relationship to investigational product will be provided. The number and percentage of subjects experiencing any treatment-emergent AE and the number of individual adverse events, overall, and by system organ class and preferred term will be tabulated. Treatment emergent adverse events will also be summarised by severity and relationship to investigational product.

Absolute values and changes from baseline in vital signs, haematology and clinical chemistry parameters will be tabulated at each visit.

Prior and concomitant medications will be listed by subject and coded using the most current World Health Organisation (WHO) drug dictionary and summarised by WHO Drug Class and preferred term for each treatment period and treatment

	group. Medical history will be listed by subject. Further details of the statistical methodology to be used in the analysis and reporting of the study results, including methods for handling missing data, and early withdrawals, will be provided in a statistical analysis plan that will be finalised prior to database lock.
Anticipated study Duration:	Approximately 9 months
Participant duration:	Maximum participation duration is 14 weeks (98 days): Screening (28 - 35 days), Treatment period 1 (28 days), Treatment period 2 (28 days), followup (7 days)

2. Study schedule of assessments and procedures

	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 child bearing potential only, blood test at screening, urine other occasions
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

3. Introduction and background information

3.1 Acute migraine

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).[3]

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.[3]

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.3

Recognition of the pathophysiology of migraine has evolved from the belief that it was a primary consequence of intracranial vasodilation, to the more recent theory that it is initiated by a complex series of neural and vascular events.[4] According to this theory, migraine is primarily a neurogenic process with secondary changes in cerebral perfusion. The headache pain itself is considered to be due to activation of the trigeminovascular pathway, but it has been suggested that there are multiple neuronal functional abnormalities which are involved in the initiation of a migraine.[5]

Migraine prevalence is reported to be between 2.6% and 21.7%, with an average of approximately 12%.[6] In the 2016 Global Burden of Disease Study,[7] migraine (including medication overuse headache) ranked in the top ten of years lived with disability in all 195 countries and territories investigated, and overall was the second largest cause of disability.

In the years prior to puberty, migraine is more common among boys than girls. However, by the onset of puberty, migraine is more prevalent in girls. Females in their late teens are about twice as likely to suffer from migraine as males of the same age.[8] The prevalence of migraine peaks in both sexes and is at its highest from ages 25 to 55 years, when there is a substantial loss of productivity because of work absences and reduced efficiency. In Australia, it is estimated that the total economic cost from migraine in 2018 was $35.7 billion, consisting of $14.3 billion of health system costs, $16.3 billion of productivity costs, and $5.1 billion of other costs.[9] There are also additional significant wellbeing costs for these individuals and their families.

Selecting the optimal treatment for a particular patient is challenging because the severity, frequency, and characteristics of migraine can vary between individuals or even within the same individual over time. Treatment plans are usually individualised and based on a number of factors, such as patient preference, the severity and frequency of attacks, co-morbidities and concomitant medications.

The American Headache Society guidance for the treatment of acute migraine[10] is to use non-steroidal anti-inflammatory drugs (NSAIDs), including aspirin, non-opioid analgesics, paracetamol, or caffeinated analgesic combinations (eg aspirin + paracetamol + caffeine) for mild-to-moderate attacks. For moderate or severe attacks and mild-to-moderate attacks that respond poorly to NSAIDs or caffeinated combinations, migraine-specific agents (triptans, dihydroergotamine) are suggested.

For some patients, acute treatments are not sufficiently effective or are not well tolerated and preventative medication may be suggested. However, non-compliance with chronic medication or side effects from treatment may reduce the effectiveness of such interventions. The availability of an effective

acute therapy, with a novel mechanism of action and good tolerability, will improve the options for patients with acute migraine who do not wish to progress to chronic preventative therapies.

Some of the clinical features of migraine, such as allodynia and hyperalgesia, resemble the symptoms of neuropathic pain, leading to the suggestion that migraine might be a neuropathic pain disorder.[11] It is in this context that it has been suggested that LAT8881, with its demonstrated activity in preclinical neuropathic pain models and evidence of inhibition of neuronal excitability (Section 3.2.1.1), might be a useful therapeutic agent for migraine.

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.

3.2 LAT8881

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

[redacted]

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

A clinical study is currently in progress to evaluate the efficacy and safety of LAT8881 in neuropathic pain. This study is being conducted at four Australian and two UK sites, and is planned to recruit up to 55 subjects, so that 44 subjects complete the study.

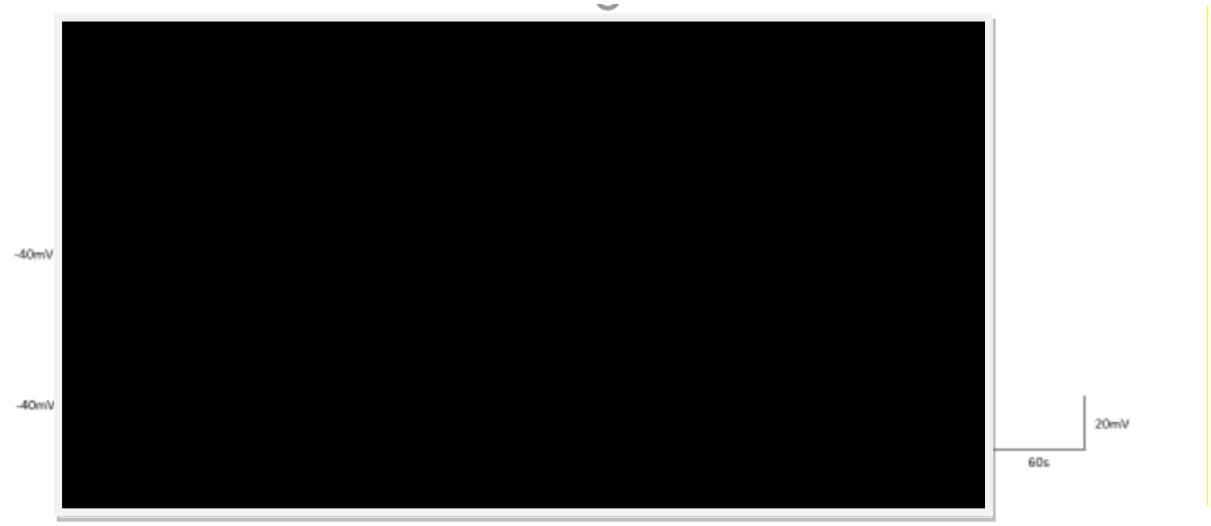
3.2.1 Non-clinical studies

3.2.1.1 Non-clinical models

As there are no established specific pharmacological models of migraine,[12] non-clinical studies supporting a role for LAT8881 in migraine are based on its activity in relieving neuropathic pain as this action has been suggested to be relevant to its potential role in migraine.[11] These studies are summarised in [redacted]. Further details are provided in the Investigator's Brochure.

