Title:

A Phase 2a, Multicenter, Randomized, Double-blind, Placebo-controlled, Crossover Study of K-645 in the Treatment of Multiple Migraine Attacks

Protocol Date:

03-June-2025

NCT:

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K-645

P003-00

A Phase IIa, Multicenter, Randomized, Double-Blind, Placebo-Controlled Crossover Study of K-645 in the Treatment of Multiple Migraine Attacks

KALLYOPE, Inc.

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New York, NY 10016

Protocol Issue Date: 03 June 2025

IND Number: 174620

Confidentiality Statement

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

INVESTIGATOR'S AGREEMENT

I have received and read the Investigator's Brochures for K-645. I have read K-645 P003-00 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

Name of Sponsor/Company: Kallyope, Inc.		
Name of Investigational Product: K-645		
Name of Active Ingredients: K-645		
Protocol Number: P003-00	**Phase: 2a**	**Country: USA**
Title of Study: A Phase IIa, Multicenter, Randomized, Double-Blind, Placebo-Controlled Crossover Study of K-645 in the Treatment of Multiple Migraine Attacks		
Study center(s): Multi-center study in US		
Studied period (years): 12-months Estimated date first patient enrolled: August 2025 Estimated date last patient completed: May, 2026		**Phase of development: 2a**
Number of participants (planned): Approximately 120		

Objectives:

Primary:

1. To evaluate the efficacy of K-645 100 mg compared with placebo in the acute treatment of migraine as measured by pain freedom at two hours post-dose.

Secondary:

1. To evaluate the efficacy of K-645 100 mg compared to placebo on freedom from the most bothersome symptom (MBS), associated with migraine, at two hours post-dose.
2. To evaluate the efficacy of K-645 100 mg compared to placebo on pain relief at 2 hours post-dose.
3. To evaluate the safety and tolerability of K-645 100 mg and 10 mg in the treatment of acute migraine.

Exploratory:

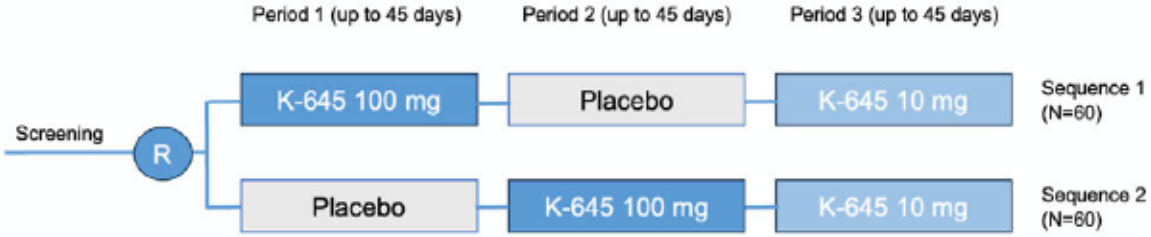
1. To evaluate the efficacy of K-645 100 mg compared to placebo on freedom from photophobia at 2 hours post-dose.
2. To evaluate the efficacy of K-645 100 mg compared to placebo on freedom from phonophobia at 2 hours post-dose.
3. To evaluate the efficacy of K-645 100 mg compared to placebo on freedom from nausea at 2 hours post-dose.
4. To evaluate the efficacy of K-645 100 mg compared to placebo on the probability of requiring rescue medication within 24 hours of initial treatment.
5. To evaluate the efficacy of K-645 100 mg compared to placebo on sustained pain freedom from 2 to 24 hours post-dose.
6. To evaluate the efficacy of K-645 100 mg compared to placebo on sustained pain relief from 2 to 24 hours post-dose.

7. To evaluate the efficacy of K-645 100 mg compared to placebo on sustained pain freedom from 2 to 48 hours post-dose.
8. To evaluate the efficacy of K-645 100 mg compared to placebo on sustained pain relief from 2 to 48 hours post-dose.
9. To evaluate the efficacy of K-645 100 mg 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.
10. To evaluate the efficacy of K-645 100 mg compared to placebo for the incidence of pain relapse from 2 to 48 hours post-dose.
11. To evaluate the efficacy of K-645 10 mg compared to placebo in the above primary, secondary, and exploratory objectives.

