Title:

A Phase 2b, Multicenter, Randomized, Double-blind, Placebo-controlled, Dose-finding Study of Elismetrep (K-304) in the Treatment of Acute Migraine

Protocol Date:

06-November-2024

NCT:

06848075

ELISMETREP (K-304)

P001

A Phase IIb, Multicenter, Randomized, Double-Blind, Placebo- Controlled, Dose-Finding Study of Elismetrep (K-304) in the Treatment of Acute Migraine

KALLYOPE, Inc.

430 East 29th Street

New York, NY 10016

Protocol Issue Date: 06-NOV-2024

IND Number: 173305

Confidentiality Statement

This protocol and all related information are confidential and proprietary property of KALLYOPE, Inc., New York, NY, U.S.A.

SIGNATURE PAGE

Sponsor's Approval

The protocol has been approved by Kallyope, Inc.

Responsible Medical Officer:

[redacted]

Chief Medical Officer

Sponsor's Authorized Officer:

Company/Sponsor signatory	Date

[redacted]

430 East 29th St.

New York, New York 10016

[redacted]

INVESTIGATOR'S AGREEMENT

I have received and read the Investigator's Brochures for elismetrep (K-304). I have read elismetrep (K-304) P001 and agree to conduct the study as outlined in the protocol and abide by all provisions of this protocol. I agree to conduct the study in accordance with generally accepted standards of Good Clinical Practice, the FDA Form 1571 and with all obligations detailed in applicable regulations and guidelines. I also agree to report all information or data in accordance with the protocol and, in particular, report any serious adverse events as defined in the protocol. I also agree to handle all clinical supplies provided by the Sponsor and collect and handle all clinical specimens in accordance with the protocol. I understand that information that identifies me will be used and disclosed as described in the protocol, and that such information may be transferred to countries that do not have laws protecting such information. Since the information in this protocol and referenced Investigator Brochure is confidential, I understand that its disclosure to any third parties, other than those involved in approval, supervision, or conduct of this trial is prohibited. I will ensure that the necessary precautions are taken to protect such information from loss, inadvertent disclosure, or access by third parties.

_____

Printed Name of Investigator

_____

Signature of Investigator

_____

Date

PROCEDURES IN CASE OF EMERGENCY

Table 1: Emergency Contact Information

Role in Study	Name	Contact Information
[redacted]		[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]

2. SYNOPSIS

<table>
<tr><td colspan="3">Name of Sponsor/Company:
Kallyope, Inc.</td></tr>
<tr><td colspan="3">Name of Investigational Product:
Elismetrep (K-304)</td></tr>
<tr><td colspan="3">Name of Active Ingredients:
K-304 (elismetrep)</td></tr>
<tr><td>Protocol Number: P001</td><td>Phase: 2b</td><td>Country: USA</td></tr>
<tr><td colspan="3">Title of Study: A Phase IIb, Multicenter, Randomized, Double-Blind, Placebo- Controlled, Dose-Finding Study of Elismetrep (K-304) in the Treatment of Acute Migraine</td></tr>
<tr><td colspan="3">Study center(s): Multi-center study in US</td></tr>
<tr><td colspan="2">Studied period (years): 12-months
Estimated date first patient enrolled: March, 2025
Estimated date last patient completed: December, 2025</td><td>Phase of development: 2b</td></tr>
<tr><td colspan="3">Number of participants (planned):
Approximately 400 (randomized 2:1:2:2:1 to placebo, 2 mg, 5 mg, 10 mg, or 20 mg)</td></tr>
<tr><td colspan="3">Objectives:
Primary:
To evaluate the efficacy of a range of dose levels of elismetrep compared with placebo in the acute treatment of migraine as measured by pain freedom at two hours post dose.
Secondary:
To evaluate the efficacy of a range of dose levels of elismetrep compared to placebo on freedom from the most bothersome symptom (MBS), associated with migraine, at two hours post dose.
To evaluate the efficacy of a range of dose levels of elismetrep compared to placebo on pain relief at 2 hours post-dose.
To evaluate the efficacy of a range of dose levels of elismetrep compared to placebo on freedom from photophobia at 2 hours post-dose.
To evaluate the efficacy of a range of dose levels of elismetrep compared to placebo on freedom from phonophobia at 2 hours post-dose.
To evaluate the efficacy of a range of dose levels of elismetrep compared to placebo on freedom from nausea at 2 hours post-dose.
To evaluate the efficacy of a range of dose levels of elismetrep compared to placebo on the probability of requiring rescue medication within 24 hours of initial treatment.
To evaluate the efficacy of a range of dose levels of elismetrep compared to placebo on sustained pain freedom from 2 to 24 hours post-dose.
To evaluate the efficacy of a range of dose levels of elismetrep compared to placebo on sustained pain relief from 2 to 24 hours post-dose.
To evaluate the efficacy of a range of dose levels of elismetrep compared to placebo on sustained pain freedom from 2 to 48 hours post-dose.</td></tr>
</table>

- To evaluate the efficacy of a range of dose levels of elismetrep compared to placebo on sustained pain relief from 2 to 48 hours post-dose.
- To evaluate the safety and tolerability of various doses of elismetrep in the treatment of acute migraine.

Exploratory:

- To evaluate the efficacy of a range of dose levels of elismetrep compared to placebo on freedom from functional disability at 2 hours post dose according to the Functional Disability scale for subjects who reported any level of disability at the migraine baseline.
- To evaluate the efficacy of a range of dose levels of elismetrep compared to placebo for the incidence of pain relapse from 2 to 48 hours post-dose.

Study Design

This will be a multi-center, randomized, double-blind, placebo-controlled, parallel-group study to evaluate the safety, tolerability, and efficacy of various doses of elismetrep in the treatment of patients with an acute migraine attack. Four hundred (400) subjects will be randomized in a 2:1:2:2:1 ratio to one of the following treatment groups: placebo or 2, 5, 10, or 20 mg of elismetrep. Randomization will be stratified according to use of background prophylactic medications for migraine (yes/no). An interim analysis will be conducted after approximately 200 subjects have been randomized (see Section 16.10). Randomization will not pause for the interim analysis.

Patients who meet all of the study entry criteria will be randomized and provided with study medication (elismetrep or placebo) to be taken on an outpatient basis as soon as they experience a moderate or severe (Grade 2 or 3) migraine headache (HA).

Subjects will use an eDiary to record migraine-related information. Upon experiencing a potentially qualifying HA, subjects will log in and answer questions designed to ascertain whether migraine headache is qualifying according to the criteria listed below and whether medications specifically prohibited 48 h prior to a qualifying migraine have been taken (Section 10.1). During the 48 hours following the dose of study medication, patients will record various measures in an electronic diary (eDiary) at specified time intervals. These measures include subjective assessments of pain severity, presence or absence of migraine-associated symptoms, degree of functional disability, use of rescue medication (yes/no), and the onset of the first moderate or severe headache recurrence (if any).

The patient will be instructed to take their study medication, as an outpatient. The patient will be instructed to treat a migraine headache if the following conditions are met:

- The migraine headache severity is moderate or severe (Grade 2 or 3).
- The migraine headache started less than four hours ago.
- The migraine headache is a new headache that has not been previously treated and is not a recurrence of a previous migraine headache (at least 48 hours must have elapsed since the complete termination of their last attack (pain and all associated symptoms)).
- No other migraine headache or headache has occurred in the previous 48 hours.
- The migraine headache is not already resolving on its own.
- Prohibited medication has not been taken (see Section 10.1).

Subjects should take study medication after answering diary questions about their current pain and symptoms and after identifying their currently most bothersome, migraine associated, symptom (phonophobia, photophobia or nausea).

The date and time of study therapy administration will be recorded in the eDiary. Patients who have headache pain reduced to a mild intensity or pain free intensity level will be considered to have achieved pain relief.

After dosing with study medication, all other headache medication is prohibited during the 2 hours post dose. Beginning two hours after taking study medication and after the 2-hour assessment has been completed, patients may take non-study rescue medication for a non-responding headache, (i.e., headache has failed to improve to Grade 1/0 (mild/no pain)), and for headache recurrence. Use of rescue medication must conform to the prescribing information of the product and the restrictions of this protocol.

Similarly, if the migraine is relieved by study medication at 2 hours after dosing but then recurs to a moderate or severe intensity level between 2 and 48 hours, the patient will be permitted to take the same rescue therapy as outlined above. In all circumstances, the patient will continue to complete his or her diary for up to 48 hours after consuming the study medication.

After being randomized, patients have up to 45 days to treat a qualifying migraine. However, once the targeted number of treated patients has been reached, the study can be stopped at any point at the discretion of the Sponsor.

Patients will return to the study site within 4-7 days after treatment to allow review of the diary, assessment of medication compliance, and safety monitoring.

If a patient has NOT experienced a qualifying migraine headache within 45 days after randomization (V2), he or she will be withdrawn from the trial and instructed to return unused study medication and diary to the study center.

The schedule of assessments is shown in Table 2.

The interactive web response system (IWRS) will be used to randomly assign patients to their treatment group. Initial drug supplies and subsequent shipments will be managed by WRS.

Subject/Criteria for Entry into the Trial

Inclusion Criteria:

A patient will be eligible to participate in this study if all of the following criteria apply:

1. Be a male or female, age 18 to 70 years, inclusive, at the time of signing informed consent.
2. Patient has greater than a one-year history of migraine with or without aura as defined by International Conference on Harmonization (IHS) criteria 1.1 and 1.2 and his/her migraines typically last between 4 to 72 hours, if untreated (Refer to Appendix A for International Classification of Headache Disorder (ICHD) III Attachment for IHS migraine definitions) as documented in the patient's medical records from his/her treating physician and confirmed by the investigator.
3. Patient has had ≥2 and ≤10 moderate or severe migraine attacks per month in each of the two months prior to screening (Visit 1).
4. Meet the following requirements:
    a. Is a male

    OR

    b. Is a female who is of non-childbearing potential defined by at least 1 of the following criteria:

    c. Postmenopausal (aged >45 years and with a minimum of 12 months of spontaneous amenorrhea with a Screening serum follicle-stimulating hormone (FSH) level in the menopausal range established for the central laboratory.

    d. Post hysterectomy, bilateral oophorectomy or bilateral salpingectomy, based on the subject's recall of their medical history.

    OR

    e. Is a female of reproductive potential and:

f. agrees to remain abstinent from heterosexual activity[a]

g. or agrees to use (or have their partner use) a birth control method that is acceptable from the first dose of study drug until the end of trial (EoT) visit. Acceptable methods of birth control are:

- combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation:
  - oral
  - intravaginal
  - transdermal
- progestogen-only hormonal contraception associated with inhibition of ovulation:
  - oral
  - injectable
  - implantable
- intrauterine device (IUD)
- intrauterine hormone-releasing system (IUS)
- bilateral tubal occlusion
- vasectomised partner
- sexual abstinence
- progestogen-only oral hormonal contraception, where inhibition of ovulation is not the primary mode of action
- male or female condom with or without spermicide
- cap, diaphragm or sponge with spermicide
- A combination of male condom with either cap, diaphragm or sponge with spermicide (double barrier methods)

[a] Abstinence can be used as the sole method of contraception if it is in line with the subject's preferred and usual lifestyle and if considered acceptable by local regulatory agencies and ethics committees. Periodic abstinence (e.g., calendar, ovulation, sympto-thermal, post-ovulation methods, etc.) and withdrawal are not acceptable methods of contraception.

This condition is waived if the subject is proven to have no child-bearing potential (eg, hysterectomy).

5. Patient voluntarily agrees to participate in the study by giving written informed consent.
6. Patient is able to read, understand and complete the study questionnaires and diary.
7. Be willing and able to comply with the study schedule of visits, all trial procedures and restrictions.
8. Be willing to use their own personal, qualified smartphone to download study specific eDiary applications for use during the study.

Exclusion Criteria:

Participants are excluded from the trial if any of the following criteria apply:

1. Is a female who is pregnant, breast-feeding or intends to become pregnant during the planned course of the study. **Note:** Participants must have a negative serum pregnancy test (β-human chorionic gonadotropin (β-hCG)) performed by the central laboratory prior to enrollment in the study and negative urine pregnancy result at the randomization visit.

Migraine history-related

2. Patient has difficulty distinguishing his/her migraine attacks from tension-type headaches.
3. Patient has a history of predominantly mild migraine attacks or migraines that usually resolve spontaneously in less than two hours.
4. Patient has more than 15 headache-days per month or has taken medication for acute headache on more than 10 days per month in any of the three months prior to screening (Visit 1).
5. Patient has brainstem (a.k.a. basilar-type) or hemiplegic migraine headache, or retinal migraine.
6. Patient was >50 years old at age of first migraine onset.
7. Patient is taking migraine prophylactic medication where the prescribed daily dose has changed during the 3 months prior to screening (Visit 1) or anticipates any change during the study. Any withdrawal of preventive medications for the treatment of migraine should be completed at least 30 days prior to screening.

Medical history related

8. Patient has, in the opinion of the investigator, other confounding pain syndromes, psychiatric conditions such as uncontrolled major depression, history of psychosis, dementia or significant neurological disorders other than migraine. [Patients who are currently being treated with non-prohibited medication (Section 10.1) for depression and symptoms are well controlled, in the opinion of the investigator, are eligible to participate in this study].
9. Patient is at imminent risk of self-harm, based on clinical interview and responses on the Columbia Suicidality Severity Rating Scale (C-SSRS), or of harm to others in the opinion of the investigator. Patients must be excluded if they report suicidal ideation with intent, with or without a plan (i.e., Type 4 or 5 on the C-SSRS) in the past 2 months or suicidal behavior in the past 6 months.
10. Has a recent history (within the past 3 years of the screening visit) or current diagnosis or evidence of endocrine, hematological, immunological, renal, respiratory, neurologic, gastrointestinal, biliary, or genitourinary abnormalities or diseases that, per the investigator's judgement, may jeopardize the subject's safety or compliance with the protocol, or otherwise interfere with interpretation of efficacy and/or safety results.
11. Has a history of malignant neoplasms within the past 5 years prior to screening. Basal and squamous cell skin cancer and any carcinoma in-situ are allowed if they have received treatment and follow-up consistent with local standard of care.
12. Patient history with current evidence of uncontrolled, unstable or recently diagnosed cardiovascular disease, such as ischemic heart disease, coronary artery vasospasm, and cerebral ischemia. Patients with Myocardial Infarction (MI), Acute Coronary Syndrome (ACS), percutaneous Coronary Intervention (PCI), cardiac surgery, stroke or transient ischemic attack (TIA) during the 6 months prior to screening.
13. Has a history of human immunodeficiency virus disease.
14. Patient has a history of gastric or small intestinal surgery (including gastric bypass surgery or banding but not including cholecystectomy or appendectomy) or has a disease that causes malabsorption.

Laboratory, vital sign, and electrocardiogram (ECG) related

15. Has a positive test result at Screening for hepatitis B surface antigen (Ag), hepatitis C virus antibody.
16. Has a screening estimated Glomerular Filtration Rate (eGFR) estimated with the Modification of Diet in Renal Disease (MDRD) equation of <45 ml/min/1.73 m^2.

17. Has a screening result for alanine aminotransferase or aspartate aminotransferase (ALT or AST) of >2.0X upper limit of normal (ULN) or total bilirubin >1.5X ULN at the Screening visit. Note: An isolated bilirubin >1.5X ULN is acceptable if bilirubin is fractionated, and direct bilirubin is within the laboratory normal range.
18. Has a corrected QT interval to Fridericia's formula (QTcF) >450 milliseconds (msec) for males and >470 msec for females at screening.
19. Has a mean value for triplicate seated systolic blood pressure >160 mmHg and/or diastolic blood pressure (BP) >95 mmHg measured after at least 5 minutes at rest at the Screening Visit.

Note: If a subject's BP is exclusionary on the first triplicate assessment at the Screening visit, they may have 1 repeat triplicate BP assessment at that visit after another rest of at least 10 minutes.