[redacted]

[redacted]



[redacted]

[redacted]

[redacted]

3.2.1.3 Non-clinical safety studies

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

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

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

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

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

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

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

3.2.2 Clinical studies

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

[redacted]

[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

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.

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

4. Study objectives

4.1 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)

4.2 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

4.3 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 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 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, compared with placebo
4. To investigate subject satisfaction with treatment
5. To investigate other factors influencing the extent of change in pain score and symptom scores in subjects with migraine

5. Study design

5.1 Overall study design

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

Figure 3. Details of the procedures during each phase are described in Section 9.

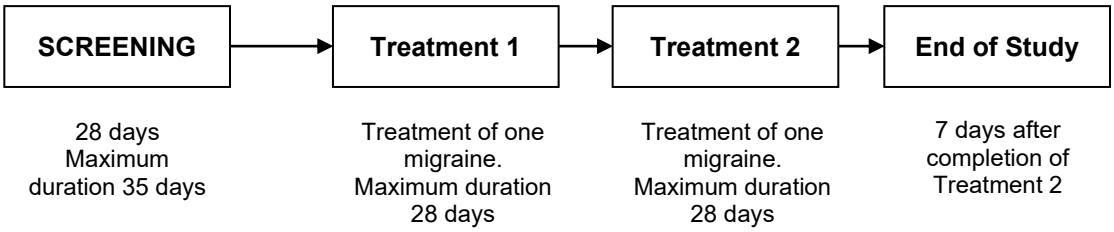


Figure 3: Overall study design for LAT-MIG-001

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. 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.

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.

5.2 Justification of study design

The design of this Phase IIa proof of concept trial as a randomised, double blind, placebo controlled, crossover study has, in general, followed clinical trial guidelines developed by the International Headache Society.[13]

The crossover design was chosen to increase efficiency. As each subject acts as his/her own control the trial requires a smaller number of subjects than for a parallel group design. The crossover design also allows subject treatment preferences to be assessed.

Period and carryover effects are potential disadvantages of a crossover trial design, but these considerations are considered unlikely to impact significantly on this study. As eligible subjects are required to have a stable pattern of migraine history, 2–8 attacks per month for the previous 12 months, and LAT8881 is a single dose, symptomatic treatment, no period effect is anticipated. Available preclinical pharmacodynamic data does not suggest that a single dose of LAT8881 would have a carryover effect, and a washout period of at least 48 hours between dosing is considered adequate. Preclinical and clinical safety data have not shown any significant adverse effects with LAT8881 that

would affect a subsequent treatment period, nor are there any notable AEs that would enable subjects to discriminate between active and placebo treatments.

5.3 Justification of dose

The dose of 60 mg is based on preclinical studies in neuropathic pain models and preclinical and clinical safety data with LAT8881. [redacted]

Full details of these preclinical and clinical studies are available in the Investigator's Brochure.

Following this study, it is planned to investigate the dose response to LAT8881 in patients with migraine headaches and to determine a minimum effective and optimal therapeutic dose.

5.4 Number of planned subjects

It is planned to have 20 subjects complete the study, defined as taking one dose of IMP in each treatment period and attending the followup (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.

5.5 Duration of study

Approximately 9 months

5.6 Duration of subject participation

Maximum participation duration is 14 weeks (98 days): Screening (28-35 days), Treatment period 1 (28 days), Treatment period 2 (28 days), followup (7 days).

5.7 Withdrawal of subjects from study

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

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

Possible reasons for discontinuation of a subject may include:

- Withdrawal of consent by the subject
- Serious or significant AE or laboratory abnormality
- Non-compliance with the protocol
- The need to take medication which may interfere with study measurements or is contraindicated
- New inter-current diseases, which may affect the safety of the IMP

- Subject is lost to followup
- Withdrawal for other reasons
- Lateral terminating the study for administrative, financial, or other reasons

Subjects withdrawing from the study will be requested to attend an End of study Visit. If the subject withdraws during the treatment period, the subject should attend the End of study visit within one week of the subject withdrawal, and/or a minimum 48 hours after last dose of IMP.

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

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

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

5.8 Replacement of subjects

Subjects who withdraw after randomisation will not be replaced.

6. Study population

6.1 Inclusion criteria

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

1 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[2]

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 (ie, 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

6.2 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 nonmigraine) 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*, non-melanoma 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

6.3 Contraception requirements

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

To prevent pregnancy in a female subject of child bearing potential (FOCBP), the FOCBP and /or partner must use a highly effective method of contraception (failure rate of <1%), during the study and for 28 days after the last dose of IMP. Such methods include:

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

- double barrier method
- male condom plus spermicide OR

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

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

6.4 Dietary, lifestyle and other restrictions

There are no specific dietary, lifestyle or other restrictions for this study, apart from those listed in the Inclusion and Exclusion criteria or the prohibited medications and treatments list.

7. Study treatments

7.1 Description

The IMP is supplied as opaque, size 0 capsules, in a high-density polyethylene bottle containing 2 capsules. One bottle will contain sufficient capsules for the treatment of one migraine headache in one treatment period.

7.2 Formulation

7.2.1 LAT8881 capsules

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

7.2.2 Placebo capsules

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

7.3 Manufacturer

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

The active and placebo blends for encapsulation is formulated and the capsules are filled [redacted] under cGMP conditions.

[redacted] is responsible for quality control and stability testing.

7.4 Storage

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

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

7.5 Packaging and labelling

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

Bottles containing the IMP capsules and the bag in which they are packed will be labelled according to Annex 13 of the PIC/S Guide to Good Manufacturing Practice.[15]

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

Details of labelling and dispensing will be provided in the Study procedures manual.

7.6 Randomisation and blinding

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

The treatment sequence each subject will receive will not be disclosed to the investigator, study site personnel, subjects, or sponsor personnel. The randomisation codes will be available to the Investigator if required for emergency unblinding purposes (see Section 8.1).

7.7 Dispensing of investigational product

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

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

7.8 Method for assigning subject study number

At screening, each subject will, in chronological order, be allocated a unique Screening number (Subject ID).