Study Design

This is a multi-center, randomized, double-blind, placebo-controlled, 3 period crossover study to evaluate the safety, tolerability, and efficacy of two dose levels of K-645 in the treatment of patients with acute migraine. Up to approximately 120 patients will be randomized to one of two treatment sequences comprised of three successive treatment periods each for treatment of distinct migraine attacks. Each patient will eventually receive each of the three treatments, one in each treatment period. Patients will receive K-645 100 mg and placebo in random order (double- blind) in the first two periods. All patients will receive K-645 10 mg in Period 3 (single-blind). The interactive web response system (IWRS) will be used to randomly assign patients to one of two sequences. In one sequence patients will be randomized to receive K-645 100 mg, placebo, and then K-645 10 mg in Periods 1, 2, and 3, respectively. In the other sequence patients will be randomized to receive placebo, K-645 100 mg, and then K-645 10 mg in Periods 1, 2, and 3, respectively.

Study Design Schematic



The study will be comprised of a screening phase (up to approximately 4 weeks), a treatment phase, which will be comprised of three treatment periods of up to 45 days each. The duration of the study for a participant is up to approximately 23 weeks.

In each treatment period, patients will be provided with a single dose of study to be taken on an outpatient basis as soon as they experience a qualifying migraine headache (HA) that meets the criteria specified below.

In each period, patients will have up to 45 days to treat a single qualifying migraine. If a patient does not have a qualifying migraine in any particular 45-day treatment period, he/she should come to the end of period visit at the specified time window, undergo procedures for that visit (Table 2), and return the unused study medication assigned to the respective treatment period. Patients should continue into the subsequent treatment period and will be issued the appropriate study medication for the next period according to their treatment sequence.

Patients will use an electronic diary (eDiary) to record migraine-related information. Upon experiencing a potentially qualifying headache, patients 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). Patients should proceed to take study medication only after it is confirmed via the eDiary that they are experiencing a qualifying migraine.

During the 48 hours following the dose of study medication, patients will record various measures in the eDiary at specified times. 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). In each period, subjects must return to the clinical research unit between Day 4 (minimum of 72 hours after study medication administration) and Day 7 for study procedures. Note: the day study medication is taken is considered Day 1 in each treatment period.

In each treatment period, 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 other type of 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).

Patients should take study medication after answering eDiary 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 and subsequently in the electronic case report forms (eCRF).

After dosing with study medication, all other headache or migraine medication is prohibited during the 2 hours post-dose period. Once the eDiary assessments at the 2-hour post-dose timepoint have been fully 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)), or for headache recurrence. Use of rescue medication must conform to the prescribing information of the product and the restrictions of this protocol.

In all circumstances and in all periods, the patient will continue to complete the eDiary entries through 48 hours after taking study medication.

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 65 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 International Classification of Headache Disorders (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 who agrees to **all** of the following:

- If partner is a non-pregnant female of child-bearing potential: To use an appropriate method of contraception, including a condom with spermicidal cream or jelly, from the first dose of study drug until ≥72 hours after the last dose of study drug (i.e. Period 3). A male participant who has had a vasectomy procedure must use a condom but is not required to use spermicidal cream or jelly.
- If partner is pregnant: To use a condom from the first dose of study drug until ≥72 hours after the last dose of study drug.

Note: Contraception/condom requirements are waived if partner is NOT of child-bearing potential (i.e. is male or is a female who is post-menopausal or surgically sterile [post-hysterectomy or bilateral salpingectomy]).

- To not donate sperm from the first dose of study drug until ≥ 72 hours after the last dose of study drug.

OR

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

- Postmenopausal defined as **one** of the following: a minimum of 12 months of spontaneous amenorrhea **OR** a minimum of 6 months of spontaneous amenorrhea with a Screening serum follicle-stimulating hormone (FSH) level >40 mIU/mL **OR** at least 6 weeks post-bilateral oophorectomy (with or without hysterectomy).
- Post hysterectomy or bilateral salpingectomy, based on the subject's recall of their medical history.
- If pre-menopausal, they must agree to not donate eggs from the first dose of study drug until 30 days after the last dose study drug.