Medication use and substance abuse related

20. Has known history of or suspected abuse of alcohol or recreational drugs at Screening.
21. Has use of soft drugs (such as marijuana or any substances containing tetrahydrocannabinol (THC) or cannabidiol (CBD)) within 3 months prior to Screening, or hard drugs (such as cocaine, illicit narcotics/opiates) within 6 months prior to Screening.
22. Has a positive drug screen at Screening. Note: If benzodiazepines are detected on the drug screen, this is not exclusionary if they are prescribed a benzodiazepine for a therapeutic purpose (e.g. for insomnia) and confirmatory documentation is obtained from the prescribing physician.
23. Is currently in violation of study requirements for prohibited and permissible concomitant medications (not already specified in other criteria) or is anticipated to violate these requirements during study participation. These requirements are detailed in Section 10.1.
24. Has any use of prescription opiate medications within 14 days of screening or any anticipated/potential use of opiates during study participation.
25. History of use of ergotamine medications on greater than/equal 10 days per month on a regular basis for greater than/equal 3 months prior to screening.
26. History of non-narcotic analgesic intake on greater than/equal 15 days per month for greater than/equal 3 months prior to screening.

Other

27. Has known or suspected hypersensitivity to trial product(s) or related products.
28. Has a history of multiple significant and/or any severe allergies (e.g., food, drug, latex allergy) or has had an anaphylactic reaction or significant intolerance to prescription or nonprescription drugs or food.
29. Has any surgery scheduled for the duration of the trial.
30. Had major surgery or donated or lost 1 unit of blood (approximately 500 mL) within 4 weeks prior to the Screening Visit; has a screening hemoglobin <11.0 g/dL (males) or <10.0 g/dL (females), or has a known hemoglobinopathy (e.g. sickle cell anemia, hemolytic anemia).
31. Has previous participation in this trial. Participation is defined as signed informed consent.
32. Has participated in any clinical trial of an approved or non-approved investigational biological medicinal product (e.g. antibody therapy) within 90 days of Screening or has participated in any clinical trial of an approved or non-approved investigational small molecule medicinal product within 30 days or 5 half-lives (whichever is longer) of Screening.
33. Has any other disorder, unwillingness or inability, not covered by any of the other exclusion criteria, which in the investigator's opinion, might jeopardize the subject's safety or compliance with the protocol, or otherwise interfere with interpretation of efficacy and/or safety results.
34. Is an employee or immediate family member (e.g., spouse, parent, child, sibling) of the Sponsor or study site.

Note: Rescreening/retesting is not permitted unless specified above.

Investigational Product, Dosage and Mode of Administration:

All study medication will be orally administered.

Elismetrep (K-304): 1 mg and 5 m capsules and matching placebo

Duration of Treatment Period: Patients have up to 45 days to treat a single migraine event with a single dose of study medication.

Endpoints

Efficacy Measures/Endpoints

Timing of all efficacy measurements is relative to the dose of study medication.

The following endpoints/measures will be derived from the response in the patient diaries:

Primary Endpoint:

- Pain freedom will be assessed using the number of evaluable subjects that report no pain at 2 hours post-dose. Pain will be measured on a 4-point Likert scale (0=none, 1=mild, 2=moderate, 3=severe.

Secondary Endpoints:

- Freedom from the most bothersome symptom (MBS) will be assessed using the number of evaluable subjects that report the absence of their MBS at 2 hours post-dose. The MBS (nausea, phonophobia or photophobia) will be measured using a binary scale (0=absent, 1=present).
- Pain relief will be assessed using the number of evaluable subjects that report a pain level of moderate or severe (responses of 2 or 3 on the 4-point Likert scale) at baseline and then report a pain level of none or mild (response of 0 or 1).
- Freedom from Photophobia will be assessed by tabulating the number of subjects that report the absence of photophobia at 2 hours post-dose in the subset of subjects that reported the presence of photophobia at headache baseline.
- Freedom from Phonophobia will be assessed by tabulating the number of subjects that report the absence of phonophobia at 2 hours post-dose in the subset of subjects that reported the presence of phonophobia at headache baseline.
- Freedom from Nausea will be assessed by tabulating the number of subjects that report the absence of nausea at 2 hours post-dose in the subset of subjects that reported the presence of nausea at headache baseline.
- The probability of requiring rescue medication will be assessed using the number of subjects that take rescue medication within 24 hours after administration of study medication.
- Sustained pain freedom, from 2 to 24 hours, will be assessed using the number of subjects that do not experience any headache pain through the time period of interest.
- Sustained pain relief, from 2 to 24 hours will be assessed using the number of subjects that do not use any rescue medications, and do not experience any moderate or severe headache pain through the time period of interest.
- Sustained pain freedom, from 2 to 48 hours, will be assessed using the number of subjects that do not experience any headache pain through the time period of interest.
- Sustained pain relief from 2 to 48 hours, will be assessed using the number of subjects that do not use any rescue medications, and do not experience any moderate or severe headache pain through the time period of interest.

Exploratory Endpoints:

- The proportion of subjects able to function normally, at 2 hours, will be assessed using the number of subjects that self-report as "normal" on the functional disability scale (functional disability: four-point scale: normal (0), mildly impaired (1), moderately impaired (2), severely impaired, requires bedrest (3) in the subset of subjects who reported any level of disability at the migraine baseline.
- Pain relapse will be assessed using the proportion of subjects with (a) mild, moderate, or severe pain (response of 1, 2 or 3 on the 4-point scale) at any time point after 2 hours post-dose; (b) missing pain data at ≤ 1 time point after 2 hours post-dose; (c) no intervening rescue medication taken at or before 48 hours post-dose evaluated for subjects with pain freedom at 2 hours post-dose within 48 hours after administration of study medication.

Safety Assessments/Endpoints

Standard pre-study and post study screening (medical history and physical examination, vital signs, ECG, laboratory tests including hematology, chemistry and urinalysis, and pregnancy test for females of childbearing potential) will be performed.

The Columbia Suicide Severity Rating Scale (C-SSRS) will be conducted according to the schedule of assessments (SOA).

Adverse experiences will be collected from the time of consent through Visit 3.

Statistical Methods:

Sample size justification:

It is anticipated that about 90% of 400 randomized subjects will have a qualifying headache in the allotted 45-day time frame, resulting in 360 evaluable for efficacy in each treatment group.

A total sample size of 360 evaluable subjects (randomized 2:1:2:2:1 into placebo, 2 mg, 5 mg, 10 mg and 20 mg) provides approximately 85.5% power for the primary endpoint of pain freedom at 2 hours post dose for the comparison between 5 mg and 10 mg vs placebo respectively with a two-sided alpha of 0.1, assuming a placebo response rate of 10% and the treatment response rate of 25% and a treatment difference of 15%.

Populations:

The following analysis sets will be evaluated and used for analysis of the data.

Enrolled subjects: Subjects who sign an informed consent form and are assigned a subject identification number.

Randomized subjects: Enrolled subjects who received a randomized treatment assignment from the IWRS.

Treated subjects: Randomized subjects who take the study medication.

Modified Intent to Treat (mITT): randomized subjects that take study therapy, have a qualifying migraine (as defined in Section 7) of moderate or severe baseline pain intensity, and provide baseline and at least one post-baseline efficacy data point (i.e. non-missing pain level, phonophobia status, photophobia status, nausea status etc). The mITT analysis set will be used for demographic, baseline characteristic and efficacy analysis. Subjects are analyzed as randomized.

The Safety Analysis set: Randomized subjects who take the study medication. The safety analysis set will be used for safety analyses and analyzed as treated.

Efficacy:

For the primary endpoint of pain freedom at 2 hours post dose in the mITT analysis population, the percentages of subjects with pain freedom at 2 hours post dose are compared between treatment and placebo using Cochran-Mantel-Haenszel (CMH) test stratified by use of background prophylactic

medications for migraine (yes/no). The percentage difference between treatment and placebo is tested at a two-sided alpha level of 0.1 for each dose level. The percentage of subjects achieving the endpoints response criteria by treatment group and the difference in percentages between treatment group and placebo will be presented with a 90% confidence interval (CI). Subjects with missing data at 2 hours post dose will be classified as failures. Sensitivity analysis will be described in the statistical analysis plan (SAP).

For secondary categorical endpoints, the CMH test stratified by use of background prophylactic medications for migraine (yes/no) will be performed.

For the probability of rescue medication use within 24-hour post-dose, the CMH test will be performed. Time to reschedule medication use through 24 hours post-dose will be assessed by treatment group using Kaplan-Meier (KM) plot. Log-rank test will be performed. Subjects who do not take rescue medication within 24 hours post-dose will be censored at 24 hours.

Safety:

Safety analyses will be based on the Safety Analysis Set. No formal statistical tests or inference will be performed for safety analyses.

Adverse events will be coded using the version of the Medical Dictionary for Regulatory Activities (MedDRA) in effect at the time of study start. AEs will be summarized as treatment-emergent AEs (TEAEs) (defined as events that are newly reported after randomization or reported to worsen in severity from baseline). The incidence of participants with at least 1 TEAE and the incidence of TEAEs by preferred term and system organ class will be presented by treatment group. The frequency and percentage of TEAEs will be presented. The incidence of participants with at least 1 TEAE assessed as related to the study drug will be summarized by treatment group. All serious AEs (SAEs) will be summarized and listed by patient. Discontinuations to study due to TEAEs will be summarized by treatment group. All adverse events will be listed by patient.

Other safety endpoints (safety laboratory endpoint, vital signs, and ECGs) will be summarized by treatment group and nominal timepoint.

Missing Data:

Every effort will be made to reduce missing data in the trial. Subjects in this study will be encouraged to remain in the study and follow the scheduled visits to provide the efficacy and safety data needed.

Methods of handling missing data in principal analyses of binary efficacy endpoints are defined as follows:

• Non-Completer = Failure: Subjects with missing data at a single time point will be classified as failures for that timepoint. This missing data imputation method will be applied to endpoints based on data from a single time point (e.g., primary endpoint at 2 hours post-dose).

• Non-Completer With Missing Data at More Than 1 Time Point = Failure: Subjects with missing data at > 1 time point post-dose in a specified time period will be classified as failures. This missing data imputation method will be applied to endpoints that are based on data from multiple time points (e.g., secondary endpoint of sustained pain freedom from 2 to 24 hours post-dose).

• The intercurrent event of rescue medication use will be handled using Rescue Medication = Failure, i.e., subjects who take rescue medication will be classified as failures for all efficacy evaluations that are reported at or after taking rescue medication.

Additional sensitivity analysis will be defined in the statistical analysis plan.

Multiplicity

The study tests the primary hypothesis that at least one of the treatment arms is superior to the placebo arm in primary endpoint of pain freedom at 2 hours post. No multiplicity adjustment will be performed for primary and secondary objectives, which will be tested at two-sided alpha of 0.1.

Interim Analysis

After approximately 200 subjects have completed the primary endpoint, an interim analysis (IA) of efficacy data will be conducted for internal decision making (see Section 16.10). No Type I error adjustments will be made since the study will not be stopped for overwhelming efficacy. The sponsor may stop the trial for futility.

Table 2: Study Schedule of Assessments

SOA													
	Screening	**Randomization**	**Treatment Period by Hour**										**End of Treatment/ Early Withdrawal[a]**
Visit Number	**1**	**2**	**0**	**0.5**	**1**	**1.5**	**2**	**3**	**4**	**6**	**8**	**24**	**48**	**3**
Study Day	**-28**	**0**	**1**											**4-7[b]**
Visit Window (days)	**N/A**													
Administrative														
Informed Consent	X													
Inclusion/ Exclusion[c]	X	X												
Migraine History[d] & Medical History/ Demographics	X													
Prior/Concomitant Med	X	X	X											X
Prior use/discontinuation of specific migraine medication CRF completion (see Section 10)		X												
Patient Training on Diary/Dispense Diary, instructions		X												
IWRS/Randomization		X												
Clinical Assessment														
Physical Examination	X	X												X
Height/Weight	X													
Heart Rate/Blood Pressure	X	X												X
Respiratory Rate/Temperature	X													X
Triplicate 12-lead ECG	X													
C-SSRS[e]	X	X												X

Table 2: Study Schedule of Assessments (Continued)

SOA														
	Screening	**Randomization**	**Treatment Period by Hour**											**End of Treatment/ Early Withdrawal[a]**
Visit Number	**1**	**2**	**0**	**0.5**	**1**	**1.5**	**2**	**3**	**4**	**6**	**8**	**24**	**48**	**3**
Study Day	**-28**	**0**	**1**											**4-7[b]**
Visit Window (days)	**N/A**													
Laboratory and Safety Assessments														
General Safety Labs: chemistry, hematology, urinalysis[f]	X	X												X
Urine Drug Screen	X													
Hepatitis Screen	X													
hCG Pregnancy Test/FSH Test[g]	X (serum)	X (urine)												X (serum)
AE Monitoring	X	X	X											X[i]
Study Drug Administration and Compliance														
Study Drug Dispensing		X												
Thermometer and instruction card dispensing		X												
Drug Compliance Check														X
Review use of rescue medication[h]														X
Patient doses with study medication			X											
Return study medication[a]														X
Patient completes diary for pain severity			X	X	X	X	X	X	X	X	X	X	X	

Table 2: Study Schedule of Assessments (Continued)

SOA													
	Screening	**Randomization**	**Treatment Period by Hour**										**End of Treatment/ Early Withdrawal[a]**
Visit Number	**1**	**2**	**0**	**0.5**	**1**	**1.5**	**2**	**3**	**4**	**6**	**8**	**24**	**48**	**3**
Study Day	**-28**	**0**	**1**											**4-7[b]**
Visit Window (days)	**N/A**													
Patient completes diary for pain associated symptoms (photophobia, phonophobia, nausea)			X	X	X	X	X	X	X	X	X	X	X	
Patient completes functional disability scale (Appendix B)			X	X	X	X	X	X	X	X	X	X	X	
Patient records use of rescue medication (yes/no) in diary							X	X	X	X	X	X	X	

[a] All subjects should attend the EoT/withdrawal visit. For subjects who did not take study medication, EoT/Withdrawal visit activities will consist only of return of study medication, collection of con-meds, collection of AEs (could be remote visit if study medication returned by mail). For patients who took study medication, all assessments listed in the SOA should be performed.
[b] Day is relative to dosing day. Dosing Day is Day 1. Subjects should return for V3 between Day 4 and Day 7 and not sooner than 72 h post dose.
[c] Just prior to Randomization, it will be confirmed that no excluded/prohibited medications are being taken and, in females of child-bearing potential, that the V2/Randomization urine pregnancy test is negative.
[d] Migraine history is to be collected by obtaining documentation of subject's medical history from relevant treating physician and investigator should verify patient meets diagnostic and entry criteria related to migraine.
[e] The "Baseline C-SSRS" should be completed at Visit 1. The "Since Last Visit C-SSRS" should be completed at Visits 2 and 3. Refer to (Appendix C).
[f] Urinalysis at Screening only. Safety labs need not be in fasted state.
[g] Serum hCG at screening (V1) and End of Treatment (V3); urine hCG at randomization visit (V2). FSH test at screening only for females of non-childbearing potential due to menopause. If screening FSH test is not consistent with menopausal status, subjects may return for a serum pregnancy test and participate under requirements for females of child-bearing potential (contraception and pregnancy testing).
[h] Use of rescue medication (Y/N) in the eDiary will be reviewed. Record details of rescue medication taken in source documents and enter data onto Rescue Medication CRF.
[i] Follow up of AEs ongoing at V3 is described in Section 15.2.5
Abbreviations: C-SSRS= Columbia Suicide Severity Rating Scale, FSH= follicle stimulating hormone, hCG = human chorionic gonadotropin

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4. LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

The following abbreviations and specialist terms are used in this study protocol.