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

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

7.9 Accountability of study supplies

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

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

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

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

7.10 Doses and treatment regimens

Subjects will be instructed to take one dose of IMP (two capsules) with water within one hour of the onset of a migraine headache of moderate to severe intensity.

7.11 Dose reduction/dose adjustments

No within-subject dose reductions or adjustments are permitted. If a subject experiences an adverse event requiring (in the investigator's opinion) temporary or permanent suspension of the IMP, the subject should be withdrawn from the study (refer to Section 5.7).

8. Treatment compliance

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

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

8.1 Unblinding

8.1.1 Medical emergency

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

Wherever possible, such emergencies should be discussed with the study medical monitor and/or sponsor before breaking the code and disclosure of the treatment allocation (or as soon as possible thereafter). The date, reason for and name of the individual breaking the code will be documented along with a list of unblinded persons.

8.1.2 End of study

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

8.2 Concomitant medications and treatments

8.2.1 Prohibited medications

Medications for migraine prophylaxis are prohibited:

- from 6 months prior to Screening and throughout the study:
    - Calcitonin gene-related peptide pathway monoclonal antibodies CGRP antagonists, eg erenumab (Aimovig)
- from 3 months prior to Screening and throughout the study
    - Antiepileptic drugs including valproate, topiramate
    - Betablockers
    - Triptans (eg naratriptan for premenstrual migraine)
    - Tricyclic antidepressants (TCAs)
    - Botulinum toxin
    - Calcium channel blockers
    - MAO-A inhibitors
    - Nerve blocks
    - Serotonin-norepinephrine (noradrenaline) reuptake inhibitor: eg venlafaxine, duloxetine
    - Selective serotonin reuptake inhibitors, eg fluoxetine, sertraline
- from Screening and throughout the study
    - NSAIDs
- Investigational drugs for prophylaxis or treatment of migraine or other medical conditions

Any other medications which may impact on pain assessments are prohibited if taken within 24 hours prior to taking the dose of IMP.

8.2.2 Prohibited treatments

The following treatments are prohibited during the study, including during the screening period:

- Neuromodulation devices, including TENS, eTENS, vagus nerve stimulation devices and acupuncture

8.2.3 Permitted medications

The following medications are permitted:

1 Rescue analgesics, 2 or more hours after dose of IMP: prescription and nonprescription drugs including Standard of Care medications for treatment of acute migraine headache

2 Other medications eg vitamins, herbal/dietary supplements (including Chinese medicines), oral and IUD contraceptives, hormone replacement therapy, not on the prohibited medications list which have been stable for 3 months prior to screening.

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

9. Study procedures

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

9.1 Subject informed consent

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

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

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

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

Screening procedures may commence immediately following signing of the ICF.

9.2 Screening visit (Visit 1)

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

During the screening procedure, Days -28 to Day – 1 inclusive, subjects will undergo screening assessments including medical history, height, weight, 12-lead ECG, vital signs, and full physical examination. In addition to eligibility criteria, medical history will include details of history of migraine headaches, average duration (shortest and longest), description of nature (throbbing, aggravating factors, unilateral/bilateral, aura), severity and associated symptoms including most troublesome symptom and relationship to menstrual cycle (menstruating females).

Concomitant medications will be recorded. Blood will be collected for routine haematology and biochemistry screening and, in female subjects of child-bearing potential, to test for pregnancy. A urine sample will be collected for urinalysis.

Subjects deemed likely to be eligible for the trial will be given two diaries after completion of the above screening tests, shown how to record and to list concomitant medications. The headache diary will be used to record menstrual cycles, and onset and nature of headaches (both migraine and non-migraine). In addition, they will be instructed to complete a migraine diary during a migraine headache to collect pain and symptom scores and concomitant medications. Scores will be recorded before taking their usual migraine medication and at 0.5, 1.0, 1.5, 2, 4, 8 and 24 hours after taking their usual migraine medication. The screening diaries will be completed for a minimum of 28 days. If the subject does not experience a migraine headache in this period or menstrual bleeding (menstruating females only), the screening diary period may be extended by 7 days, ie up to 35 days total.

Note that diary entries completed prior to Day 1 will be used only to confirm compliance with diary completion requirements on the day of a migraine headache, to verify the nature of migraine headache and the subject's most troublesome symptom.

9.3 First treatment period (Visit 2)

Subjects will return to the unit on Day 1 (Visit 2) with their diaries completed from Day -28 to Day -1 inclusive. If a subject has not experienced a migraine headache or menstrual bleeding (menstruating females only) during the 28-day period, the screening diary period may be extended to 35 days.

On Day 1, assessments including 12-lead ECG, vital signs, a targeted physical examination, recording of concomitant medications, review of the subject's diaries, blood and urine sampling for safety monitoring, and urine sampling for pregnancy testing in FOCBP, will be conducted. Results from safety monitoring tests are not required prior to randomisation.

Eligibility will be confirmed and subjects will be randomised to LAT8881 60 mg or placebo.

Subjects will leave the unit with their two diaries, and one dose of IMP and instructions to take the dose within one hour of the onset of a migraine headache of moderate to severe intensity (NRS ≥4). The headache diary will be used to record menstrual cycles and onset and nature of headaches (both migraine and non-migraine). The migraine diary will be used during a migraine headache to collect pain and symptom scores and concomitant medications before taking the IMP and at 0.5, 1.0, 1.5, 2, 4, 8 and 24 hours after taking the dose. No analgesics or antimigraine medication other than medications for routine prophylaxis not on the Prohibited medicines list may be taken within 24 hours prior to taking the dose of IMP. Rescue medication is permitted a minimum of 2 hours post dose. The subject's symptoms including nausea, photophobia and phonophobia plus the subject's most troublesome symptom if other than nausea, photophobia or phonophobia will be recorded immediately before dosing and at 0.5, 1.0, 1.5, 2, 4, 8 and 24 hours after taking the dose. Episodes of vomiting will also be recorded.

The subject will be instructed to phone the clinic within 24 hours (or one business day) of taking the dose.

On Day 15, if the subject has not phoned the clinic, the subject will be phoned to remind them to complete their diaries, and to phone the clinic when the dose has been taken.

Subjects will return to the clinic for Visit 3 within 5 business days after taking the dose or a maximum of 28 days after Visit 2. Subjects should be reminded to bring their diaries and medication container to the visit.

9.4 Visit 3

Assessments including 12-lead ECG vital signs, a targeted physical examination and concomitant medications will be recorded and the subject's diaries will be reviewed. Blood and urine samples will be taken for safety monitoring and pregnancy testing (FOCBP). Subject satisfaction with Treatment Period 1 IMP will be recorded (if dose taken). Results from safety monitoring tests are not required prior to dosing.