OR

c. Is a female of reproductive potential and:

- agrees to not donate eggs from the first dose of study drug until 30 days after the last dose study drug.

  AND

- agrees to remain abstinent from heterosexual activity[a,b] **or**
- agrees to use (or have their partner use) a birth control method that is highly effective[b]. Acceptable methods of birth control are:
  - Combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation
  - Progestogen-only contraception (e.g. oral, injectable, implant) associated with inhibition of ovulation
  - Intrauterine device (IUD)
  - Intrauterine hormone-releasing system (IUS)
  - Bilateral tubal occlusion
  - Vasectomized partner

[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.

[b] **Note**: Participants must agree that they will **not** attempt to become pregnant during the cycles of study drug administration or the menstrual cycle following the last dose of study medication.

5. Voluntarily agrees to participate in the study by giving written informed consent.
6. 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 and 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:** Female participants of child-bearing potential 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. Has difficulty distinguishing his/her migraine attacks from tension-type headaches.
3. Has a history of predominantly mild migraine attacks or migraines that usually resolve spontaneously in less than two hours.
4. 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. Has brainstem (a.k.a. basilar-type) or hemiplegic migraine headache, or retinal migraine.
6. Was >50 years old at age of first migraine onset.
7. 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.
8. Stopped preventive migraine medication(s) within 30 days prior to Screening for small molecules or 90 days for antibodies.

Medical history related

9. 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].
10. 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.
11. 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.

12. 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.
13. Has a history and/or 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.
14. 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.
15. Has any family history of congenital hypogonadotropic hypogonadism in a first-degree relative unless a specific genetic cause has been confirmed which does not involve mutation of TAC3R (the NK3R gene) or TAC3 (the neurokinin B gene).

Laboratory, vital sign, and electrocardiogram (ECG) related

16. Has any positive test result for hepatitis B surface antigen, hepatitis C virus antibody, or human immunodeficiency antibody, at the Screening Visit.
17. Has a Screening estimated Glomerular Filtration Rate (eGFR) estimated with the Modification of Diet in Renal Disease (MDRD) equation of <60 ml/min/1.73 m^2.
18. 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.
19. Has a mean of triplicate corrected QT interval to Fridericia's formula (QTcF) >450 milliseconds (msec) for males and >470 msec for females at Screening.
20. 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

21. Has known history of or suspected abuse of alcohol or recreational drugs at Screening.
22. 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.
23. Has a positive drug screen at Screening or Randomization. **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.
    - If amphetamines are detected on the drug screen, this is not exclusionary if the subject is taking a stimulant medication (e.g. Adderall) for a therapeutic purpose (e.g. for attention deficit hyperactivity disorder (ADHD)), confirmatory documentation is obtained from the prescribing physician, and the stimulant medication in question is known to be detected as amphetamine on the drug screen being used.

24. 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.
25. Has any use of prescription opiate medications within 14 days of Screening or any anticipated/potential use of opiates during study participation.
26. Has 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.
27. Has history of non-narcotic analgesic intake on greater than/equal 15 days per month for greater than/equal 3 months prior to Screening.

Other

28. Has known or suspected hypersensitivity to trial product(s) or related products.
29. 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.
30. Has any surgery scheduled for the duration of the trial.
31. 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).
32. Has previous participation in this trial. Participation is defined as signed informed consent.
33. 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.
34. 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.
35. Is an employee or immediate family member (e.g., spouse, parent, child, sibling) of the Sponsor or study site.
36. Is unable or unwilling to refrain from consumption of grapefruit, grapefruit juice, 2 weeks prior to administration of the first dose of study drug, throughout the study, and until the Follow-up Visit.

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

Investigational product, dosage and mode of administration:

All study medication will be orally administered.