Table 3: Abbreviations and Specialist Terms

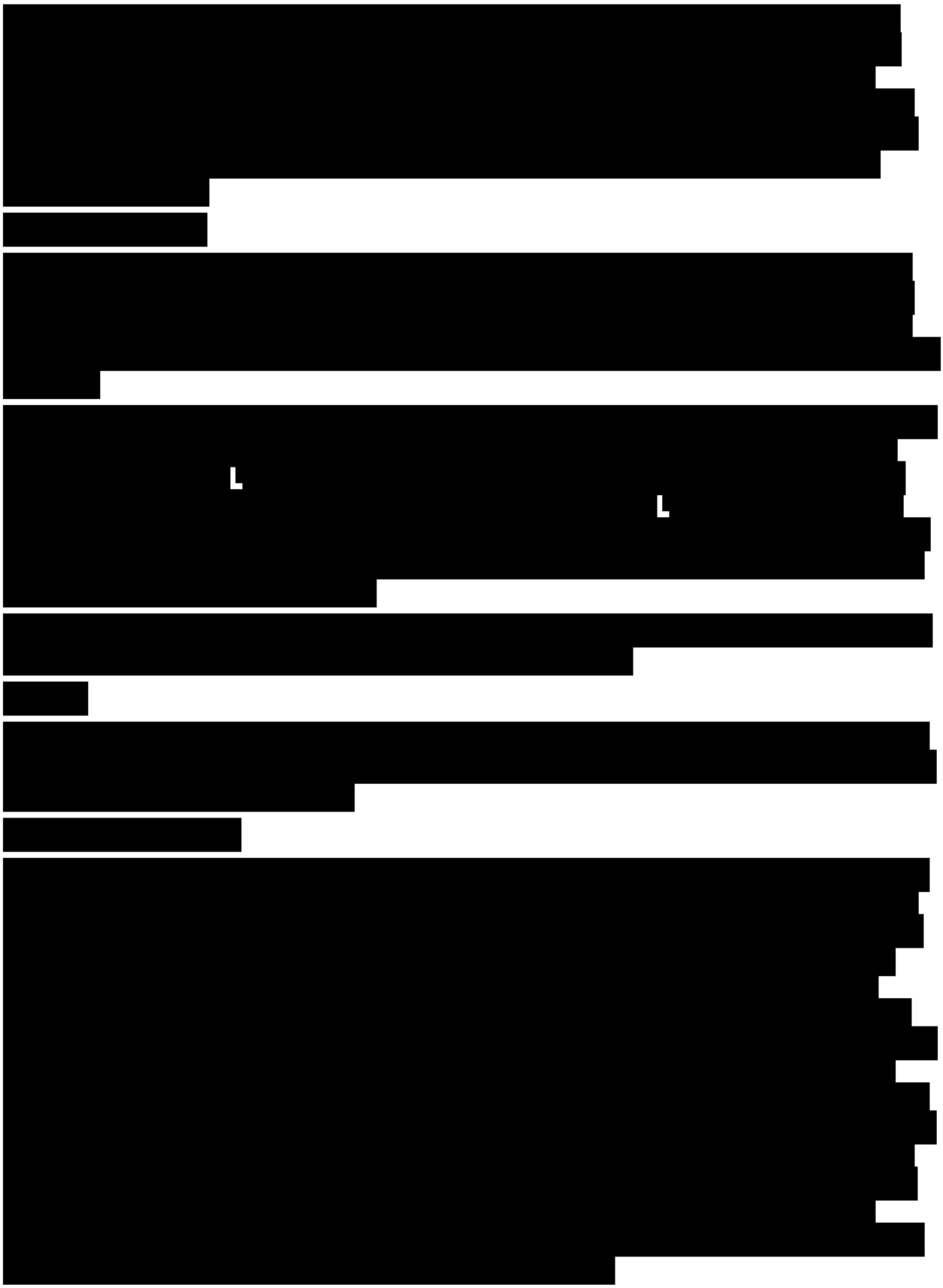
Abbreviation or Specialist Term	Explanation
ACS	Acute coronary syndrome
AE	Adverse event
AESI	Adverse events of special interest
Ag	Antigen
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
AUC	Area under the concentration-time curve
AUC_{0-24h}	Area under the concentration time curve from time 0 to 24 hours
BID	Twice daily dosing
BMI	Body mass index
BP	Blood pressure
CBD	Cannabidiol
CFR	Code of Federal Regulations Code of Federal Regulations
CGRP	Calcitonin-gene related peptide
CGRPR	Calcitonin gene-related peptide receptor
CI	Confidence interval
C_{max}	Maximum concentration
CMH	Cochran-Mantel-Haenszel
CMQ	Company MedDRA query
CRF	Case report form
CSR	Clinical study report
C-SSRS	Columbia Suicidality Severity Rating Scale
CTCG	Clinical Trials Coordination Group
CYP	Cytochrome P450
DART	Development and reproductive toxicology
DRG	Dorsal root ganglion
ECG	Electrocardiogram
eCRF	Electronic case report form

Abbreviation or Specialist Term	Explanation
eDiary	Electronic diary
eGFR	Estimated glomerular filtration rate
EOT	End of treatment
FDAAA	Food and Drug Administration Amendments Act
FDAMA	Food and Drug Administration Modernization Act
FSH	Follicle stimulating hormone
g	Gram
GCP	Good Clinical Practice
GGT	Gamma-glutamyl transferase
GWA	genome-wide association
HA	Headache
hCG	Human chorionic gonadotropin
HDPE	High density polyethylene
HPMC	Hydroxypropyl cellulose
hr or h	Hour
IA	Interim analysis
IB	Investigational Brochure
ICH	International Conference on Harmonization
ICHD	International Classification of Headache Disorders
ID	Identification
IEC	Independent Ethics Committee
IgG	Immunoglobulin G
IgM	Immunoglobulin M
IHS	International Headache Society
IMP	Investigational medicinal product
IRB	Institutional Review Board
IUD	Intrauterine device
IUS	Intrauterine hormone-releasing system
IWRS	Interactive web response system
kg	Kilogram
Ki	Inhibitor constant
KM	Kaplan-Meier

Abbreviation or Specialist Term	Explanation
LFT	Liver function test
m	Meter
MBA	Multiple biochemical analysis
MBS	Most bothersome symptoms
MCH	Mean corpuscular hemoglobin
MCHC	Mean corpuscular hemoglobin concentration
MCV	Mean corpuscular volume
MDRD	Modification of Diet in Renal Disease
MedDRA	Medical Dictionary for Regulatory Activities
mg	Milligram
MI	Myocardial infarction
min	Minute
mITT	Modified intent-to-treat
mL	Milliliter
mmHg	Millimeters of mercury
mpk	Milligram per kilogram
msec	Millisecond
N	Number
ng	Nanogram
NOAEL	No adverse effect level
NSAID	Nonsteroidal anti-inflammatory drug
NTG	Nitroglycerin
OAT	Organic anion transporter
PCI	Percutaneous coronary intervention
PD	Pharmacodynamic
PE	Physical examination
PF	Pain freedom
PK	Pharmacokinetic
PR	Pain relief, or period, in milliseconds, that extends from the beginning of the P wave until the beginning of the QRS in an ECG tracing
QD	Once daily
QTc	QT corrected

Abbreviation or Specialist Term	Explanation
QTcF	QT corrected with Fridericia's formula
RBC	Red blood cells
RDW	Red cell distribution width
SAE	Serious adverse event
SAP	Statistical analysis plan
SAR	Serious adverse reaction
SD	Standard deviation
SOA	Schedule of assessments
SUSAR	Suspected unexpected serious adverse reaction
TEAE	Treatment emergent adverse event
THC	Tetrahydrocannabinol
TIA	Transient ischemic attack
T_{max}	Time of maximum concentration
TRPM8	Transient receptor potential melastatin 8
TSH	Thyroid stimulating hormone
ULN	Upper limit of normal
VMS	Vasomotor symptoms
WBC	White blood cells
β-hCG	β-human chorionic gonadotropin
μM	Micromolar

[redacted]



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6. TRIAL OBJECTIVES, HYPOTHESES

6.1. Primary Objectives

To evaluate the efficacy of a range of dose levels of elismetrep compared with placebo in the acute treatment of migraine as measured by pain freedom at two hours post dose.

6.2. Secondary Objectives

- To evaluate the efficacy of a range of dose levels of elismetrep compared to placebo on freedom from the most bothersome symptom (MBS), associated with migraine, at two hours post dose.
- To evaluate the efficacy of a range of dose levels of elismetrep compared to placebo on pain relief at 2 hours post-dose.
- To evaluate the efficacy of a range of dose levels of elismetrep compared to placebo on freedom from photophobia at 2 hours post-dose.
- To evaluate the efficacy of a range of dose levels of elismetrep compared to placebo on freedom from phonophobia at 2 hours post-dose.
- To evaluate the efficacy of a range of dose levels of elismetrep compared to placebo on freedom from nausea at 2 hours post-dose.
- To evaluate the efficacy of a range of dose levels of elismetrep compared to placebo on the probability of requiring rescue medication within 24 hours of initial treatment.
- To evaluate the efficacy of a range of dose levels of elismetrep compared to placebo on sustained pain freedom from 2 to 24 hours post-dose.
- To evaluate the efficacy of a range of dose levels of elismetrep compared to placebo on sustained pain relief from 2 to 24 hours post-dose.
- To evaluate the efficacy of a range of dose levels of elismetrep compared to placebo on sustained pain freedom from 2 to 48 hours post-dose.
- To evaluate the efficacy of a range of dose levels of elismetrep compared to placebo on sustained pain relief from 2 to 48 hours post-dose.
- To evaluate the safety and tolerability of various doses of elismetrep in the treatment of acute migraine.

6.3. Exploratory Objectives

- To evaluate the efficacy of a range of dose levels of elismetrep compared to placebo on freedom from functional disability at 2 hours post dose according to the Functional Disability scale for subjects who reported any level of disability at the migraine baseline.
- To evaluate the efficacy of a range of dose levels of elismetrep compared to placebo for the incidence of pain relapse from 2 to 48 hours post-dose.

7. INVESTIGATIONAL PLAN

7.1. Overall Study Design

This will be a multi-center, randomized, double-blind, placebo-controlled, parallel-group study to evaluate the safety, tolerability, and efficacy of various doses of elismetrep in the treatment of patients with an acute migraine attack. Four hundred (400) subjects will be randomized in a 2:1:2:2:1 ratio to one of the following treatment groups: placebo or 2, 5, 10, or 20 mg of elismetrep. Randomization will be stratified according to use of background prophylactic medications for migraine (yes/no). An interim analysis will be conducted after approximately 200 subjects have been randomized (see Section 16.10). Randomization will not pause for the interim analysis.

Patients who meet all of the study entry criteria will be randomized and provided with study medication (elismetrep or placebo) to be taken on an outpatient basis as soon as they experience a moderate or severe (Grade 2 or 3) migraine headache (HA).

Subjects will use an electronic diary(eDiary) to record migraine-related information. Upon experiencing a potentially qualifying HA, subjects will log in and answer questions designed to ascertain whether migraine headache is qualifying according to the criteria listed below and whether medications specifically prohibited 48 h prior to a qualifying migraine have been taken (Section 10.1). During the 48 hours following the dose of study medication, patients will record various measures in an eDiary at specified time intervals. These measures include subjective assessments of pain severity, presence or absence of migraine-associated symptoms, degree of functional disability (Appendix B), use of rescue medication (yes/no), and the onset of the first moderate or severe headache recurrence (if any).

The patient will be instructed to take their study medication, as an outpatient. The patient will be instructed to treat a migraine headache if the following conditions are met:

- The migraine headache severity is moderate or severe (Grade 2 or 3).
- The migraine headache started less than four hours ago.
- The migraine headache is a new headache that has not been previously treated and is not a recurrence of a previous migraine headache (at least 48 hours must have elapsed since the complete termination of their last attack (pain and all associated symptoms)).
- No other migraine headache or headache has occurred in the previous 48 hours.
- The migraine headache is not already resolving on its own.
- Prohibited medication has not been taken (see Section 10.1).

Subjects should take study medication after answering diary questions about their current pain and symptoms and after identifying their currently most bothersome, migraine associated, symptom (phonophobia, photophobia or nausea).

The date and time of study therapy administration will be recorded in the eDiary. Patients who have headache pain reduced to a mild intensity or pain free intensity level will be considered to have achieved pain relief.

After dosing with study medication, all other headache medication is prohibited during the 2 hours post dose. Beginning two hours after taking study medication and after the 2-hour assessment has been completed, patients may take non-study rescue medication for a non-responding headache, (i.e., headache has failed to improve to Grade 1/0 (mild/no pain)), and for headache recurrence. Use of rescue medication must conform to the prescribing information of the product and the restrictions of this protocol.

Similarly, if the migraine is relieved by study medication at 2 hours after dosing but then recurs to a moderate or severe intensity level between 2 and 48 hours, the patient will be permitted to take the same rescue therapy as outlined above. In all circumstances, the patient will continue to complete his or her diary for up to 48 hours after consuming the study medication.

After being randomized, patients have up to 45 days to treat a qualifying migraine. However, once the targeted number of treated patients has been reached, the study can be stopped at any point at the discretion of the Sponsor.

Patients will return to the study site within 4-7 days after treatment to allow review of the diary, assessment of medication compliance, and safety monitoring.

If a patient has NOT experienced a qualifying migraine headache of sufficient severity within 45 days after randomization (V2), he or she will be withdrawn from the trial and instructed to return unused study medication and diary to the study center.

The schedule of assessments is shown in Table 2.

The interactive web response system (IWRS) will be used to randomly assign patients to their treatment group. Initial drug supplies and subsequent shipments will be managed by IWRS.

7.2. Number of Participants

Approximately up to 400 participants will be enrolled.

7.3. Treatment Assignment

7.3.1. Assignment of Screening and Randomization Numbers

All consented participants will be given a unique screening number that will be used to identify the subject for all procedures that occur before randomization or allocation. Each subject will be assigned only one screening number. Screening numbers must not be reused for different participants. Participants who meet all criteria for enrollment will be assigned a randomization number and randomized after Visit 2.

7.3.2. Study Drug Assignment

The randomization number encodes the subject assignment to either placebo, 2 mg, 5 mg, 10 mg, or 20 mg elismetrep according to the randomization schedule generated before the study. Each subject will be dispensed study drug in a double-blinded manner, labeled with his/her unique randomization number, throughout the study. Subjects will be assigned to their respective treatment groups via IWRS using the following stratification variables: use of background prophylactic medications for migraine (yes/no). Eligible patients will be allocated 2:1:2:2:1 ratio to one of the following treatment groups: placebo or 2, 5, 10, or 20 mg of elismetrep.

7.3.3. Subject Replacement

No participants will be replaced.

7.4. Dose Adjustment Criteria

No dose adjustment will be allowed.

7.5. Criteria for Study Termination

The overall study begins when the first subject signs the study informed consent form.

The overall study ends when the last subject completes the last planned or follow-up visit/interaction associated with a planned visit (this can be a phone contact), discontinues from the study, or is lost to follow-up (e.g., the Investigator is unable to contact the subject).

Study termination because of non-safety reasons, such as the following:

- A finding (e.g., PK, pharmacodynamics (PD), efficacy) from another nonclinical or clinical study using the study treatment(s) results in the study being stopped for a non-safety related reason.
- The study is stopped because of nonscientific and non-safety reasons, such as slow enrollment.

Study termination because of safety reasons:

Early study termination because of unanticipated concerns of safety to the study participants arising from clinical or nonclinical studies with the study treatment(s), comparator(s), drug(s) of the same class, or methodology(ies) used in this study.

7.5.1. Criteria for Premature Termination or Suspension of Trial or Site

A study site may be terminated prematurely or suspended if the site (including the Investigator) is found in significant violation of Good Clinical Practice (GCP), protocol, or contractual agreement, or is unable to ensure adequate performance of the study, or as otherwise permitted by the contractual agreement.