Treatment period 2

Subjects will leave the clinic with their diaries and one dose of IMP (alternate treatment), to take the dose within one hour of the onset of a migraine of moderate to severe intensity (NRS ≥ 4), but not less than 48 hours after last dose, and instructions to complete the diaries as for Treatment period 1. No analgesics or antimigraine medication other than medications for routine prophylaxis not on the Prohibited medicines list may be taken within 24 hours prior to taking the dose of IMP. Rescue medication is permitted a minimum of 2 hours post dose.

The subject's symptoms including, nausea, photophobia and phonophobia plus the subject's most troublesome symptom if other than nausea, photophobia or phonophobia will be recorded at the time of dosing and at 0.5, 1.0, 1.5, 2, 4, 8 and 24 hours after taking the dose. Episodes of vomiting will also be recorded

The subject will be instructed to phone the clinic within 24 hours (or one business day) of taking the second dose.

If the subject has not phoned the clinic, the subject will be phoned 14 days after Visit 3 to remind them to complete their diaries, and to phone the clinic when the dose has been taken.

Subjects will return to the clinic for Visit 4 within 5 business days after taking the dose or a maximum of 28 days after Visit 3.

9.5 End of second treatment period (Visit 4)

Subjects will return to the clinic with their diaries and medication containers at completion of Treatment Period 2.

Blood and urine samples will be taken for safety analysis. 12-lead ECG, vital signs, concomitant medications, targeted physical examination results and adverse events will be recorded. Subjects will be asked to complete assessments for subject satisfaction for Treatment period 2, if dose taken and overall preference for Treatment 1 or 2 if both doses have been taken.

9.6 End of study (Visit 5)

Subjects will be phoned one week after Visit 4 to review any new or changed adverse events or changes in concomitant medications.

9.7 Early withdrawal visit

An early withdrawal visit should be conducted within one week of the subject withdrawal, and/or a minimum 48 hours after last dose of IMP.

Subjects who are completing an early withdrawal visit will return with their diaries and unused IMP.

Blood and urine samples will be taken for safety analysis. 12-lead ECG, vital signs, concomitant medications, targeted physical examination results and adverse events will be recorded. Subjects will be asked to complete assessments for subject satisfaction.

10. Study endpoints

10.1 Primary endpoint

Change in migraine headache pain score, using an 11-point NRS, (0 = none, 10 = worst imaginable), from the time of dosing (t = 0 min) 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.

10.2 Secondary 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

10.3 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

10.4 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

11. Study measurements

11.1 Clinical assessments

11.1.1 Medical history

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

A migraine history, to include frequency, duration and severity of headaches, will be recorded. Sufficient information should be collected to confirm the diagnosis, ie intensity, throbbing/nonthrobbing, aggravating factors, aura, unilateral or bilateral, associated symptoms, eg photophobia, phonophobia, nausea, vomiting, cognitive impairment, dizziness, functional disability, most troublesome symptom.

11.1.2 Demographics

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

11.1.3 Electrocardiogram

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

Any subject with an abnormal ECG at screening that is considered clinically significant will be excluded from the study.

11.1.4 Vital signs

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

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

11.1.5 Physical examination

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

A full physical examination is to be performed at the first screening visit. At other scheduled time points, a targeted (symptom directed) physical examination, as clinically indicated, is to be performed.

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

11.1.6 Height and weight

Height (centimetres) and weight (kilogram), without shoes, will be measured and BMI calculated.

11.2 Laboratory assessments

11.2.1 Clinical safety testing

Blood samples will be tested at one nominated laboratory per study site. Urinalysis (dipstick) will be performed at the investigational site.

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

The following tests will be performed.

11.2.1.1 Haematology

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

11.2.1.2 Clinical chemistry

Glucose, sodium, potassium, chloride, bicarbonate, calcium (corrected), creatinine, urea, uric acid, amylase, lipase, triglyceride, HDL-cholesterol, LDL-cholesterol, total cholesterol, total protein, lactate dehydrogenase, creatine kinase, C-reactive protein, albumin, phosphate

11.2.1.3 Liver function tests

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

11.2.1.4 Coagulation

Activated partial thromboplastin time, international normalised ratio

11.2.1.5 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.

11.2.2 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 at other time points.

11.3 Adverse event monitoring

Subjects will be asked by direct questioning at each visit whether they have experienced any AEs. AEs will be assessed as described in Section 13.2.

11.4 Concomitant medications

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

11.5 Efficacy assessments

11.5.1 Pain intensity

Migraine pain intensity will be recorded using the NRS in a subject migraine diary at the start of dosing (t

= 0 min) 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.

11.5.2 Migraine symptoms

Each subject will specify his/her most troublesome symptom at baseline (Day 1).

On the day of a migraine headache, baseline information about the headache should be recorded to verify that the headache was an acute migraine headache including headache intensity, aura, presence or absence of associated symptoms, unilaterality or bilaterality of the headache, aggravation by exercise, throbbing or nonthrobbing.

The subject's symptoms will be recorded on an 11-point Likert scale. This scale allows the subject to record the presence of the symptom from 0 = no symptoms to 10 being severe symptoms. Symptom assessments will be recorded in the subject's diary prior to dosing (t = 0 min) and at 0.5, 1, 1.5, 2, 4, 8 and 24 hours post dose. Symptoms to be recorded include nausea, photophobia and phonophobia plus the subject's most troublesome symptom (eg cognitive impairment, dizziness and functional disability) if other than nausea, photophobia or phonophobia. Episodes of vomiting will also be recorded.

11.5.3 Subject satisfaction

Subject satisfaction with treatment will be recorded at the end of each treatment period on a 7-point Likert scale, with 1 = very satisfied and 7 being very dissatisfied. Subjects will also be asked to record their satisfaction compared with their usual anti-migraine therapy. Subjects will be asked to complete the satisfaction survey for each Treatment period only if the dose has been taken for that period and the Treatment Preference survey only if doses have been taken in both Treatment periods.