K-645: 10 mg and 100 mg capsules and matching placebo

Duration of Treatment Period: In each treatment period, patients have up to 45 days to treat a migraine event with a single dose of study medication. The total duration of the treatment period is up to approximately 19 weeks.

Endpoints

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

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).

Exploratory endpoints:

- 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.

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) 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 C-SSRS will be conducted at according to the Schedule (SOA).

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

Statistical methods:

Sample size justification:

With 120 subjects randomized to two treatment sequences, it is anticipated that about 80% of subjects will have a qualifying headache in the first two periods, which would provide 96 qualifying migraine attacks in each of the placebo arm and high dose arm. Assuming a placebo response rate of 10% and the treatment response rate of 25% and a treatment difference of 15%, 96 qualifying migraine attacks in each treatment group provide approximately >87.4% power for the primary endpoint of pain freedom at 2 hours post-dose for the comparison between the high dose vs placebo respectively with a two-sided alpha of 0.10.

Populations:

The following analysis sets will be evaluated and used for analysis of the data. The data for each treatment (i.e., high or low dose or placebo) from different periods are pooled for analysis.

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:

The primary endpoint of pain freedom at 2 hours post-dose will be analyzed using the mITT analysis population. Subjects with missing data at 2 hours post-dose will be classified as failures. A logistic regression analysis will be conducted to evaluate the effect of treatment on pain freedom at 2 hours, adjusting for the following covariates: treatment group, treatment sequence, treatment period, and the use of background prophylactic medications for migraine (yes/no). The proportion of subjects achieving the endpoint response criteria will be reported by treatment group. Additionally, odds ratios with 90% confidence intervals will be presented to compare the likelihood of achieving pain freedom between the K-645 high dose, low dose, and placebo groups. Sensitivity analysis will be described in the statistical analysis plan (SAP).

For secondary and exploratory categorical endpoints, the logistic regression will be performed.

For the probability of rescue medication use within 24-hour post-dose, the logistic regression will be performed. Time to rescue 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., endpoints at 2 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.

This missing data imputation method will be specified in the statistical analysis plan for 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). Additional sensitivity analysis will be defined in the statistical analysis plan.

Multiplicity

The study tests the primary hypothesis that at K-645 high dose is superior to the placebo arm in primary endpoint of pain freedom at 2 hours post-dose. 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 100 migraine headaches have been treated in Periods 1 or 2 (as determined by responses in the eDiaries), 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	**Treatment Phase**						
	Screening	**Randomization**	**Treatment Period 1**	**EoP1[a]**	**Treatment Period 2**	**EoP2[a]**	**Treatment Period 3**	**EoP3[a] EoT (ET Visit)[b]**
Visit Number and Day Range[c]	**V1**	**V2**	**Qualified Migraine eDiary Entry Up to 45 days from V2**	**V3 Day 4–7 post P1 dose or 45 days from V2 if no HA**	**Qualified Migraine eDiary Entry Up to 45 days from Visit 3**	**V4 Day 4–7 days post P2 dose or 45 Days from V3 if no HA**	**Qualified Migraine eDiary Entry Up to 45 days from Visit 4**	**V5 Day 4–7 post P3 dose or 45 days from V4**
Administrative								
Informed Consent	X							
Inclusion/Exclusion Criteria	X	X[d]						
Medical & Migraine Hx[e]	X							
Prior/Concomitant Medication Review	X	X		X		X		X
Prior use/discontinuation of specific migraine medication CRF completion		X						
Clinical Assessments								
Physical Examination	X	X		X		X		X
Height (screening only)/weight	X	X		X		X		X

Table 2: Study Schedule of Assessments (Continued)