7.5.2. Procedures for Premature Termination or Suspension of the Trial or Site

In the event that the Sponsor, an Investigational Review Board (IRB)/Independent Ethics Committee (IEC), or regulatory authority elects to terminate or suspend the study or the participation of an investigational site, a study-specific procedure for early termination or suspension will be provided by the Sponsor; the procedure will be followed by applicable investigational sites during the course of termination or study suspension.

8. SELECTION AND WITHDRAWAL OF PARTICIPANTS

8.1. Subject Inclusion Criteria

A patient will be eligible to participate in this study if all of the following criteria apply:

1. Be a male or female, age 18 to 70 years, inclusive, at the time of signing informed consent.
2. Patient has greater than a one-year history of migraine with or without aura as defined by International Headache Society (IHS) criteria 1.1 and 1.2 and his/her migraines typically last between 4 to 72 hours, if untreated (Refer to Appendix A for ICHD III Attachment for IHS migraine definitions) as documented in the patient's medical records from his/her treating physician and confirmed by the investigator.
3. Patient has had ≥2 and ≤10 moderate or severe migraine attacks per month in each of the two months prior to screening (Visit 1).
4. Meet the following requirements:
    a. Is a male

    OR

    b. Is a female who is of non-childbearing potential defined by at least 1 of the following criteria:
    c. Postmenopausal (aged >45 years and with a minimum of 12 months of spontaneous amenorrhea with a Screening serum follicle-stimulating hormone (FSH) level in the menopausal range established by the central laboratory.
    d. Post hysterectomy, bilateral oophorectomy or bilateral salpingectomy, based on the subject's recall of their medical history.

    OR

    e. Is a female of reproductive potential and:
    f. agrees to remain abstinent from heterosexual activity[a]
    g. or agrees to use (or have their partner use) a birth control method that is acceptable from the first dose of study drug until the EoT visit. Acceptable methods of birth control are:

        – combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation:

            • oral

            • intravaginal

            • transdermal

        – progestogen-only hormonal contraception associated with inhibition of ovulation:

            • oral

- injectable
- implantable

– intrauterine device (IUD)

– intrauterine hormone-releasing system (IUS)

– bilateral tubal occlusion

– vasectomised partner

– sexual abstinence

– progestogen-only oral hormonal contraception, where inhibition of ovulation is not the primary mode of action

– male or female condom with or without spermicide

– cap, diaphragm or sponge with spermicide

– A combination of male condom with either cap, diaphragm or sponge with spermicide (double barrier methods)

[a] Abstinence can be used as the sole method of contraception if it is in line with the subject's preferred and usual lifestyle and if considered acceptable by local regulatory agencies and ethics committees. Periodic abstinence (e.g., calendar, ovulation, sympto-thermal, post-ovulation methods, etc.) and withdrawal are not acceptable methods of contraception.

This condition is waived if the subject is proven to have no child-bearing potential (eg, hysterectomy).

5. Patient voluntarily agrees to participate in the study by giving written informed consent.
6. Patient is able to read, understand and complete the study questionnaires and diary.
7. Be willing and able to comply with the study schedule of visits, all trial procedures and restrictions.
8. Be willing to use their own personal, qualified smartphone to download study specific eDiary applications for use during the study.

8.2. Subject Exclusion Criteria

Participants are excluded from the trial if any of the following criteria apply:

1. Is a female who is pregnant, breast-feeding or intends to become pregnant during the planned course of the study. **Note:** Participants must have a negative serum pregnancy test (β-human chorionic gonadotropin (β-hCG)) performed by the central laboratory prior to enrollment in the study and negative urine pregnancy result at the randomization visit.

<u>Migraine history-related</u>

2. Patient has difficulty distinguishing his/her migraine attacks from tension-type headaches.
3. Patient has a history of predominantly mild migraine attacks or migraines that usually resolve spontaneously in less than two hours.

4. Patient has more than 15 headache-days per month or has taken medication for acute headache on more than 10 days per month in any of the three months prior to screening (Visit 1).
5. Patient has brainstem (a.k.a. basilar-type) or hemiplegic migraine headache, or retinal migraine.
6. Patient was >50 years old at age of first migraine onset.
7. Patient is taking migraine prophylactic medication where the prescribed daily dose has changed during the 3 months prior to screening (Visit 1) or anticipates any change during the study. Any withdrawal of preventive medications for the treatment of migraine should be completed at least 30 days prior to screening.

Medical history related

8. Patient has, in the opinion of the investigator, other confounding pain syndromes, psychiatric conditions such as uncontrolled major depression, history of psychosis, dementia or significant neurological disorders other than migraine. [Patients who are currently being treated with non-prohibited medication (Section 10.1) for depression and symptoms are well controlled, in the opinion of the investigator, are eligible to participate in this study].
9. Patient is at imminent risk of self-harm, based on clinical interview and responses on the Columbia Suicidality Severity Rating Scale (C-SSRS), or of harm to others in the opinion of the investigator. Patients must be excluded if they report suicidal ideation with intent, with or without a plan (i.e., Type 4 or 5 on the C-SSRS) in the past 2 months or suicidal behavior in the past 6 months.
10. Has a recent history (within the past 3 years of the screening visit) or current diagnosis or evidence of endocrine, hematological, immunological, renal, respiratory, neurologic, gastrointestinal, biliary, or genitourinary abnormalities or diseases that, per the investigator's judgement, may jeopardize the subject's safety or compliance with the protocol, or otherwise interfere with interpretation of efficacy and/or safety results.
11. Has a history of malignant neoplasms within the past 5 years prior to screening. Basal and squamous cell skin cancer and any carcinoma in-situ are allowed if they have received treatment and follow-up consistent with local standard of care.
12. Patient history with current evidence of uncontrolled, unstable or recently diagnosed cardiovascular disease, such as ischemic heart disease, coronary artery vasospasm, and cerebral ischemia. Patients with Myocardial Infarction (MI), Acute Coronary Syndrome (ACS), percutaneous Coronary Intervention (PCI), cardiac surgery, stroke or transient ischemic attack (TIA) during the 6 months prior to screening.
13. Has a history of human immunodeficiency virus disease.
14. Patient has a history of gastric or small intestinal surgery (including gastric bypass surgery or banding but not including cholecystectomy or appendectomy) or has a disease that causes malabsorption.

Laboratory, vital sign, and ECG related

15. Has a positive test result at Screening for hepatitis B surface antigen (Ag), hepatitis C virus antibody.

16. Has a screening estimated Glomerular Filtration Rate (eGFR) estimated with the Modification of Diet in Renal Disease (MDRD) equation of <45 ml/min/1.73 m^2.
17. Has a screening result for alanine aminotransferase or aspartate aminotransferase (ALT or AST) of >2.0X upper limit of normal (ULN) or total bilirubin >1.5X ULN at the Screening visit. Note: An isolated bilirubin >1.5X ULN is acceptable if bilirubin is fractionated, and direct bilirubin is within the laboratory normal range.
18. Has a corrected QT interval to Fridericia's formula (QTcF) >450 milliseconds (msec) for males and >470 msec for females at screening.
19. Has a mean value for triplicate seated systolic blood pressure >160 mmHg and/or diastolic blood pressure (BP) >95 mmHg measured after at least 5 minutes at rest at the Screening Visit.

Note: If a subject's BP is exclusionary on the first triplicate assessment at the Screening visit, they may have 1 repeat triplicate BP assessment at that visit after another rest of at least 10 minutes.

Medication use and substance abuse related

20. Has known history of or suspected abuse of alcohol or recreational drugs at Screening.
21. Has use of soft drugs (such as marijuana or any substances containing tetrahydrocannabinol (THC) or cannabidiol (CBD)) within 3 months prior to Screening, or hard drugs (such as cocaine, illicit narcotics/opiates) within 6 months prior to Screening.
22. Has a positive drug screen at Screening. Note: If benzodiazepines are detected on the drug screen, this is not exclusionary if they are prescribed a benzodiazepine for a therapeutic purpose (e.g. for insomnia) and confirmatory documentation is obtained from the prescribing physician.
23. Is currently in violation of study requirements for prohibited and permissible concomitant medications (not already specified in other criteria) or is anticipated to violate these requirements during study participation. These requirements are detailed in Section 10.1.
24. Has any use of prescription opiate medications within 14 days of screening or any anticipated/potential use of opiates during study participation.
25. History of use of ergotamine medications on greater than/equal 10 days per month on a regular basis for greater than/equal 3 months prior to screening.
26. History of non-narcotic analgesic intake on greater than/equal 15 days per month for greater than/equal 3 months prior to screening.

Other

27. Has known or suspected hypersensitivity to trial product(s) or related products.
28. Has a history of multiple significant and/or any severe allergies (e.g., food, drug, latex allergy) or has had an anaphylactic reaction or significant intolerance to prescription or nonprescription drugs or food.
29. Has any surgery scheduled for the duration of the trial.

30. Had major surgery or donated or lost 1 unit of blood (approximately 500 mL) within 4 weeks prior to the Screening Visit; has a screening hemoglobin <11.0 g/dL (males) or <10.0 g/dL (females), or has a known hemoglobinopathy (e.g. sickle cell anemia, hemolytic anemia).
31. Has previous participation in this trial. Participation is defined as signed informed consent.
32. Has participated in any clinical trial of an approved or non-approved investigational biological medicinal product (e.g. antibody therapy) within 90 days of Screening or has participated in any clinical trial of an approved or non-approved investigational small molecule medicinal product within 30 days or 5 half-lives (whichever is longer) of Screening.
33. Has any other disorder, unwillingness or inability, not covered by any of the other exclusion criteria, which in the investigator's opinion, might jeopardize the subject's safety or compliance with the protocol, or otherwise interfere with interpretation of efficacy and/or safety results.
34. Is an employee or immediate family member (e.g., spouse, parent, child, sibling) of the Sponsor or study site.

Note: Rescreening/retesting is not permitted unless specified above.

8.3. Subject Withdrawal Criteria

8.3.1. Discontinuation

This is a single migraine attack/single dose trial. For the purposes of this trial, discontinuation from the trial is defined as being randomized and not returning to complete the final study visit (Visit 3). The reasons for discontinuation are as follows:

- Adverse event
- Voluntary withdrawal by the subject
- Lost to follow up
- Pregnancy
- Death
- Investigator decision
- Subject non-compliance with the protocol (for reason other than already noted in this section)

The reason for discontinuation should be recorded in the case report form (CRF). In all cases, subjects must return for their EoT visit.

Although a subject is not obliged to give his/her reason(s) for withdrawing early, the investigator must make a reasonable effort to ascertain the reason(s), while fully respecting the subject's rights. Where the reasons are obtained, the primary reason for withdrawal must be specified in the end of trial form in the CRF.

Additionally, where the reason for discontinuation is investigator decision, the reason should also be captured. It is important that the investigator confirm the reason is not redundant with other reasons captured in the existing list of reasons specified herein.

Patient data captured through the point of voluntary withdrawal will remain in relevant data systems.

If a subject ends his/her participation from the study or from taking the study medication, the investigator must request the subject to still complete the ‘end of treatment’ visit (Visit 3). Subjects who fail to complete the required Visit 3 will be considered “non-completers” in the trial.

Final drug accountability must be performed even if the subject is not able to come to the trial site.

8.3.2. Lost to Follow-up

A subject will be considered lost to follow-up, and a non-completer, if he or she repeatedly fails to attend scheduled visits and is unable to be contacted by the trial site.

The following actions must be taken if a subject fails to return to the trial site for a required visit:

- The site must attempt to contact the subject and reschedule the missed visit as soon as possible, to confirm whether investigational product (IP) has been taken or not, to counsel the subject on the importance of maintaining the assigned visit schedule, and to ascertain whether the subject wishes to and/or should continue in the trial, and to ensure return of any study medication.
- Before a subject is deemed lost to follow-up, the investigator must make every effort to regain contact with the subject (where possible, at least three telephone calls and, if necessary, a certified letter to the subject's last known mailing address or local equivalent methods). These contact attempts should be documented in the subject's source document. Should the subject continue to be unreachable at the ‘end of treatment’ visit, he/she will be considered as lost to 'follow-up' and a non-completer.

9. STUDY SCHEDULE AND STUDY PROCEDURES

The order of priority can be changed during the study with joint agreement of the Investigator and KALLYOPE, Inc.

Any nonscheduled procedures required for urgent evaluation of safety concerns take precedence over all routine scheduled procedures.

- Adherence to the trial design requirements, including those specified in the flowchart, is essential and required for trial conduct.
- Assessments should be carried out according to the clinic's standard of practice unless otherwise specified in the current section. Efforts should be made to limit the bias between assessments.
- Source data of clinical assessments performed and recorded in the CRF must be available and will usually be the subject's medical records. Additional recording to be considered source data includes, but is not limited to laboratory reports, ECG and Mental Health assessments.
- Review of mental health assessment instruments, ECG and laboratory reports must be documented either on the documents or in the subject's source documents.
  - Repeat laboratory samples may be taken for technical issues.
  - Efficacy assessments and procedures are described in Section 14
  - Safety assessments and procedures are described in Section 15
  - Procedures related to AE evaluation and reporting are in Section 15.2
  - Procedures around study drug admin are in Section 13

9.1. Prestudy (Screening) Procedures

Informed consent must be obtained before any trial related activity.

Within approximately 4 weeks of screening, potential participants will be evaluated to determine that they fulfill the entry requirements as set forth in the Inclusion and Exclusion Criteria. The Investigator will discuss with each subject the nature of the study, its requirements, and its restrictions.

The pre-study screening assessments (V1) are detailed in the Schedule of Assessments (SOA). Subjects need not be fasted for this visit.

- All screening evaluations must be completed and reviewed to confirm that potential subjects meet all eligibility criteria.
- The investigator will maintain a screening log to record details of all subjects screened and to confirm eligibility or record reason for screen failure, as applicable.
- At Screening, subjects will be provided with a card stating that they are participating in a trial and giving contact details of relevant trial site staff.
- For details on the timing of procedures, please refer to Table 2.

9.2. Randomization Visit

Procedures for this visit are in Table 2. After confirming eligibility subjects will be randomized and provided with study medication. They will also receive training on use of the eDiary. Importantly, site personnel will counsel patients on when study medication should be taken (upon qualifying headache and for a headache where the subject anticipated being awake and able to complete the diary entries, particularly for the first 2 hours post dose). The importance of timely and complete diary entry, particularly at the 2-h timepoint, will be emphasized. Subjects will also receive thermometers and an instruction card for at home post-dose temperature monitoring (see Section 15.1.2 for details). The CRF related to prior use of specific migraine medications should be completed at V2.

9.3. Procedures Treatment Period

Treatment will occur in the outpatient setting. Patients will complete the e diary once they experience a qualifying headache and will take investigational medicinal product (IMP) once they have answered the initial diary questions to confirm that the headache is indeed qualifying. Subjects will also record their MBS in the diary prior to dosing. Procedures are in Table 2.

9.4. Poststudy Procedures

Participants will return to the clinical research unit for V3 (End of Treatment Visit). Participants need not fast for this visit. The specific assessments to be performed are list in the SOA (Table 2). All subjects should return for this visit regardless of whether study medication was taken or not. For subjects who did not take study medication, EoT visit procedures will consist of return of study medication, collection of AEs, and collection of concomitant medications. For subjects who did take study medication, the procedures outlined in Table 2 will be completed.

10. MEDICATION RESTRICTIONS

10.1. Prior and Concomitant Medications

Participants should be instructed not to start any new medications (prescription or non-prescription) or supplements without first consulting with the investigator. If this is not possible due to medical urgency, the participant should inform the investigator as soon as possible.