12. Study oversight

12.1 Within-subject stopping criteria

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

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

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

12.2 Suspension or premature termination of the study

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

- The discovery of unexpected, serious, or unacceptable risk to subjects enrolled in the study;
- A decision on the part of Sponsor to suspend, discontinue, or shorten the study;
- Study conduct at a study site may warrant termination under conditions that include the following:
    - Failure of investigator(s) to enrol eligible subjects into the study;
    - Failure of the investigator to comply with country-specific regulations;
    - Submission of false information from the research facility to the sponsor, the clinical monitor, or a regulatory authority;
    - Insufficient adherence to protocol requirements;
    - A conflict of interest of the investigator, his/her institution, or site personnel that could negatively impact the integrity of the clinical study;
    - Institution or Ethics Committee under investigation for cause.

Any decision by the sponsor on stopping or restarting the study must be discussed with the investigator. All actions are to be documented and the Ethics committee (EC) and regulatory (competent) authority notified in writing as required by local regulations. Should a protocol amendment be required, this will be managed in accordance with Section 15.1.4. The study must not recommence recruitment or dosing until approval is received in writing from the EC (if/as required by the EC).

If the study is to be terminated for safety reasons, any further administration of IMP will be stopped.

If the study is terminated for safety reasons, subjects will be followed up for a minimum of two weeks following the last exposure to IMP, at which time an End of study visit should be conducted. Refer to Section 9.6 for follow up assessments. Any AEs/SAEs ongoing at the time of the End of study visit will be followed to resolution or stabilisation (whichever is the sooner).

13. Adverse events

13.1 Definitions

13.1.1 Adverse event

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

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

Laboratory reference ranges are defined by upper or lower limits of parameters of the respective laboratory. The investigator should ensure that each parameter out of the normal range is assessed for clinical significance and the potential for being an AE (refer to Section 13.3). An adverse event is defined as 'serious' when it meets one of the pre-defined outcomes as described in Section 13.1.6.

13.1.2 Adverse drug reaction/Suspected adverse (drug) reaction

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

13.1.3 Suspected unexpected serious adverse reactions

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

For regulatory reporting purposes, SUSARS will be unblinded.

13.1.4 Causality

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

Not related:	AE with an incompatible time relationship to IMP administration, and that could be explained by underlying disease or other drugs or is incontrovertibly not related to the Investigational Product
Possibly related:	AE with a reasonable time relationship to IMP administration, but which also could be explained by concurrent disease or other medications.
Probably related:	AE with a reasonable time relationship to IMP administration that is unlikely to be attributed to concurrent disease or other medications.
Definitely related:	AE with plausible time relationship to IMP administration and which cannot be explained by concurrent disease or concomitant medications.

13.1.5 Severity (intensity) of adverse event

Grade refers to the intensity of an AE and should not be confused with seriousness (refer Section 13.1.6).

Grade 1	Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
Grade 2	Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental Activities of Daily Living (ADL*).
Grade 3	Severe or medically significant but not immediately life-threatening; hospitalisation or prolongation of hospitalisation indicated; disabling; limiting self-care ADL**.
Grade 4	Life-threatening consequences; urgent intervention indicated.
Grade 5	Death related to AE.

Activities of daily living (ADL)

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

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

13.1.6 Serious adverse event

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

- Results in death,
- Is life-threatening.
- Life-threatening in the definition of serious refers to an event in which the subject was at risk of death at the time of the event, it does not refer to an event which hypothetically might have caused death if it were more severe.
- Requires inpatient hospitalisation or prolongation of existing hospitalisation.
- Hospitalisation is defined as inpatient admission or care regardless of duration. Out-patient treatment in an emergency room is not in itself an SAE, although the reasons for it may be. Elective surgery, or hospital admissions and/or surgical operations planned before or during this study are not considered AEs if the illness or disease existed before the subject was enrolled in the study, provided that it did not deteriorate in an unexpected way during the study.
- Results in persistent or significant disability/incapacity.
- Is a congenital anomaly/birth defect.
- Is medically important or is a medically significant event.

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

13.2 Recording of adverse events

In this study, events from Screening to prior to first dose of IMP will be captured as medical history. All

events occurring during and following the first administration of IMP will be reported as AEs or SAEs (if criteria met) until the completion of the End of study visit.

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

It is preferable that AEs and SAEs be reported as diagnoses if available, rather than individual signs and symptoms. SAEs should be reported and documented in accordance with the procedures in Section 13.4. The following data should be documented for each AE: the description of the event, start and stop dates, intensity, causality and outcome must be recorded, as well as any actions taken.

13.3 Clinical lab abnormalities and other abnormal assessments

Abnormal laboratory findings (eg, clinical chemistry, haematology, and urinalysis) or other abnormal assessments (eg, ECG, vital signs) per se are not reported as AEs. However, those abnormal findings that are deemed clinically significant or are associated with signs and/or symptoms must be recorded as AEs (and recorded as an SAE if they meet the criteria of being serious) as described previously. Clinically significant abnormal laboratory or other abnormal findings that are present at baseline and worsen after first dose of IMP are to be considered AEs (and SAEs if serious).

The investigator should exercise his or her medical and scientific judgment in deciding whether an abnormal laboratory finding or other abnormal assessment is clinically significant. Usually, the abnormality should be associated with a clinically evident sign or symptom, or be likely to result in an evident sign or symptom in the near term, to be considered clinically significant. A clinically significant laboratory abnormality in the absence of clinical symptoms may jeopardize the subject and may require intervention to prevent immediate consequences.

13.4 Reporting of serious adverse events

Any SAE must be reported by the investigator if it occurs during the clinical study or within 2 weeks of the subject having received the last dose of IMP, whether or not the SAE is considered to be related to the IMP. This shall include pregnancy in a female subject or in a female partner of a male study subject. Instances of death, congenital abnormality or an event that is of such clinical concern as to influence the overall assessment of safety, if brought to the attention of the investigator at any time after cessation of IMP administration and linked by the investigator to this study, should be reported to the sponsor.

The investigator must report an SAE on an SAE report form and forward the SAE report form, the AE form and the concomitant medication form to the sponsor or delegate **within 24 hours of becoming aware of the SAE** and **regardless of causality**. All pregnancies in a female subject or in a female partner of a male study subject should be reported on a Pregnancy report form following the same reporting process and timelines required for SAEs.

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

Followup information on SAEs must also be reported by the investigational site to the sponsor within the same time frame. If a non-serious AE becomes serious, this and other relevant followup information must also be provided within 24 hours of the investigator becoming aware.

All SAEs will be recorded in the subject's source documents and the CRF.

It is the responsibility of the sponsor to determine whether a reported SAE fits the classification of a SUSAR (refer to Section 13.1.3). If the sponsor considers the SAE to be drug related (ie an adverse drug

reaction), unexpected and fulfils the criteria for a suspected unexpected serious adverse reaction (SUSAR), the sponsor has the responsibility to expedite the reporting to all concerned investigators, to the EC where required, and to the appropriate regulatory authorities within the pre-defined timelines.