SOA								
	Screening	Treatment Phase						
	Screening	Randomization	Treatment Period 1	EoP1[a]	Treatment Period 2	EoP2[a]	Treatment Period 3	EoP3[a] EoT (ET Visit)[b]
Visit Number and Day Range[c]	V1	V2	Qualified Migraine eDiary Entry Up to 45 days from V2	V3 Day 4-7 post P1 dose or 45 days from V2 if no HA	Qualified Migraine eDiary Entry Up to 45 days from Visit 3	V4 Day 4-7 days post P2 dose or 45 Days from V3 if no HA	Qualified Migraine eDiary Entry Up to 45 days from Visit 4	V5 Day 4-7 post P3 dose or 45 days from V4
HR/BP	X	X		X		X		X
Respiratory Rate/Temperature	X	X		X		X		X
Triplicate 12-lead ECG	X							X
C-SSRS[f]	X	X		X		X		X
eDiary Patient Training and Attestation		X						
eDiary Daily Notification and/or Status of Headache			X		X		X	
Site Monitoring & Contacts to Patient for eDiary Compliance			X (phone/text/ email)	X	X (phone/text/ email)	X	X (phone/text/ email)	X

Table 2: Study Schedule of Assessments (Continued)

SOA								
	Screening	**Treatment Phase**						
	Screening	**Randomization**	**Treatment Period 1**	**EoP1[a]**	**Treatment Period 2**	**EoP2[a]**	**Treatment Period 3**	**EoP3[a] EoT (ET Visit)[b]**
Visit Number and Day Range[c]	**V1**	**V2**	**Qualified Migraine eDiary Entry Up to 45 days from V2**	**V3 Day 4–7 post P1 dose or 45 days from V2 if no HA**	**Qualified Migraine eDiary Entry Up to 45 days from Visit 3**	**V4 Day 4–7 days post P2 dose or 45 Days from V3 if no HA**	**Qualified Migraine eDiary Entry Up to 45 days from Visit 4**	**V5 Day 4–7 post P3 dose or 45 days from V4**
Laboratory and Safety Assessments								
General Safety Labs: chemistry, hematology[g]	X	X		X		X		X
Urinalysis and Coagulation	X							X
Urine Drug Screen	X	X						
Hepatitis Screen	X							
HIV Screen	X							
hCG Pregnancy Test/FSH Test[h]	X	X		X		X		X
AE Monitoring	X	X	X	X	X	X	X	X
Menstrual cycle history (premenopausal subjects only)[i]		X		X		X		X
Review & Record rescue medication				X		X		X

Table 2: Study Schedule of Assessments (Continued)

SOA								
	Screening	**Treatment Phase**						
	Screening	**Randomization**	**Treatment Period 1**	**EoP1[a]**	**Treatment Period 2**	**EoP2[a]**	**Treatment Period 3**	**EoP3[a] EoT (ET Visit)[b]**
Visit Number and Day Range[c]	**V1**	**V2**	**Qualified Migraine eDiary Entry Up to 45 days from V2**	**V3 Day 4–7 post P1 dose or 45 days from V2 if no HA**	**Qualified Migraine eDiary Entry Up to 45 days from Visit 3**	**V4 Day 4–7 days post P2 dose or 45 Days from V3 if no HA**	**Qualified Migraine eDiary Entry Up to 45 days from Visit 4**	**V5 Day 4–7 post P3 dose or 45 days from V4**
Study Drug Administration and Accountability								
IWR Study Drug Dispensing		X		X		X		
Drug Compliance and Accountability				X		X		X

[a] Subjects who have a qualified migraine and take study medication are required to attend the EOP visit within 4 to 7 days post dose. Each period is up to 45 days in duration.

[b] All subjects who took at least 1 dose of IP should attend the EoP3/EoT visit (V5). 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.

[c] In each Treatment Period, Day is relative to dosing Day, which is considered Day 1 for the purposes of assigning relative days for AEs, for eDiary assessments, and for determining scheduling of the next EoP visits. In each Period, subjects should return to the clinic for the Period EoP visit between Day 4 and Day 7 and not sooner than 72 hours after dosing.

[d] 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.

[e] Migraine history is to be collected and maintained in the source records. Sites are to obtain documentation of subject's migraine medical history from relevant treating physician and investigator should verify patient meets diagnostic and entry criteria related to migraine.

[f] The "Baseline C-SSRS" should be completed at Visit 1. The "Since Last Visit C-SSRS" should be completed at subsequent visits. Refer to Appendix C.