Any medication (including over-the-counter and prescription medicines) other than the trial product, that the participant is taking at the time of screening or receives during the trial must be recorded on the appropriate electronic case report form (eCRF). Information collected will include:

1. Medication name
2. Indication
3. Dates of administration including start and stop dates
4. Dose

Medications or vaccinations specifically prohibited in the exclusion criteria or below are not allowed during the ongoing trial. If there is a clinical indication for any medication or vaccination specifically prohibited during the trial, discontinuation may be required. The investigator should discuss any questions regarding this with the Sponsor Clinical Director. The final decision on any supportive therapy or vaccination rests with the investigator and/or the subject's primary physician. However, the decision to continue the subject on trial therapy requires the agreement of the Sponsor.

Instructions for Documenting Prior Use of Select Migraine Medications

The sites will be required to collect information about each subject's prior acute migraine medications usage pertaining to the list of medications below. The timeframe for collection of this information is the subject entire lifetime.

- Almotriptan tablet (Axert®, generic)
- Eletriptan tablet (Relpax®, generic)
- Frovatriptan tablet (Frova®, generic)
- Naratriptan tablet (Amerge®, generic)
- Rizatriptan tablet (standard or disintegrating; Maxalt®, generic)
- Sumatriptan tablet (Imitrex®, Treximet®, generic)
- Sumatriptan SQ injection (Imitrex®, Zembrace Symtouch®, generic)
- Sumatriptan nasal (Imitrex®, Onzetra®, Tosymra®, generic)
- Zolmitriptan tablet (standard or disintegrating; Zomig®, generic)
- Zolmitriptan nasal (Zomig®, generic)
- Ubrogepant (Ubrelvy®)

- Rimegepant (Nurtec®) for acute migraine
- Zavegepant (Zavzpret®)

For each of the medications listed above, the investigator is to ask and record if the patient has used any of the medications. For each medication that has been used, the subject should be asked if they continue to use the medication or have stopped using the medication. Note that transitions between brand and generic preparations of the same dosage form of a drug are considered continuous use of one drug without stoppage. However, a switch between administration routes of the same drug is considered stoppage of the first dosage form. For example, if a subject has switched from oral sumatriptan tablets to SQ injectable sumatriptan, they are considered to have stopped sumatriptan tablets.

If they stopped a medication, the investigator is to inquire and record the single most important reason the medication was stopped as one of the following:

- Insufficient efficacy
- Adverse event(s)/side effect(s)
- Development of a contraindication to use of the specific agent (e.g., new diagnosis of cardiovascular disease necessitated discontinuation of a triptan)
- Other (e.g. change in coverage) or unknown

This information should be recorded in the CRF at Visit 2 (only for randomized patients).

Prohibited Medications

Medications listed below are prohibited from screening through the End of Treatment visit.

1. Marijuana: Legal (including medicinal marijuana and any marijuana-derived product including THC or CBD) or illegal use is prohibited.
2. Supplements and/or Traditional Medicines: The introduction of *new* agents during the course of the study is not allowed. The use of prior agents is described below.
3. Use of narcotic medication, such as heroin, opium in the form of morphine and codeine, oxycodone and is prohibited,
4. Use of barbiturates is prohibited.

Medications Prior to Study Treatment

The following medications are prohibited within **48 hours prior to study medication**:

- any triptan
- any ergot derivative
- any opiate
- any other form of analgesic
- any non-steroidal anti-inflammatory (NSAIDs) agent
- any antiemetic agent

- any CGRP antagonist approved and used for acute migraine treatment (ubrogepant and zavegepant, and rimegepant)
- any ditan

Medications for Migraine Prophylaxis

Standard migraine prophylaxis (e.g., beta-blocker, tricyclic antidepressant, topiramate, botulinum toxin, valproic acid, CGRP antagonists approved only for preventive migraine treatment (atogepant, anti-CGRP or calcitonin gene-related peptide receptor [CGRPR] antibodies)) will be permitted, with the exception of phenytoin and carbamazepine which are prohibited. Patients taking migraine prophylactic medication must be on a stable dose (prescribed daily dose should not change) for at least three months prior to screening and throughout the study period. Any withdrawal of preventive medications for the treatment of migraine should be completed at least 30 days prior to screening. Additionally, any prophylactic medication regimen should not be altered during the study.

Medications Following Study Treatment (Rescue Medication)

If the patient continues to have moderate or severe migraine headache pain 2 hours after taking the study medication OR if their migraine headache comes back within 48 hours, the patient will be allowed to take their own rescue migraine medication. Rescue medication may include analgesics (e.g., NSAIDs), anti-emetics, triptans or other medication not explicitly excluded, CGPRs antagonists for acute use (ubrogepant, rimegepant, zavegepant). Use of rescue medication must conform to the label of the product and the restrictions of this protocol. Rescue medication should not be taken before completing the 2-h diary assessments.

Patients will be instructed to record use of rescue medications (Y/N) they have used 48 hours prior to dosing with study medication. Any questions regarding the permissibility of a medication should be directed to the Sponsor's clinical monitor.

Supplements and/or Traditional Medicines: The use of herbal supplements and other natural products is allowed provided doses have been stable for at least 90 days prior to the screening visit. Increases in dose/frequency during the study are prohibited. Use of all such agents should be captured on the prior/concomitant medication CRFs.

Drug-drug Interaction Considerations

Due to the potential for elismetrep to inhibit CYP2C8, substrates of CYP2C8 are prohibited. These include but are not limited to paclitaxel, pioglitazone, repaglinide.

Contact the Sponsor if there are any questions about potential drug interactions with concomitant medications.

11. STUDY RESTRICTIONS AND REQUIREMENTS

11.1. Dietary and Physical Activity Requirements and Restrictions

11.1.1. Alcohol Restrictions

None.

11.1.2. Caffeine Restrictions

Patients will be asked to refrain from consuming caffeine for 2 hours after they take study medication.

11.1.3. Activity Restrictions

Patients will be asked to refrain from sleeping for 2 hours after they take study medication.

11.1.4. Diary

Patients will be required to complete diary entries beginning at the time of migraine onset of a qualifying migraine and up to 48 hours post-treatment. Patients will use a diary to record their date and time of dosing with study medication, as well as the efficacy assessments described in Section 14 of this protocol.

Emphasis should be made to patients to make every effort to provide real-time diary entries for the 2-hour and 24-hour time points.

Subjects will be provided with the diary and trained on diary use at V2.

11.2. Contraceptive Requirements

Male study participants:

There are no requirements for males to use contraception. Sperm donation is not prohibited.

Female study participants of reproductive potential

- Must agree to remain abstinent from heterosexual activity[a]
  - or agrees to use (or have their partner use) a birth control method that is acceptable from the first dose of study drug until the EoT visit. Acceptable methods of birth control are:
    - combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation:
      - oral
      - intravaginal
      - transdermal
    - progestogen-only hormonal contraception associated with inhibition of ovulation:
      - oral

  - injectable
  - implantable
- intrauterine device (IUD)
- intrauterine hormone-releasing system (IUS)
- bilateral tubal occlusion
- vasectomised partner
- sexual abstinence
- progestogen-only oral hormonal contraception, where inhibition of ovulation is not the primary mode of action
- male or female condom with or without spermicide
- cap, diaphragm or sponge with spermicide
- A combination of male condom with either cap, diaphragm or sponge with spermicide (double barrier methods)

[a] Abstinence can be used as the sole method of contraception if it is in line with the subject's preferred and usual lifestyle and if considered acceptable by local regulatory agencies and ethics committees. Periodic abstinence (e.g., calendar, ovulation, sympto-thermal, post-ovulation methods, etc.) and withdrawal are not acceptable methods of contraception.

This condition is waived if the subject is proven to have no child-bearing potential (eg, hysterectomy).

The criteria specified in Section 8.1 must be met for a female subject to be considered not of reproductive potential for the purpose of this study.

Pregnancy Testing

Women of reproductive potential participating in the study will be tested for serum β-hCG upon entry at the pre-treatment screening visit (Visit 1) and again at the post-treatment visit (Visit 3). Females of reproductive potential will have a urine β-hCG at the randomization visit (V2) prior to randomization).

12. RANDOMIZATION AND BLINDING

12.1. Randomization and Blinding

12.1.1. Randomization Code Creation and Storage

Randomization personnel of the Sponsor or designee will generate the randomization schedule. All randomization information will be stored in a secured area, accessible only by authorized personnel.

12.1.2. Clinical Study Drug Blinding

This is a double-blind study where the Sponsor, site staff and participants will be blinded to the treatment assignment.

12.1.3. Clinical Trial Blind Maintenance/Unblinding Procedure (Blinded Studies Only)

The study drug blind shall not be broken by the investigator unless information concerning the study drug is necessary for the medical treatment of the subject. If possible, the Sponsor medical monitor should be contacted before the blind is broken, unless doing so poses a risk to subject safety. The need for investigator unblinding should be discussed with the Sponsor first unless the unblinding needs to occur urgently to ensure subject safety.

Unblinding will be performed per the standard operating procedures of the study site. Any intentional or unintentional unblinding will be documented in the unblinding log and Clinical Study Report (CSR). Unblinding related to the interim analysis is described in Section 16.10.

13. STUDY DRUG MATERIALS AND MANAGEMENT

13.1. Study Drug

In this protocol, the term study medication refers to all or any of the drugs defined below and in Table 4.

Details regarding the dosage form description and strengths of the active drug and placebo can be found in the Pharmacy Manual or equivalent manual. Study drug will be packaged to support enrollment and replacement of participants as required.

The study drug will be supplied to the study site / Investigator by the Sponsor with the following medication in a double-blind manner:

- Elismetrep (K-304) 1 mg and 5 mg capsules and matching placebo capsules. Capsules will be provided in high-density polyethylene (HDPE) bottles. Participants and study staff are blinded as to the study treatment they receive.

Study medication will be labeled with a single-panel label that will contain, but will not be limited to, the following: Sponsor's name and address, protocol number, packaging job/lot number, caution statement and storage conditions.

Table 4: Elismetrep (K-304) Investigational Product

	Investigational Product
Product Name:	Elismetrep (K-304)
Dosage Form:	Dry filled capsules
Unit Dose	Capsules: placebo, 1-mg, 5-mg potencies
Route of Administration	Oral
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]

Additional reference information and administration instructions can be found in the Pharmacy Manual/equivalent document.

13.2. Study Drug Packaging and Labeling

A clinical label will be affixed to study drug containers in accordance with local regulatory requirements.

13.3. Study Drug Storage

Study drug must be stored in a secure, limited-access location under the storage conditions specified on the label and must remain in the original container until dispensed. A daily temperature log of the drug storage area must be maintained.

Elismetrep and matching placebo capsules should be stored at room temperature (15° C to 25° C). The temperature excursion information can be found in the pharmacy manual or in the referenced compounding manual when applicable. Receipt and dispensing of study drug must be recorded by authorized personnel at the study site.

13.4. Administration

Participants will be blinded to treatment assignment and dose level at all times.

Study medication may be taken without regard to food. Upon experiencing a qualifying migraine and prior to dosing, subjects should answer the questions in the diary to ensure the migraine is a qualifying migraine before taking study medication. Subjects should also record their MBS in the diary prior to dosing after confirming that the headache is qualifying.

13.4.1. Dose Timing

Subjects will be instructed to take study medication in the outpatient setting after answering diary questions (1) to verify the migraine is a qualifying migraine, (2) about their current pain and symptoms, and (3) identifying their currently most bothersome, migraine associated, symptom (phonophobia, photophobia or nausea).

The patient will be instructed to treat a migraine headache if the following conditions are met:

- The migraine headache severity is moderate or severe (Grade 2 or 3).
- The migraine headache started less than four hours ago.
- The migraine headache is a new headache that has not been previously treated and is not a recurrence of a previous migraine headache (at least 24 or 48 hours must have elapsed since the complete termination of their last attack (pain and all associated symptoms).
- No other migraine headache or headache has occurred in the previous 48 hours.
- The migraine headache is not already resolving on its own.
- Prohibited medication has not been taken (see Section 10).

Subjects will be counseled that if they experience a headache which could be qualifying but plan to “sleep if off” or otherwise anticipate not being able to complete the diary entries, particularly the 2h assessments, the subject should not take the study medication and should consider waiting to treat a subsequent headache within the 45-day window.

13.5. Study Drug Accountability

The Investigator is responsible for keeping accurate records of the study drug received from the Sponsor or designee, the amount dispensed to and returned by the participants, and the amount remaining at the end of the study. For all study sites, the local country sponsor personnel or designee will provide appropriate documentation that must be completed for study drug accountability, return, and destruction.

All ancillary supplies will be provided by either the study site or the Sponsor or designee, depending upon availability. The list of ancillary supplies and source information can be found in the Pharmacy Manual or in the referenced compounding manual when applicable. If provided

by the Sponsor, unused ancillary supplies will be accounted for and disposed of as directed by the Sponsor or designee.

13.6. Study Drug Handling and Disposal

For all study sites, the local country sponsor personnel or designee will provide appropriate documentation that must be completed for study drug accountability, return, and destruction.

13.7. Treatment Compliance

Treatment compliance will be monitored throughout the duration of the study. Study medication will be reconciled at specified visit(s) per SoA. Actual dosing compliance is to be confirmed between the site staff and subjects at specified study visit(s) and upon return of the subject investigational medicinal product (IMP).

14. EFFICACY ASSESSMENTS

14.1. Pain

Subjects will use a an eDiary to record their migraine pain score, on a 4-point numeric rating [no pain, mild pain, moderate pain, severe pain] at the time points indicated in the SOA (Table 2). Training on the diary will occur at V2.

14.2. Associated Symptoms (Nausea, Photophobia, Phonophobia)

The migraine associated symptoms of photophobia, phonophobia and nausea are measured on a two-point scale (present or absent), using the diary, at the time points listed in Table 2. All assessment is done using the diary.

The subjects are also asked to identify their most bothersome symptom in the diary (nausea, phonophobia or photophobia) at the onset of the migraine to be treated**.** The diary question on most bothersome symptom should be answered prior to taking study medication.

14.3. Rescue Medication

The subject's use of rescue medication (yes/no) is recorded by the subject in the diary. The specific medication used will not be recorded in the diary but should be captured/recorded at the EoT visit in the concomitant medication/rescue medication CRF.

Refer to Section 10.1 for instructions regarding rescue medications.

14.4. Functional Disability

Impact of treatment on functional disability will be assessed using a single-question scale[10]. Subjects rate the level of disability they perceive as a result of their migraine in performing normal actions with the question, "How much is your migraine interfering with your normal activities?" This will done in the diary, at the times indicated in Table 2, using a 4 point numeric rating scale with response options: No disability, able to function normally (0), Mild Impairment, can still do everything but with difficulty (1), Moderate Impairment, unable to do some things (2), Severe impairment- cannot do all or most things, bed rest may be necessary (3).

15. ASSESSMENT OF SAFETY

15.1. Safety Parameters

15.1.1. Demographic/Medical History

Qualified site personnel will collect subject significant medical history (past and concurrent medical conditions), per the clinical site' s standard of care and appropriate clinical judgment, and subject demographics.

Qualified site personnel will review subject prior and concomitant medication use. Medications are defined as prescription and over-the-counter drugs, vaccines, supplements, nutraceuticals, and oral herbal preparations.

Participant medical records are required to document that a subject has a diagnosis of migraine for at least 1 year prior to screening (inclusion criterion #2). Pharmacy records documenting prescription of a drug for the treatment of migraine can satisfy this requirement as can records from a medical provider.

15.1.2. Vital Signs

Body temperature will be measured with a tympanic thermometer.

Body weight will be measured in kilograms (kg).

Height is measured without shoes in centimeters (one decimal). Body mass index (BMI) will be calculated from screening data and must agree. Height will be measured at Screening only. Body mass index equals a subject' s weight in kilograms divided by the square of the height in meters (body mass index=kg/m^2). Body mass index will be rounded to the nearest whole number according to the standard convention of 0.1 to 0.4, round down, and 0.5 to 0.9, round up.