The investigator must notify their EC of SAEs occurring at the site, within the time period and in accordance with requirements specified by the EC.

The sponsor and/or delegate will promptly notify all relevant investigators and the regulatory authorities of findings that could adversely affect the safety of subjects, impact on the conduct of the study or alter the ethics approval/favourable opinion of the study.

13.5 Followup of adverse events and serious adverse events

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

14. Statistical analysis

14.1 General considerations

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

The descriptive summary for the categorical variables will include counts and percentages. The descriptive summary for the continuous variables will include number of subjects (n), means, medians, standard deviations, and minimum and maximum values. All data will be listed for all subjects. Treatment period order will be ignored in any treatment comparisons. Results will be presented in a descriptive format by treatment within each treatment period and overall. Treatment comparisons will take into account the paired nature of the treatment responses where feasible. As this is a Phase IIa proof of concept study, no formal statistical hypotheses are being specified although some may be investigated as part of the data presentation, in which case corresponding 95% confidence intervals will be presented and p-values of <0.05 will be declared statistically significant.

14.2 Sample size

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

14.3 Analysis populations

14.3.1 Full analysis set

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

14.3.2 Per protocol population

A per-protocol (PP) population will be used for efficacy analyses and to analyse exploratory endpoints. The PP population will be based on IMP exposure, including the time of any episodes of vomiting and major protocol deviations.

14.3.3 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.

14.4 Subject disposition

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

14.5 Analysis of efficacy data

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

summary tables and results will be presented for the FAS population.

Individual pain score-time profiles for each treatment within each subject will be presented graphically. The difference between the NRS pain scores at each timepoint for LAT8881 60 mg compared with placebo within each subject will be estimated and presented graphically. The number of subjects, mean, standard deviation, minimum and maximum NRS pain score at each timepoint, change from baseline, difference between treatments at each timepoint and change from baseline difference between treatments will be presented for each treatment overall and within each treatment period.

Nausea, photophobia and phonophobia symptom scores will be summarised and presented in the same way as the pain scores. The number and percent of headaches with each most troublesome symptom of migraine including nausea, cognitive impairment, dizziness, functional disability, photophobia and phonophobia will be summarised for each treatment. The most troublesome symptom scores will be summarised and presented in the same way as the pain scores.

The number and percent of subjects with 'no headache pain' at each time point will be presented for each treatment. Two-way tables will present the presence/absence of pain classified for each treatment at each timepoint. Absence of pain will be defined as a pain NRS score of 0 or 1.

The number and percent of subjects who are “sustained pain-free” at 24 hours after dose of IMP will be presented by treatment. A two-way table will present the “sustained pain-free” status for subjects on each treatment.

The number and percent of subjects will be summarised by their first pain-free timepoint. A two-way table will present the classification of each subject’s first pain-free timepoint by treatment. Kaplan-Meier curves will present the time to first pain-free timepoint.

Patient satisfaction for each treatment recorded on a 7-point Likert scale and the within-subject difference between treatments will be summarised. The mean difference between treatments will be compared with a paired t-test and the 95% confidence interval for the mean difference will be presented. Additional exploratory analyses to investigate the association between change in headache pain and symptom scores and selected subject baseline characteristics will be undertaken in a similar fashion with descriptive statistics.

14.5.1 Analgesic use

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

14.6 Analysis of safety data

14.6.1 Extent of exposure

The number of subjects exposed to study treatment, and total IMP administered within each period and overall, will be summarised.

14.6.2 Adverse events

Adverse events will be coded using the Medical dictionary for regulatory activities (MedDRA) and summarised by system organ class (SOC) and preferred term (PT).

A summary of the number and percentage of subjects with the following adverse events will be prepared:

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

- Adverse events by intensity
- Adverse events by relationship to IMP

All summaries of adverse events will include only treatment emergent adverse events (TEAEs). Refer Section 13.1 for adverse event definitions.

14.6.3 Clinical laboratory evaluations

Safety laboratory data (haematology, biochemistry, and urinalysis) will be summarised by visit and treatment. All laboratory data will be included in the data listings. In addition, a separate listing of laboratory data for subjects with clinically significant abnormal results will be prepared.

14.6.4 Other safety measures

Vital signs (body temperature, respiratory rate, heart rate, and blood pressure) will be summarised by baseline and treatment overall and for each treatment within the treatment sequence. Changes over time in vital signs will be summarised.

Physical examination data will be listed only.

The number and percentage of subjects receiving concomitant medications will be tabulated overall and by medication received.

15. Study management

15.1 Regulatory and ethical considerations

15.1.1 Regulatory compliance and ethical conduct

This study must be conducted in compliance with the study protocol, the requirements and obligations of the International Conference on Harmonisation (ICH) and Good Clinical Practice (GCP) guidelines, Integrated Addendum to ICH E6(R1): Guideline for Good Clinical Practice E6(R2),[1] the World Medical Association Declaration of Helsinki[16] and its amendments and all applicable local guidelines, laws and regulations.

Investigators and other site personnel will undergo appropriate study-specific training during the study site initiation visit. Before initiation of the study at the site(s), the written approval / favourable opinion of the local and/or national independent ethics committee(s) and relevant health authority(ies) will be sought and obtained.

15.1.2 Ethics committee review

Prior to the initiation of the study, the protocol and associated documentation (including all materials used to recruit subjects for the study) must be given a favourable opinion by an ethics committee (EC). A copy of this written approval and any correspondence with the EC will be provided to the sponsor.

The investigator must obtain approval from the sponsor before potential subjects can undergo any study-specific screening procedures.

The investigator will comply with any additional requirements imposed by the EC. The investigator must submit progress reports to the EC according to local regulations and guidelines. The investigator must also provide their EC with any reports of SAEs from the study site in accordance with the EC's requirements and timelines.

15.1.3 Informed consent process

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

The subject's signed and dated informed consent must be obtained before conducting any procedure specifically for the study. The investigator must store the original, signed ICF with the subject's medical records. A copy of the signed and dated ICF must be given to the subject.

Subjects who are incompetent and unable to freely provide informed consent and subjects who are unable to read or speak English without the assistance of an interpreter will not be invited to participate in the study.

If new information arises during the study that may affect the safety of the subjects, the protocol and ICF will be amended as appropriate and submitted to the EC as outlined in Section 15.1.4. Following approval by the EC, subjects will be advised by letter of any safety related updates that may impact during the post-study period and be invited to discuss any concerns with the investigator. When applicable, subjects may be requested to re-consent to ongoing their participation in the study.

15.1.4 Protocol amendments

The signed, EC-approved protocol must not be changed without the agreement of the sponsor. If it is necessary for an EC-approved study protocol to be amended, the relevant EC and, if required, the local

regulatory authority must be informed and asked for its opinion as to whether a re-evaluation of the ethical aspects of the study is necessary.

The investigator must not implement any deviation from, or change to the protocol, without agreement by the sponsor and prior review and documented approval/favourable opinion of the amendment from the relevant EC, except where it is necessary to eliminate an immediate hazard to study subjects, or where the change(s) involve(s) only logistical or administrative aspect(s) of the study, for example, change in monitor(s) or change of telephone number(s).

If a protocol amendment requires a change to the Participant information sheet (PIS) or Informed consent form (ICF), approval of the revised PIS and ICF by the sponsor and EC is required before the updated document can be used.

Following approval, the sponsor (or delegate) will distribute new versions of amended documents (eg protocol, PIS, ICF) to the site.

15.1.5 Protocol deviations

No deviations from or changes to the protocol will be implemented without documented approval from the EC of an amendment, except where necessary to eliminate an immediate hazard(s) to study subjects or when the change(s) involves only logistical or administrative aspects of the study.

Any deviations from or changes to the protocol which were implemented to eliminate an immediate hazard and the proposed amendment, if appropriate, should be submitted to the EC for review and approval as soon as possible.

Should any protocol deviation occur, it must be reported to the study monitor as soon as is reasonably practical. If a major protocol deviation occurs, the investigator must notify the sponsor and the appropriate EC as soon as possible or as per local requirements.

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

15.2 Quality control and quality assurance

15.2.1 Training of staff

Each individual involved in the study must be qualified by education, training and experience to perform his or her respective tasks.

Site staff may be trained at investigator meetings and initiation visits by the sponsor or their designees.

15.2.2 Study monitoring

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

Before the start of the study, a study monitor appointed by the sponsor will evaluate the investigational site to ensure facilities are adequate and to discuss responsibilities with the site staff with regards to following the protocol and regulatory and ethical requirements.

During the study, the study monitor will regularly visit the site to monitor and confirm protocol, regulatory and ethical adherence, confirm data accuracy and provide information and support as needed.

The investigator is responsible for maintaining source documents. The investigator must agree to allow the study monitor direct access to all relevant documents at each monitoring visit, including electronic medical records, and to allocate their time and the time of their staff to the study monitor to discuss findings and any relevant issues.

Site staff will be provided with contact details for the study monitor and back-up persons in the event they have queries or require assistance.

15.2.3 Data management and quality control

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

Data generated within this clinical study will be handled according to the relevant SOPs of the sponsor and/or their delegate(s). An electronic CRF (eCRF) will be created by the data management group for recording of the required data and integration into the study database. All data (including electronically available data, ie eCRF and laboratory data) will be integrated into a validated Data Management System with full audit trail capability (ie a computerised log of all subsequent changes to the data will be recorded). Automated checks will be made against the data to ensure completeness and consistency. The database and check programs will be validated before implementation. AEs will be coded using MedDRA and medications will be coded using the current version of the WHO drug dictionary.

Missing or inconsistent data will be queried via system generated queries to the investigator for clarification. Subsequent modifications to the database will be documented.

Data collection and entry into the eCRF will be completed by authorised study site personnel designated by the investigator. Appropriate training and security measures will be completed with the investigator and all authorised study site personnel prior to the study being initiated and any data being entered for any study subjects.

The eCRFs should always reflect the latest observations on the subjects participating in the study; therefore, the eCRFs are to be completed as soon as possible during or after the subject's visit. The investigator must verify that all data entries in the eCRFs are accurate and correct. If some assessments are not done, or if certain information is not available or not applicable or unknown, this should be indicated in the eCRF. The investigator will be required to sign off on the final clinical data.

During the study the study monitor will review the eCRFs and evaluate them for completeness and consistency. The eCRF will be compared with the source documents to ensure that there are no discrepancies. All entries, corrections and alterations are to be made by the investigator or designee.

The study monitor cannot enter data into the eCRFs. If corrections are needed, the responsible study monitor or data manager will raise a query and the appropriate investigational staff will be required to provide an answer. All queries and resultant data changes will have an electronic audit trail, meaning that the name of the investigational staff responding to the query, time and date stamp are captured.

The eCRF is considered a data entry form and should not constitute the original, or source document, unless otherwise specified. Source documents are documents used by the investigator or study site that relate to the subject's medical record, that verify the existence of the subject, the inclusion and exclusion criteria and all records covering the subject's participation in the study. They include, but are not limited to, laboratory reports, hospital records, subject files, etc.

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

15.2.4 Audits and inspections

An audit is a systematic and independent examination of study related activities and documents to determine whether the evaluated study activities were conducted and the data were recorded, analysed and accurately reported according to the protocol, the sponsor's standard procedures or those of the sponsor's designees, ICH GCP and applicable regulatory requirements.

In accordance with ICH GCP, this study may be selected for audit. Inspection of site facilities (eg pharmacy, medication storage areas, laboratories) and review of study-related records may occur by the sponsor, sponsor's representative, ethics committee or regulatory authority to evaluate the study conduct and compliance with the protocol, ICH GCP, and applicable regulatory requirements.

The regulatory authority or ethics committee inspectors are responsible for contacting and visiting the investigative site for the purpose of inspecting the facilities, if required, and, upon request, inspecting the various records of the study (eg source documents, CRFs, essential documentation, and other pertinent data) ensuring that subject confidentiality is respected.

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

15.3 Documentation, record access and archiving

15.3.1 Maintenance of essential documents/supplements at study site during the study

At the beginning of the study, an Investigator's Study File will be established at the study sites. The investigator/institution is responsible for maintaining the study documents during the study as specified in the ICH GCP[1] guidelines and applicable regulatory requirement(s). The investigator/institution must take measures to prevent accidental or premature destruction of these documents.

These files must be suitable and available for inspection at any time by the sponsor, study monitor, and/or applicable regulatory authorities.

15.3.2 Data protection

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

Personal information will be treated as confidential, but may need to be reviewed by authorised representatives of the sponsor (and/or delegate), the EC and regulatory authority(ies). The subject's consent to direct access to his/her original medical records for data verification purposes must be obtained prior to that subject's involvement in the study.