Vital sign measurements include a triplicate measurement of sitting blood pressure and heart rate. Blood pressure and heart rate will be measured using an automated, oscillometric blood pressure measuring device at time points noted in the SOA (Table 2). The following method should be used to record sitting blood pressure and heart rate for participants in triplicate:

- Participants will refrain from nicotine-containing products and/or ingesting caffeine for at least 30 minutes preceding the measurements.
  - Participants should be seated in a chair with their back supported, feet flat on the floor and arm bared (free of restrictions such as rolled up sleeves) and supported at heart level.
  - The appropriate cuff size must be used to ensure accurate measurement.
  - Measurements should be taken on the same arm at each visit (preferably the non-dominant arm).
  - Measurements should begin after at least 5 minutes of rest.
  - The three measurements of both the blood pressure and heart rate must be taken approximately 2 minutes apart with the triplicate set recorded in the source document and eCRFs.

- Assessment of heart rate can be manual (rather than using an automated device); however, when done manually, heart rate must be measured in the brachial/radial artery for at least 30 seconds.
- Other procedures should not be performed during the time of the blood pressure and heart rate measurements.

At home temperature monitoring

Subjects will be provided with a thermometer to monitor temperature in the post-dose period.

If after taking study medication and for up to 48h after taking study medication, a subject experiences any symptoms of reduction in body temperature such as feeling cold or chills, they should check their temperature. If the temperature is <35 ºC, they should continue to check their temperature every three hours until their temperature is > 35 ºC. If their temperature is below 34 degrees Celsius for at least 2 checks, the study subject should contact the clinical investigator. These events (readings below 34ºC for at least two consecutive measurements) should be recorded as AEs.

If they feel cold, subjects should also be instructed to use methods to prevent further heat loss including layering of clothes, use of heating devices, drinking hot beverages, avoiding alcoholic drinks.

Subjects will be provided instructions for temperature monitoring and for countermeasures.

15.1.3. Physical Examination (PE)

Qualified site personnel will conduct full PE during visits noted in the SOA.

The PE will include assessment of skin, head, ears, eyes, nose, throat, neck, thyroid, lungs, heart, cardiovascular, abdomen, lymph nodes, and musculoskeletal system/extremities. Interim PEs will be performed at the discretion of the Investigator, if necessary, to evaluate AEs or clinical laboratory abnormalities.

15.1.4. Electrocardiogram (ECG)

A triplicate 12-lead ECG will be collected at all the timepoints specified in the Schedule of Assessments following a rest period of at least 5 minutes.

The Investigator will interpret the Safety ECG using 1 of the following categories: within normal limits, abnormal but not clinically significant, or abnormal and clinically significant. The time that the ECG was performed will be recorded.

The following parameters will be recorded on the eCRF from the subject's ECG trace: heart rate, QRS interval, PR interval, QT interval, and QT (corrected) (Fridericia) ($QTcF = QT/(RR^{1/3})$).

Trial sites will calculate the triplicate average QTcF at the screening visit to assess the QTcF exclusion criterion. No other calculation of ECG parameter averages is required for trial sites.

The Investigator will be responsible for providing the interpretation of all safety ECGs (normal/abnormal). These results will be reviewed by the Investigator for subject safety and will be provided in an appropriate format with the clinical study report.

An electronic copy of the 12-lead ECG, which includes the Investigator's approval or a copy of the 12-lead ECG with the Investigator's signature and date of assessment, will be filed with the source and captured in the appropriate eCRF where required. If the original ECG is printed on thermal paper, the ECG report must be photocopied and signed by the Investigator or archival quality paper can be utilized for ECG printouts, with a 25-year (or more) guarantee from the manufacturer (assuming appropriate storage conditions are satisfied). If a photocopy is made, it will be filed with the original ECG in the source.

15.1.5. Laboratory Assessments

Laboratory samples will be collected in accordance with acceptable laboratory procedures. Except for screening safety laboratory samples, safety laboratory samples will be collected at the time points and observing fasting requirements where stipulated in the Schedule of Assessments.

15.1.5.1. Hematology

Hematology includes the following assessments:

White blood cell (WBC) count[a]	Hemoglobin
Red blood cell (RBC) count[b]	Hematocrit
Platelet count	

[a] Differential white blood cell count will include percentages for neutrophils, lymphocytes, monocytes, eosinophils, and basophils and absolute counts for neutrophils, lymphocytes, monocytes, eosinophils, and basophils.
[b] Differential red blood cell count will include mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH), mean corpuscular hemoglobin concentration (MCHC), red cell distribution width (RDW).

15.1.5.2. Blood Chemistry

Blood chemistry testing includes the following assessments:

Alanine aminotransferase (ALT)	Phosphorus
Albumin	Potassium
Alkaline phosphatase (ALP)	Sodium
Aspartate aminotransferase (AST)	Total bilirubin
Bicarbonate	Direct bilirubin
Chloride	Total Protein
Creatinine	Urea
Calcium	Gamma-glutamyl transferase (GGT)
Glucose	Magnesium
	Calculated eGFR (MDRD)

Please refer to Section 8.3 for subject discontinuation criteria related to abnormal liver test results, and Appendix D for details on management and follow-up of liver function test (LFT) elevations.

15.1.5.3. Urinalysis

Urinalysis includes the following assessments (Screening Visit only):

Dipstick:	Microscopic:
Nitrite	WBC
Protein	RBC
Glucose	Epithelial cells
pH	Casts (specify)
Specific gravity	
Ketones	
Bilirubin	
Urobilinogen	
Leucocyte Esterase	
Blood	

15.1.5.4. Virus Serology

Hepatitis B surface antigen, and hepatitis C virus antibody will be assessed at screening.

15.1.5.5. Drug Screen

The urine drug screening assessment will include the following tests:

Amphetamines, barbiturates, benzodiazepines, tetrahydrocannabinol (THC), cocaine/metabolites, 3,4-methylenedioxy-methamphetamine, methadone/metabolite, opiates.

15.1.5.6. Pregnancy Screen

Women of reproductive potential (see Section 8.1 for definition) participating in the study will be tested for serum β-hCG upon entry at the pre-treatment screening visit (Visit 1) and again at the post-treatment visit (Visit 3). Additionally, a urine hCG test will be conducted at V2 prior to randomization.

15.1.6. C-SSRS

The C-SSRS will be completed as indicated in the Study Flow Chart (and unscheduled visits as clinically indicated) (Appendix C). In addition, patients who at any time during this study spontaneously report AEs of suicidal ideation with intent (with or without a plan) or behavior, either as outpatient or during visit interviews, must be assessed by the investigator and referred for further mental health evaluation as clinically indicated. Patients with treatment-emergent suicidal ideation and/or behavior must be evaluated that day by a psychiatrist or other trained mental health professional who is a licensed psychologist, social worker or nurse practitioner (or comparable professional qualification in countries outside the United States). Only patients whose suicidal ideation is passive, who expressly deny any intent to act, and who, after evaluation, are not judged to be at serious risk for self-harm during the course of the study may

continue in the study; others must be discontinued from study participation and receive appropriate clinical follow-up care to assure their safety.

The "Baseline" version of the C-SSRS will be used at Screening (V1), since it assesses suicidality over the course of a subject's lifetime. The lifetime assessment is only needed once, so **the "Since Last Visit" version** of the C-SSRS will be used at V2 and V3 and at any unscheduled visits.

15.2. Adverse Events and Serious Adverse Events

15.2.1. Definition of Adverse Events (AEs) and Serious Adverse Events (SAEs)

15.2.1.1. Adverse Event (AE)

An Adverse Event/Experience is any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment [ICH E2A].

The following can be considered AEs:

- An exacerbation of a pre-existing illness
- An increase in frequency or intensity of a pre-existing episodic event or condition
- A condition detected or diagnosed after the initiation of treatment with study medication, even though it may have been present prior to the start of the study.
- Continuous persistent disease or symptoms present at baseline that worsen after informed consent or following the initiation of treatment with study medication.
- Laboratory values and ECG findings: Changes in laboratory values or ECG parameters may be considered AEs if they are judged to be clinically significant (i.e., if some action or intervention is required or if the Investigator judges the change to be beyond the range of normal physiologic fluctuation). If the value results in a discontinuation of investigational study drug, then the occurrence should be reported as an AE.
- If abnormal laboratory values or ECG findings are the result of pathology for which there is an overall diagnosis (e.g., increased creatinine in renal failure), the diagnosis only should be reported appropriately as an AE. Any laboratory AE should be recorded in the eCRF, whether or not it is related to study drug.
- Any change in vital signs that are considered clinically significant by the Investigator may be recorded as an AE. If the value results in a discontinuation of investigational study drug, then the occurrence should be reported as an AE.

Progression of treatment indication (migraine) including new or worsening of anticipated clinical signs or symptoms, which are collected as clinical efficacy variables (e.g., migraine, nausea, photophobia, phonophobia) and assessed as unequivocally associated with the disease progression and /or lack of efficacy, should NOT be reported as AEs unless the disease progression is greater than anticipated in the natural course of the disease.

15.2.1.2. Serious Adverse Event (SAE)

A serious adverse event is any untoward medical occurrence that at any dose:

- Results in death
- Is immediately life-threatening
- Requires in-patient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability or incapacity
- Results in a congenital abnormality or birth defect
- Is an important medical event that may jeopardize the patient or may require medical intervention to prevent one of the outcomes listed above.

Further Details and Clarifications on the AE Definition

The following events are NOT considered Adverse Events

- Stable chronic conditions that are present prior to clinical trial entry and do not worsen. These will be accounted for in the subject's medical history.
- Laboratory values that are abnormal but not of clinical significance. This includes a laboratory re-test and/or continued monitoring of an abnormal value. In addition, repeated or additional noninvasive testing for verification, evaluation or monitoring of a laboratory or ECG abnormality is not considered an AE.
- Medical or surgical procedures (e.g., surgery, endoscopy, tooth extraction, or transfusion); the condition that leads to the procedure is an AE
- Situations where an untoward medical occurrence has not occurred (e.g., hospitalizations for cosmetic surgery or elective surgery or social/convenience admissions)

15.2.2. Time Period and Frequency for Collecting AE and SAE Information

All AEs and SAEs will be collected from time of consent through the End of Treatment visit.

15.2.3. Identifying AEs and SAEs

Adverse events spontaneously reported by the patient/subject and/or in response to an open question from the study personnel or revealed by observation will be recorded during the study at the investigational site.

15.2.4. Recording of AEs and SAEs

All AEs that occur after any patient/subject has been consented, before treatment, during treatment, during all visits, and through the EoT visit following the cessation of treatment, whether or not they are related to the study drug, must be recorded on the eCRFs provided by Kallyope, Inc.

Each event should be recorded to represent a single diagnosis. Accompanying signs (including abnormal laboratory values or ECG findings) or symptoms should NOT be recorded as additional AEs. If a diagnosis is unknown, sign(s) or symptom(s) should be recorded appropriately as an AE(s) and updated once the information becomes available.

The following information will be documented for each event:

- Event term
- Start and end date and time
- Pattern of AE (frequency)
- Severity/intensity
- Causality Assessment (Investigator's opinion of the causal relationship between the event and administration of study drug[s])
- Action taken with trial drug
- Outcome of event
- Seriousness

Event Term

The AE term should be reported in standard and current medical terminology (e.g., MedDRA) when possible.

Start Date

The start date of the AE is the date that the first signs/symptoms were noted by the patient/subject and/or Investigator.

End Date

The end date of the AE is the date at which the patient/subject recovered, the event resolved but with sequelae, or the patient/subject died.

Pattern of AE (Frequency)

Episodic AEs (e.g., headache) or those which occur repeatedly over a period of non-consecutive days are intermittent. All other events are continuous.

Severity/Intensity

It is important to distinguish between serious and severe AEs. Severity is a measure of intensity whereas seriousness is defined by the criteria under Section 15.2.1.2. An AE of severe intensity may or may not be considered “serious.”

Intensity will be assessed according to the following scale:

- Mild (awareness of sign or symptom, but easily tolerated)
- Moderate (discomfort sufficient to cause interference with normal activities)
- Severe (incapacitating, with inability to perform normal activities)

Causality Assessment

An Investigator who is qualified in medicine must make the determination of relationship to the study drug for each AE.

The relationship of each AE to study drug will be assessed using the following categories:

Related: An AE that follows a reasonable temporal sequence from administration of study drug (including the course after withdrawal of the study drug), or for which a causal relationship is at least a reasonable possibility that the study drug caused the AE, ie, it is medically plausible. “Reasonable possibility means” there is evidence to suggest a causal relationship between the study drug and the AE.

Not Related: An AE that does not follow a reasonable temporal sequence from administration of study drug and/or that can reasonably be explained by other factors, such as underlying diseases, complications, concomitant medications, and/or concurrent treatments.

Action Taken with Study Treatment

- Drug withdrawn (ie, discontinuation due to an AE) - a study medication is stopped due to the particular AE.
- Dose not changed - the particular AE did not require stopping a study medication.
- Unknown - only to be used if it has not been possible to determine what action has been taken.
- Not applicable - a study medication was stopped for a reason other than the particular AE, e.g., the study has been terminated, the subject died, dosing with study medication had not yet started or dosing with study medication was already stopped before the onset of the AE.
- Dose reduced - the dose was reduced due to the particular AE.
- Dose increased - the dose was increased due to the particular AE.
- Drug interrupted - the dose was interrupted due to the particular AE.

Outcome

- Recovered/resolved - subject returned to first assessment status with respect to the AE.
- Recovering/resolving - the intensity is lowered by one or more stages: the diagnosis has or signs/symptoms have almost disappeared; the abnormal laboratory value improved, but has not returned to the normal range or to the baseline value; the subject died from a cause other than the particular AE with the condition remaining "recovering/resolving."
- Not recovered/not resolved - there is no change in the diagnosis, signs or symptoms; the intensity of the diagnosis, signs /symptoms or laboratory value on the last day of the observed study period has become worse than when it started; is an irreversible congenital anomaly; the subject died from another cause with the particular AE state remaining "Not recovered/not resolved."
- Recovered/ Resolved with sequelae - the subject recovered from an acute AE but was left with permanent/significant impairment (e.g., recovered from a cardiovascular accident but with some persisting paresis).
- Fatal - an AE that is considered as the cause of death.

- Unknown - the course of the AE cannot be followed up due to hospital change or residence change at the end of the subject's participation in the study.

Seriousness

- See Section 15.2.1.2 for the criteria for an SAE. Seriousness is a factor in determining regulatory obligations.

15.2.5. Follow-Up of AEs and SAEs

All participants/participants experiencing AEs, whether considered associated with the use of the study medication or not, must be monitored until the symptoms subside (the patient's/subject's health has returned to baseline status) and any clinically relevant changes in laboratory values have returned to baseline, or until there is a satisfactory explanation for the changes observed, regardless of whether the patient/subject is still participating in the study. The exception are nonserious AEs that begin prior to the first exposure to investigational product, related or unrelated to the study procedure, which need not be followed-up for the purposes of the protocol.

All appropriate therapeutic measures will be undertaken and recorded. Where appropriate, medical tests and examinations will be performed to document resolution of the event(s).

15.2.6. Reporting Serious Adverse Events (AEs) to the Sponsor

The study designated SAE form (or equivalent) must be completed, in English, and signed by the Investigator immediately or within 24 hours of first onset or notification of the event.

The SAE must also be entered into the electronic data capture (EDC) within 24 hours of the Investigator's (or other study personnel's) initial knowledge of the event. A paper form may be used as back-up.

The SAE form should be transmitted within 24 hours of awareness by email to the safety mailbox address listed below and in Table 1.

[redacted]

The information should be completed as fully as possible but contain, at a minimum:

- A short description of the event and the reason why the event is categorized as serious
- Subject identification number
- Investigator's name/site
- Name of the study medication(s)
- Causality assessment

The Investigator must verify the accuracy of the information recorded on the SAE pages with the corresponding source documents. Supporting documents (e.g. discharge summaries, imaging reports, ECGs, laboratory tests, autopsy reports, etc.) should also be provided with the SAE or as soon as obtained.