Subjects will be informed that data will be held on file by the sponsor and that these data may be viewed by staff including the study monitor and by external auditors on behalf of the sponsor and appropriate regulatory authorities. Subjects will also be informed that a study report will be prepared and may be submitted to regulatory authorities and that the study results may be published. However, subjects will be identified in such reports only by study identification number (Subject ID), gender and age. All subject data will be held in strict confidence.

The PIS will explain that electronic study data will be stored in a computer database, maintaining confidentiality in accordance with the applicable local privacy regulations. Subject data in the database will be identified by Subject ID number only. Electronic CRFs will also identify subjects by Subject ID only and will be maintained and stored in accordance with the applicable local privacy regulations.

The PIS will also explain that for data verification purposes, authorised representatives of the investigator, sponsor, regulatory authorities or ECs may require direct access to parts of the hospital or practice records relevant to the study including the subject's source documents and/or medical record.

15.3.3 Data retention & archiving

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

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

At completion of the study the investigator is responsible for the archiving of the study records for their site.

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

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

15.4 Study administration

15.4.1 Study agreements

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

Payments will relate to the number of subjects as well as the cost of clinical visits, laboratory investigations and other services outside of normal routine examinations and specifically connected with the conduct of this study. This agreement will cover payment for eCRFs fully completed in conformity with the protocol. The fee for subjects who withdraw prematurely from the study will be on a pro-rata basis reflecting the percentage of study activities completed.

Neither the sponsor nor its designee is financially responsible for further testing/treatment of any medical condition that may be detected during the screening process. In addition, in the absence of specific arrangements, neither the sponsor nor its designee is financially responsible for further treatment of the subject's condition beyond the time period specifically outlined in this protocol.

The investigator(s) must comply with all the terms, conditions and obligations of the study agreement for this study. In the event of any inconsistency between this protocol and the study agreement, the study agreement shall prevail.

15.4.2 Confidentiality

In signing the final protocol, every participating investigator agrees to keep all information and results concerning the study and the investigational product confidential for as long as the data remain

unpublished. The confidentiality obligation applies to all personnel involved at the study site. However, authorised regulatory officials and the sponsor's personnel (or their representatives) will be allowed full access to inspect and copy the records. All IMPs, subject bodily fluids and/or other materials collected shall be used solely in accordance with this protocol, unless otherwise agreed to in writing by the sponsor and the EC.

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

15.4.3 Insurance

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

Further details of this and financial arrangements are specified in the agreements with the study site.

15.4.4 Reporting

A final integrated clinical/statistical report will be prepared that is compliant with the ICH Note for Guidance: Structure and Content of Clinical Study Reports (CPMP/ICH/137/95)[17].

15.4.5 Publication policy

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

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

Except for legal reasons, the investigator will not reveal the result of the study to a third party without a mutual agreement about the analysis and interpretation of the data with the sponsor.

16. References

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

[2] IHS Classification ICHD-3 https://www.ichd-3.org/1-migraine/

[3] Headache Classification Committee of the International Headache Society (IHS) The International Classification of Headache Disorders, 3rd edition. Cephalalgia. 2018 Jan; 38 (1):1-211. doi: 10.1177/0333102417738202

[4] Chawla J. Migraine Headache. Medscape Jan 31, 2019 Available at https://emedicine.medscape.com/article/1142556-overview. Accessed 1 May, 2019

[5] Burstein R, Noseda R, Borsook D. Migraine: multiple processes, complex pathophysiology. J Neurosci. 2015 Apr 29; 35(17):6619-29. doi: 10.1523/JNEUROSCI.0373-15.2015

[6] Yeh WZ, Blizzard L, Taylor BV. What is the actual prevalence of migraine? Brain Behav. 2018 Jun;8(6):e00950. doi: 10.1002/brb3.950. Epub 2018 May 2.

[7] GBD 2016 Disease and Injury Incidence and Prevalence Collaborators. Global, regional, and national incidence, prevalence, and years lived with disability for 328 diseases and injuries for 195 countries, 1990-2016: a systematic analysis for the Global Burden of Disease Study 2016. Lancet. 2017 Sep 16; 390: 1211-1259. doi: 10.1016/S0140-6736(17)32154-2.

[8] Lipton RB, Bigal ME. Migraine: epidemiology, impact, and risk factors for progression. Headache. 2005 Apr;45 Suppl 1:S3-S13

[9] Deloitte Access Economics. Migraine in Australia Whitepaper. Prepared for Novartis Australia 2018. Available at https://www2.deloitte.com/content/dam/Deloitte/au/Documents/Economics/deloitte-au-economics-migraine-australia-whitepaper-101018.pdf. Accessed 26 April, 2019.

[10] American Headache Society 2018.The American Headache Society position statement on integrating new migraine treatments into clinical practice. Headache 2019; 59: 1-18

[11] Biondi DM. Is migraine a neuropathic pain syndrome? Curr Pain Headache Rep. 2006 Jun;10(3):167-78.

[12] European Medicines Agency. Guideline on Clinical Investigation of Medicinal Products for the Treatment of Migraine, Doc. Ref. CPMP/EWP/788/01 Rev. 1. London, 24 January 2007

[13] Diener HC, Tassorelli C, Dodick DW, Silberstein SD, Lipton RB, Ashina M, Becker WJ, Ferrari MD, Goadsby PJ, Pozo-Rosich P, Wang SJ, Mandrekar J; International Headache Society Clinical Trials Standing Committee. Guidelines of the International Headache Society for controlled trials of acute treatment of migraine attacks in adults: Fourth edition. Cephalalgia. 2019 Feb 26

[14] FDA Guidance for Industry. Estimating the Maximum Safe Starting Dose in Initial Clinical Trials for Therapeutics in Adult Healthy Volunteers. July 2005

[15] Pharmaceutical Inspection Convention Pharmaceutical Inspection Co-Operation Scheme. Guide to Good Manufacturing Practice for Medicinal Products Annexes [Internet]. Geneva: PIC/S Secretariat; 1 January 2017. Available from https://www.picscheme.org/en/publications?tri=gmp (accessed 17 March 2018)

[16] World Medical Association. World Medical Association Declaration of Helsinki: ethical principles for medical research involving human subjects. JAMA. 2013;310(20):2191-2194

[17] International Conference on Harmonisation (ICH) Note for Guidance: Structure and Content of Clinical Study Reports. CPMP/ICH/137/95, December 1995.