Additional follow-up information, if requested or becomes available at a later date, should be transmitted to Kallyope, Inc. and its designated contact address within 24 hours of receipt. The

investigator should complete a follow-up SAE form. All SAE information, including initial and all follow-ups, should be kept with the appropriate section of the CRF and/or study file.

All SAEs should be followed up as described in Section 15.2.5. The timelines and procedure for follow-up reports are the same as those for the initial report.

15.2.7. Reporting AEs to Regulatory Authorities and IRBs/IECs

The Sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study intervention under clinical investigation. The Sponsor will comply with country-specific regulatory requirements for safety reporting to regulatory authorities, IRBs/IECs, and investigators.

A SAE may qualify for expedited reporting to regulatory authorities if it is determined to be a sudden unexpected serious adverse reaction (SUSAR). A SUSAR is an AE associated with the use of the study drug which is serious, unexpected, and assessed as related to the study drug. An AE is considered “unexpected” if the nature of the AE is not consistent with what is not listed in the Reference Safety Information section of the Investigator Brochure. Reports that add significant information on specificity or severity of a known, already documented serious adverse event constitute unexpected events. The Sponsor is responsible for determining whether a SAE is expected or unexpected for the purpose of regulatory reporting.

The Sponsor or its designated representative will be responsible for reporting all suspected unexpected serious adverse reactions (SUSARs) and any other applicable SAEs to regulatory authorities, Investigators, and IRBs or IECs, as applicable, in accordance with national regulations in the countries where the study is conducted. Relative to the first awareness of the event by/or further provision to the sponsor or sponsor' s designee, SUSARs will be submitted within 7 days for fatal and life-threatening SUSARs and 15 days for non-fatal and non-life-threatening SUSARs, unless otherwise required by national regulations. The Sponsor will also prepare an expedited report for other safety issues where these might materially alter the current benefit-risk assessment of an investigational medicinal product or that would be sufficient to consider changes in the investigational medicinal products administration or in the overall conduct of the trial.

It is the Principal Investigator’s responsibility to promptly notify the IRB or IEC of all SAEs that occur at his or her site. Investigators will also be notified of all SUSARs (7/15 Day Safety Reports) that occur during the clinical trial. Each site is responsible for notifying its IRB or IEC of these additional SAEs, in accordance with its regulations and guidelines.

15.2.8. Adverse Events of Special Interest (AESI)

An AESI is an AE (serious or non-serious) of scientific and medical interest to the Sponsor’s product or program. Ongoing monitoring and rapid communication to the Sponsor is requested as such an event might warrant further investigation in order to further characterize it.

AESIs and any follow-up information must be reported to the Sponsor within 24 hours of first awareness (Section 15.2.6).

- For this study, there are no AESIs.

15.2.9. Pregnancy and Lactation

Although pregnancy and lactation are not considered an AE, it is the responsibility of the Investigator to report the pregnancy/lactation in either a female subject or the partner of a male subject to the Sponsor and its designee during the trial (within 24 hours) up until the post-study Visit. All participants and partners of participants who become pregnant after the start of study intervention (ingestion of study drug) must be followed to the completion or termination of pregnancy.

Should a pregnancy occur following ingestion of study drug, it must be recorded on the eCRFs and designated pregnancy form and reported within 24 hours to the designated safety mailbox at:

[redacted]

Pregnancy, in itself, is not regarded as an AE unless a negative or consequential outcome occurs in the participant or child/fetus, or there is a suspicion that the study drug may have interfered with the effectiveness of a contraceptive medication.

Pregnancy outcomes (e.g. spontaneous abortion, missed abortion, benign hydatidiform mole, blighted ovum, ectopic pregnancy, pre-eclampsia, fetal death, intrauterine death, miscarriage, and stillbirth must be reported as SAEs (important medical events). If the pregnancy continues to term, the outcome (health of infant) must also be followed up and documented even if the patient was discontinued from the study. All reports of congenital abnormalities/birth defects are SAEs. SAEs should be reported as per Section 15.2.6.

16. STATISTICS

16.1. General Statistical Considerations

A Statistical Analysis Plan (SAP) will be developed and finalized before database lock and will describe details of the summaries and analyses to be performed. Any changes in the planned analyses will be reported in the clinical study report (CSR).

All summaries and analyses will be presented in tabular or graphical form. Continuous data will be summarized by reporting number of observations, mean, standard deviation (SD), median, minimum, and maximum by treatment and visit. Categorical data will be summarized using frequency tables reporting the number and percentage of participants falling within each category by treatment and by visit.

All tests of treatment effects will be conducted at a two-sided alpha level of 0.1 and/or two-sided 90% confidence interval, unless otherwise stated.

Baseline will be taken as the last available observation prior to dosing during the double-blind treatment period.

16.2. Sample Size Justification

It is anticipated that about 90% of 400 randomized subjects will have a qualifying headache in the allotted 45-day time frame, resulting in 360 evaluable subjects for efficacy in each treatment group.

A total sample size of 360 evaluable subjects (randomized 2:1:2:2:1 into placebo, 2 mg, 5 mg, 10 mg and 20 mg) provides approximately 85.5% power for the primary endpoint of pain freedom at 2 hours post dose for the comparison between 5 mg and 10 mg vs placebo respectively with a two-sided alpha of 0.1, assuming a placebo response rate of 10% and the treatment response rate of 25% and a treatment difference of 15%.

16.3. Analysis Populations

The following analysis sets will be evaluated and used for analysis of the data.

Enrolled subjects: subjects who sign an informed consent form and are assigned a subject identification number.

Randomized subjects: Enrolled subjects who received a randomized treatment assignment from the IWRS

Treated subjects: Randomized subjects who take the study medication.

Modified Intent to Treat (mITT): randomized subjects that take study therapy, have a qualifying migraine of moderate or severe baseline pain intensity (as defined in Section 7), and provide baseline and at least one post-baseline efficacy data point (i.e. non-missing pain level, phonophobia status, photophobia status, nausea status etc). The mITT analysis set will be used for demographic, baseline characteristic and efficacy analysis. Subjects are analyzed as randomized.

The Safety Analysis set: Randomized subjects who take the study medication. The safety analysis set will be used for safety analyses and analyzed as treated.

16.4. Disposition

The number and percentage of participants who were randomized, and randomized but did not receive the study product as randomized will be summarized by treatment group. The number and percentage of participants who completed the double-blind treatment and/or the study, prematurely discontinued to study, and primary reason for discontinuation will be summarized by treatment group.

16.5. Demographics and Baseline Characteristics

Demographic and baseline characteristics will be summarized by treatment group. Descriptive statistics (N, mean, SD, median, minimum, and maximum) will be generated for continuous demographic variables and baseline characteristics variables (e.g., age, height, weight, and BMI). The number and percentage of participants in each class of the categorical demographic variables and baseline characteristics variables (e.g., gender, ethnicity, race) will be summarized. Individual subject demographic and baseline characteristics data will be listed.

16.6. Efficacy Analyses

16.6.1. Endpoints/Measures

Timing of all efficacy measurements is relative to the dose of study medication.

The following endpoints/measures will be derived from the response in the patient diaries:

Primary:

- Pain freedom will be assessed using the number of evaluable subjects that report no pain at 2 hours post-dose. Pain will be measured on a 4-point Likert scale (0=none, 1=mild, 2=moderate, 3=severe).

Secondary:

- Freedom from the most bothersome symptom (MBS) will be assessed using the number of evaluable subjects that report the absence of their MBS at 2 hours post-dose. The MBS (nausea, phonophobia or photophobia) will be measured using a binary scale (0=absent, 1=present).
- Pain relief will be assessed using the number of evaluable subjects that report a pain level of moderate or severe (responses of 2 or 3 on the 4-point Likert scale) at baseline and then report a pain level of none or mild (response of 0 or 1).
- Freedom from Photophobia will be assessed by tabulating the number of subjects that report the absence of photophobia at 2 hours post-dose in the subset of subjects that reported the presence of photophobia at headache baseline.
- Freedom from Phonophobia will be assessed by tabulating the number of subjects that report the absence of phonophobia at 2 hours post-dose in the subset of subjects that reported the presence of phonophobia at headache baseline.

- Freedom from Nausea will be assessed by tabulating the number of subjects that report the absence of nausea at 2 hours post-dose in the subset of subjects that reported the presence of nausea at headache baseline.
- The probability of requiring rescue medication will be assessed using the number of subjects that take rescue medication within 24 hours after administration of study medication.
- Sustained pain freedom, from 2 to 24 hours, will be assessed using the number of subjects that do not experience any headache pain through the time period of interest.
- Sustained pain relief, from 2 to 24 hours will be assessed using the number of subjects that do not use any rescue medications, and do not experience any moderate or severe headache pain through the time period of interest.
- Sustained pain freedom, from 2 to 48 hours, will be assessed using the number of subjects that do not experience any headache pain through the time period of interest.
- Sustained pain relief from 2 to 48 hours, will be assessed using the number of subjects that do not use any rescue medications, and do not experience any moderate or severe headache pain through the time period of interest.

Exploratory:

- The proportion of subjects able to function normally, at 2 hours, will be assessed using the number of subjects that self-report as "normal" on the functional disability scale (functional disability: four-point scale: normal (0), mildly impaired (1), moderately impaired (2), severely impaired, requires bedrest (3) in the subset of subjects who reported any level of disability at the migraine baseline.
- Pain relapse will be assessed using the proportion of subjects with (a) mild, moderate, or severe pain (response of 1, 2 or 3 on the 4-point scale) at any time point after 2 hours post-dose; (b) missing pain data at ≤ 1 time point after 2 hours post-dose; (c) no intervening rescue medication taken at or before 48 hours post-dose evaluated for subjects with pain freedom at 2 hours post-dose within 48 hours after administration of study medication.

16.6.2. Primary Endpoint Analysis

For the primary endpoints of pain freedom at 2 hours post dose in the mITT analysis population. The percentages of subjects with pain freedom at 2 hours post dose are compared between treatment and placebo using Cochran-Mantel-Haenszel (CMH) test stratified by use of background prophylactic medications for migraine (yes/no). The percentage difference between treatment and placebo is tested at a two-sided alpha level of 0.1 for each dose level. The percentage of subjects achieving the endpoints response criteria by treatment group and the difference in percentages between treatment group and placebo will be presented with a 90% confidence interval (CI). Subjects with missing data at 2 hours post dose will be classified as failures. Sensitivity analysis will be described in the SAP.

16.6.3. Secondary Endpoints Analysis

For secondary categorical endpoints, the same statistical analysis will be applied using CMH test stratified by use of background prophylactic medications for migraine (yes/no). Subjects with missing data or with measurements after using rescue medications will be classified as failure (for timepoints analyses using post-rescue observations).

For the probability of rescue medication use within 24-hour post-dose, the CMH test will be performed. Time to reschedule medication use through 24 hours post-dose will be assessed by treatment group using Kaplan-Meier (KM) plot. Log-rank test will be performed. Subjects who do not take rescue medication within 24 hours post-dose will be censored at 24 hours.

16.6.4. Exploratory Endpoints Analysis

For exploratory categorical endpoints, the same statistical analysis will be applied using CMH test stratified by use of background prophylactic medications for migraine (yes/no). Subjects with missing data or measurement after using rescue medications will be classified as failure.

16.7. Safety Analyses

Safety analyses will be based on the Safety Analysis Set. No formal statistical tests or inference will be performed for safety analyses. All summaries will be summarized by treatment.

16.7.1. Treatment-emergent Adverse Events (TEAE)

Safety analyses will be based on the Safety Analysis Set. No formal statistical tests or inference will be performed for safety analyses.

Adverse events will be coded using the version of the Medical Dictionary for Regulatory Activities (MedDRA) in effect at the start of the study. AEs will be summarized as TEAEs (defined as events that are newly reported after randomization or reported to worsen in severity from baseline). The incidence of participants with at least 1 TEAE and the incidence of TEAEs by preferred term and system organ class will be presented by treatment group. The frequency and percentage of TEAEs will be presented. The incidence of participants with at least 1 TEAE assessed as related to the study drug will be summarized by treatment group. All SAEs will be listed by patient. If a sufficient number of SAEs are reported, summaries will be included. Discontinuations to study due to TEAEs will be summarized by treatment group. All adverse events will be listed by patient.

16.7.2. Clinical Laboratory Evaluation

Baseline, post baseline measurements and changes from baseline for clinical laboratory evaluations will be summarized by treatment and timepoint. Individual measurements of laboratory tests from hematology, chemistry, and urinalysis that meet KALLYOPE, Inc.'s abnormal criteria will be summarized.

16.7.3. Vital Signs

Baseline, post baseline measurements and changes from baseline for vital sign data will be summarized by treatment and timepoint.

16.7.4. Electrocardiogram

All electrocardiogram data will be provided in the data listings.

16.7.5. Prior and Concomitant Medications

Prior and concomitant medications will be summarized by treatment group. Rescue medication use will be summarized by treatment group.

16.8. Missing Data Handling

Every effort will be made to reduce missing data in the trial. Subjects in this study will be encouraged to remain in the study and follow the scheduled visits to provide the efficacy and safety data needed.

Methods of handling missing data in principal analyses of binary efficacy endpoints are defined as follows:

- Non-Completer = Failure: Subjects with missing data at a single time point will be classified as failures. This missing data imputation method will be applied to endpoints based on data from a single time point (e.g., co-primary endpoints at 2 hours post-dose).
- Non-Completer With Missing Data at More Than 1 Time Point = Failure: Subjects with missing data at > 1 time point post-dose in a specified time period will be classified as failures. This missing data imputation method will be applied to endpoints that are based on data from multiple time points (e.g., secondary endpoint of sustained pain freedom from 2 to 24 hours post-dose).
- The intercurrent event of rescue medication use will be handled using Rescue Medication = Failure, i.e., subjects who take rescue medication will be classified as failures for all efficacy evaluations that are reported at or after taking rescue medication.

Additional sensitivity analysis will be defined in the statistical analysis plan.

16.9. Multiplicity

The study tests the primary hypothesis that at least one of the treatment arms is superior to the placebo arm in primary endpoint of pain freedom at 2 hours post. No multiplicity adjustment will be performed for primary and secondary objectives, which will be tested at two-sided alpha of 0.1.

16.10. Interim Analysis

After approximately 200 subjects have completed the primary endpoint, an interim analysis (IA) of efficacy data will be conducted for internal decision making. An external contractor statistician will be unblinded to the randomization schedule. The external statistician will provide group level summary efficacy data on the primary endpoint to selected sponsor personnel. The sponsor personnel who become unblinded to the group level summary efficacy data for this IA will have no further contact with study sites until after the final database lock. All Investigators, study site personnel, and subjects, and sponsor personnel in the study team will remain blinded to treatment assignments until after the end of the study. Details are provided in the study unblinding plan.

No Type I error adjustments will be made since the study will not be stopped for overwhelming efficacy. The sponsor may stop the trial for futility.

17. ADMINISTRATIVE AND REGULATORY DETAILS

17.1. Direct Access to Source Data/Documents

17.1.1. Study Monitoring

Study progress will be monitored by the Sponsor or its representative as frequently as necessary to perform source document verification, ensure a accurate data collection, protocol compliance, and study conduct in accordance with accepted regulatory requirements. The Principal Investigator must make all the subject data available to the monitor for review during the planned site monitoring visits. Arrangements for monitoring visits will be made in advance, except in emergency cases.

17.1.2. Audits and Inspections

Authorized representatives of Kallyope, Inc., a regulatory authority, an Independent Ethics Committee or an Institutional Review Board may conduct inspections or audits of the clinical study. If the investigator is notified of an inspection by a regulatory authority the investigator agrees to notify the Sponsor -- medical monitor immediately. The investigator agrees to provide to representatives of a regulatory agency or Sponsor -- access to records, facilities, and personnel for the effective conduct of any inspection or audit.

17.2. Institutional Review Board (IRB)/ Independent Ethics Committee (IEC)

The Principal Investigator must obtain IRB/IEC approval for the investigation. Initial IRB/IEC approval, and all materials approved by the IRB/IEC for this study including the patient consent form and recruitment materials must be maintained by the Investigator and made available for inspection.

17.3. Written Informed Consent

The Principal Investigator(s) at each center will administer an IRB/EC approved informed consents to all subjects who are screened on this trial. The subject's/patient's signed and dated informed consent must be obtained before conducting any study procedures.

17.4. Data Handling and Recordkeeping

17.4.1. Data Collection and Reporting

Data for this study will be collected using eCRFs. The Investigator and study site staff will receive system documentation, training, and support for the use of the eCRF.

All protocol-required information collected during the study must be entered by the Investigator or designated representative in the source documents and eCRF. All data entry, modification, or deletion will be recorded automatically in an electronic audit trail indicating the individual subject, original value, the new value, the reason for change, who made the change, and when the change was made. All data changes will be clearly indicated with a means to locate prior values. The system will be secured to prevent unauthorized access to the data or the system. This

will include the requirement for a user identification (ID) and password to enter or change data. The Investigator will maintain a list of individuals who are authorized to enter or correct data and their system ID.

The Investigator or designated sub-Investigator, following review of the data in the eCRF, will confirm the validity of each subject's data by electronic signature.

17.5. Retention of Records

The investigator must maintain adequate and accurate records to enable the conduct of the study to be fully documented and the study data to be subsequently verified. These documents should be classified into at least the following two categories: (1) investigator's study file, and (2) subject clinical source documents. Refer to (Refer to ICH E6 (R2) Good clinical practice Section 8 Essential documents for the conduct of a clinical trial).

The Principal Investigator must maintain all documentation relating to the study for a period of 2 years after the last marketing application approval, or if not approved 2 years following the discontinuance of the test article for investigation. If it becomes necessary for Kallyope, Inc. or the Regulatory Authority to review any documentation relating to the study, the Investigator must permit access to such records.

17.6. PK and PD Sample Retention

No blood for PK or PD analysis is being collected in this study.

17.7. Publication Policy

The Investigator is obliged to provide the Sponsor with complete test results and all data derived information available to other study Investigators or to regulatory agencies, except as required by law or regulation. Except as otherwise allowable in the clinical study site agreement, any public disclosure (including publicly accessible websites) related to the protocol or study results, other than study recruitment materials and/or advertisements, is the sole responsibility of the Sponsor.

Investigators will be asked to review primary publications. The Sponsor may publish any data and information from the study (including data and information generated by the Investigator). Manuscript authorship for any peer-reviewed publication will appropriately reflect contributions to the production and review of the document. All publications and presentations must be prepared in accordance with this section and the Clinical Study Site Agreement. In the event of any discrepancy between the protocol and the Clinical Study Site Agreement, the Clinical Study Site Agreement will prevail.

Investigators must seek approval from the Sponsor prior to publishing information from this trial. The Sponsor must have the opportunity to review all proposed abstracts, manuscripts, or presentations regarding this trial 45 days prior to submission for publication/presentation. Any information identified by the Sponsor as confidential must be deleted prior to submission; this confidentiality does not include efficacy and safety results. Sponsor review can be expedited to meet publication timelines.

17.8. Financial Disclosure

Investigators who participate on this study will be required to provide the sponsor and/or its designees financial disclosure documentation as required per regulatory requirements. Financial Disclosure requirements are outlined in the US Food and Drug Administration Regulations, Financial Disclosure by Clinical Investigators (21 CFR Part 54).

17.9. Compliance with Law, Audit, and Debarment

By signing this protocol, the Investigator agrees to conduct the trial in an efficient and diligent manner and in conformance with this protocol; generally accepted standards of Good Clinical Practice (eg, International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use Good Clinical Practice: Consolidated Guideline and other generally accepted standards of good clinical practice); and all applicable federal, state and local laws, rules and regulations relating to the conduct of the clinical trial.

The Investigator also agrees to allow monitoring, audits, IRB/ERC review and regulatory authority inspection of trial-related documents and procedures and provide for direct access to all trial-related source data and documents.

The Investigator agrees not to seek reimbursement from participants, their insurance providers or from government programs for procedures included as part of the trial reimbursed to the Investigator by the Sponsor.

The Investigator shall prepare and maintain complete and accurate trial documentation in compliance with GCP standards and applicable federal, state, and local laws, rules, and regulations; and, for each subject participating in the trial, provide all data, and, upon completion or termination of the clinical trial, submit any other reports to the Sponsor as required by this protocol or as otherwise required pursuant to any agreement with the Sponsor.

Trial documentation will be promptly and fully disclosed to the Sponsor by the Investigator upon request and also shall be made available at the trial site upon request for inspection, copying, review and audit at reasonable times by representatives of the Sponsor or any regulatory authorities. The Investigator agrees to promptly take any reasonable steps that are requested by the Sponsor as a result of an audit to cure deficiencies in the trial documentation and worksheets/case report forms.

The Investigator must maintain copies of all documentation and records relating to the conduct of the trial in compliance with all applicable legal and regulatory requirements. This documentation includes, but is not limited to, the protocol, worksheets/case report forms, advertising for subject participation, adverse event reports, subject source data, correspondence with regulatory authorities and IRBs/ERCs, consent forms, Investigator's curricula vitae, monitor visit logs, laboratory reference ranges, laboratory certification or quality control procedures and laboratory director curriculum vitae. By signing this protocol, the Investigator agrees that documentation shall be retained until at least 2 years after the last approval of a marketing application in an ICH region or until there are no pending or contemplated marketing applications in an ICH region or until at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product. Because the clinical development and marketing application process is variable, it is anticipated that the retention period can be up to 15 years or longer after protocol database lock. The Sponsor will determine

the minimum retention period and notify the Investigator when documents may be destroyed. The sponsor also recognizes that documents may need to be retained for a longer period if required by local regulatory requirements. All trial documents shall be made available if required by relevant regulatory authorities. The Investigator must consult with and obtain written approval by the Sponsor prior to discarding trial and/or subject files.

ICH GCP guidelines recommend that the Investigator inform the subject's primary physician about the subject's participation in the trial if the subject has a primary physician and if the subject agrees to the primary physician being informed.

The Investigator will promptly inform the Sponsor of any regulatory authority inspection conducted for this trial.

Persons debarred from conducting or working on clinical trials by any court or regulatory authority will not be allowed to conduct or work on this Sponsor's trials. The Investigator will immediately disclose in writing to the Sponsor if any person who is involved in conducting the trial is debarred or if any proceeding for debarment is pending or, to the best of the Investigator's knowledge, threatened.

In the event the Sponsor prematurely terminates a particular trial site, the Sponsor will promptly notify that trial site's IRB/IEC.

17.10. Compliance with Trial Registration and Results Posting Requirements

Under the terms of the Food and Drug Administration Modernization Act (FDAMA) and the Food and Drug Administration Amendments Act (FDAAA), the Sponsor of the trial is solely responsible for determining whether the trial and its results are subject to the requirements for submission to the Clinical Trials Data Bank, http://www.clinicaltrials.gov. KALLYOPE, as Sponsor of this trial, will review this protocol and submit the information necessary to fulfill these requirements. KALLYOPE entries are not limited to FDAMA/FDAAA mandated trials. Information posted will allow participants to identify potentially appropriate trials for their disease conditions and pursue participation by calling a central contact number for further information on appropriate trial locations and trial site contact information.

By signing this protocol, the Investigator acknowledges that the statutory obligations under FDAMA/FDAAA are that of the Sponsor and agrees not to submit any information about this trial or its results to the Clinical Trials Data Bank.

17.11. Confidentiality

17.11.1. Confidentiality of Data

By signing this protocol, the Investigator affirms to the Sponsor that information furnished to the Investigator by the Sponsor will be maintained in confidence, and such information will be divulged to the institutional review board, ethics review committee (IRB/ERC) or similar expert committee; affiliated institution and employees, only under an appropriate understanding of confidentiality with such board or committee, affiliated institution and employees. Data generated by this trial will be considered confidential by the Investigator, except to the extent

that it is included in a publication as provided in the Publications section (Section 17.7) of this protocol.

17.11.2. Confidentiality of Subject Records

By signing this protocol, the Investigator agrees that the Sponsor (or Sponsor representative), IRB/ERC, or regulatory authority representatives may consult and/or copy trial documents in order to verify worksheet/case report form data. The subject is informed about this process within the Informed Consent Form. Participants will be identified in CRFs and other documents submitted to the Sponsor only in a pseudonymized form (eg, by a subject number and/or birth year, but not by name).

By signing this protocol, the Investigator agrees to treat all subject data used and disclosed in connection with this trial in accordance with all applicable privacy laws, rules, and regulations.

17.11.3. Confidentiality of Investigator Information

By signing this protocol, the Investigator recognizes that certain personal identifying information with respect to the Investigator, and all sub-Investigators and trial site personnel, may be used and disclosed for trial management purposes, as part of a regulatory submissions, and as required by law. This information may include:

1. name, address, telephone number and e-mail address;
2. hospital or clinic address and telephone number;
3. curriculum vitae or other summary of qualifications and credentials; and
4. other professional documentation.
5. financial information such as the declaration of financial interests, if applicable, and other financial information collected for the purpose of payment and reporting of payments in connection with the conduct of trials.

Consistent with the purposes described above, this information may be transmitted to the Sponsor, and subsidiaries, affiliates, and agents of the Sponsor, in your country and other countries, including countries that do not have laws protecting such information. Additionally, the Investigator's name and business contact information may be included when reporting certain serious adverse events to regulatory authorities or to other Investigators. By signing this protocol, the Investigator expressly consents to these uses and disclosures.

If this is a multicenter trial, in order to facilitate contact between Investigators, the Sponsor may share an Investigator's name and contact information with other participating Investigators upon request.

18. REFERENCES

1. Yang L, Xu M, Bhuiyan SA, Li J, Zhao J, Cohrs RJ, Susterich JT, Signorelli S, Green U, Stone JR, Levy D, Lennerz JK, Renthal W. Human and mouse trigeminal ganglia cell atlas implicates multiple cell types in migraine. Neuron. 2022 Jun 1;110(11):1806-1821.e8. doi: 10.1016/j.neuron.2022.03.003. Epub 2022 Mar 28. PMID: 35349784; PMCID: PMC9338779.
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19. APPENDICES

Appendix A: IHS ICHD Criteria

Appendix B: Functional Disability Scale – Single Question - EXAMPLE

Appendix C: C-SSRS - Baseline/Screening Version 1/14/09 – EXAMPLE

Appendix D: Management of Participants with Elevated Liver Enzymes (ALT or AST ≥3X ULN)

APPENDIX A. IHS ICHD CRITERIA

Refer to the following link: 1. Migraine - ICHD-3

The outline below gives an outline of the criteria.

APPENDIX B. FUNCTIONAL DISABILITY SCALE – SINGLE QUESTION – EXAMPLE

Question:

How much is your migraine interfering with your normal activities?"

Response Options:

No disability, able to function normally (0), Mild Impairment, can still do everything but with difficulty (1), Moderate Impairment, unable to do some things (2), Severe impairment- cannot do all or most things, bed rest may be necessary (3).

APPENDIX C. C-SSRS - BASELINE/SCREENING VERSION 14JANUARY2009 – EXAMPLE

APPENDIX D. MANAGEMENT OF PARTICIPANTS WITH ELEVATED LIVER ENZYMES (ALT OR AST ≥X ULN)

If baseline ALT/AST is normal (below the laboratory ULN), increases to ≥3X ULN are defined as clinically significant in this study. If baseline ALT/AST is elevated (> the laboratory ULN), increases that are both ≥3X ULN ***and*** ≥2X baseline are defined as clinically significant in this study. The Investigator will review safety labs and determine if an ALT/AST meets either of these thresholds. In studies where a central laboratory is used, the central lab will also alert the Investigator if these thresholds are met.

When a randomized subject who is receiving IMP has an ALT or AST elevation beyond these thresholds, the Investigator should start close observation if the criteria below are met.

Note: ALT and AST should be evaluated against these criteria independently.

Criteria for starting close observation: If the criteria noted here are met and there is no immediately obvious alternate cause of the ALT/AST elevation, **close observation (see below) must initiate.**

If the participant's baseline (predose Day 1) ALT/AST value is normal (≤ lab ULN)

- ALT/AST is ≥3X the ULN

If the participant's baseline (predose Day 1) ALT/AST value is elevated (> lab ULN)

- ALT/AST is ≥3X the ULN **and** ≥2x baseline.

Close observation

Close observation includes liver biochemistry monitoring and assessment of etiology as detailed below. **If monitoring requirements cannot be met for any reason, IMP dosing must be interrupted.**

Monitoring

- Repeat testing must occur within 48-72 hours. This should include liver biochemistries (ALT, AST, alkaline phosphatase, GGT, total bilirubin, INR) and creatinine phosphokinase (CPK)**.**
- Liver biochemistries (ALT, AST, alkaline phosphatase, GGT, total bilirubin, INR) should be repeated at least twice weekly.
  - Frequency can decrease to once weekly with approval of the Sponsor medical monitor if abnormalities are stable for ≥2 weeks.
  - Close monitoring may stop if abnormalities have normalized or returned to ~ baseline for ≥4 weeks, if both the investigator and the Sponsor medical monitor agree this is appropriate.
  - **Dosing must be interrupted if any criteria for interruption (see B above) are met.**

Etiology assessment

- **Questions to assess etiology:** Investigate potential causes for the subject's elevated liver enzymes using the questions below. Answers to questions should be recorded in the subject's source documents and appropriate eCRFs.

1. Has the subject recently:
   a. Had a change in his/her pattern of alcohol use?

b. Administered an illegal drug(s)?
c. Been exposed to a chemical agent or other environmental toxin?
d. Consumed any unusual food (e.g., mushrooms), seasonal foods, or initiated treatment with new herbal/nutritional supplements?
e. Initiated a new diet regimen, started a rigorous exercise program, or experienced any form of severe physical exertion?
f. Traveled to another country or region?

2. Does the subject have a relevant concomitant illness (e.g., cholelithiasis, hepatitis, etc.) or has the subject had potential exposure to viral hepatitis (transfusion, tattoo, new sexual partner)?

3. Does the subject have a relevant medical history (e.g., autoimmune disorder, cancer, Gilbert's syndrome, obesity, Wilson's disease, NASH, alcohol or infectious hepatitis, biliary tract disease, hemochromatosis)?

4. Has the subject:
   a. recently been treated with a concomitant medication(s) with demonstrated or suspected effects on the liver (e.g., acetaminophen, amiodarone, aspirin, chlorpromazine, dantrolene, erythromycin, halothane, isoniazid, methyldopa, nitrofurantoin, oxyphenisatin, perhexiline maleate, phenytoin, propylthiouracil, rifampin, sulfonamides, tetracyclines)?
   b. initiated treatment with another new medication?

- **Additional Laboratory/Imaging Evaluations to assess etiology:** In participants for whom an etiology for the abnormal liver enzymes is unknown or whose elevated liver enzymes persist for >1 week:

1. Consider performing serologic tests including: (a) Hepatitis A (Immunoglobulin M, IgM); (b) Hepatitis B (surface Antigen (Ag) and core IgM); (c) Hepatitis C (antibody); (d) Hepatitis E (Immunoglobulin G (IgG) and IgM). Obtain consent prior to testing, if required locally. Additional evaluations may be performed at the discretion of the Investigator.

2. Consider an ultrasound of the subject's RUQ and additional scans [endoscopic retrograde cholangiopancreatography (ERCP) or magnetic resonance cholangiopancreatography (MRCP) if needed].

- Refer to the FDA Guidance for Industry on pre-marketing clinical evaluation for drug-induced liver injury (https://www.fda.gov/media/116737/download) for additional guidance on assessment of etiology.