[g] Safety labs need not be in fasted state.

[h] Serum hCG at Screening (V1) and EoP3/EoT (V5). Urine hCG at the randomization visit (V2), EoP1 (V3) and EoP2 (V4) for females of childbearing potential. 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).

[i.] Complete menstrual history CRF.
Abbreviations: EOP = End of Period; ET = End of Trial; EoT = End of Treatment; C-SSRS= Columbia Suicide Severity Rating Scale, FSH= follicle stimulating hormone, hCG = human chorionic gonadotropin

Table 3: Subject Treatment Period Schedule of eDiary Assessments by Hour

	eDiary Assessments by Hour (Time 0 = time of dosing)										
Time (h) relative to dose	**Immediately pre-dose**	**0.5**	**1.0**	**1.5**	**2.0**	**3**	**4**	**6**	**8**	**24**	**48**
Patient completes diary questions to confirm whether current migraine is a Qualifying Migraine for treatment with study medication	X										
Patient completes diary for pain severity	X	X	X	X	X	X	X	X	X	X	X
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	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

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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 4: Abbreviations and Special Terms

Abbreviation or Specialist Term	Explanation
ACS	Acute coronary syndrome
ADHD	Attention deficit hyperactivity disorder
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
BLQ	Below limit of quantitation
BMI	Body mass index
BP	Blood pressure
CAPA	Corrective and preventative action
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
CNS	Central nervous system
CPK	Creatine phosphokinase
CRF	Case report form
CSR	Clinical study report
C-SSRS	Columbia Suicidality Severity Rating Scale
CTCG	Clinical Trials Coordination Group
CV	Coefficient of variation/cardiovascular
DART	Development and reproductive toxicology

Abbreviation or Specialist Term	Explanation
DILI	Drug induced liver injury
ECG	Electrocardiogram
eCRF	Electronic case report form
EDC	Electronic data capture
eDiary	Electronic diary
eGFR	Estimated glomerular filtration rate
EOP	End of period
EOT	End of treatment
ERCP	Endoscopic retrograde cholangiopancreatography
ET	Early termination
FDAAA	Food and Drug Administration Amendments Act
FDAMA	Food and Drug Administration Modernization Act
FHM	Familial hemiplegic migraine
FIH	First in human
FSH	Follicle stimulating hormone
g	Gram
GCP	Good Clinical Practice
GGT	Gamma-glutamyl transferase
GI	Gastrointestinal
HA	Headache
hCG	Human chorionic gonadotropin
HDPE	High density polyethylene
HPG	Hypothalamic-pituitary-gonadal
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

Abbreviation or Specialist Term	Explanation
IgM	Immunoglobulin M
IHS	International Headache Society
IMP	Investigational medicinal product
INR	International normalized ratio
IRB	Institutional Review Board
IUD	Intrauterine device
IUS	Intrauterine hormone-releasing system
IWRS	Interactive web response system
kg	Kilogram
KM	Kaplan-Meier
KNDy	kisspeptin/neurokinin B/dynorphin
LFT	Liver function test
LH	Luteinizing hormone
m	Meter
MAD	Multiple ascending dose
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
MRCP	Magnetic resonance cholangiopancreatopraphy
msec	Millisecond
N	Number

Abbreviation or Specialist Term	Explanation
ng	Nanogram
NK3R	Neurokinin 3 receptor
NKB	Neurokinin B
NSAID	Nonsteroidal anti-inflammatory drug
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
PT	Preferred term, prothrombin time
PTT	Partial thromboplastin time
QD	Once daily
QTc	QT corrected
QTcF	QT corrected with Fridericia's formula
RBC	Red blood cells
RDW	Red cell distribution width
RUQ	Right upper quadrant
SAD	Single ascending dose
SAE	Serious adverse event
SAP	Statistical analysis plan
SAR	Serious adverse reaction
SD	Standard deviation
SHM	Sporadic hemiplegic migraine
SOA	Schedule of assessments
SOC	System organ class
SUSAR	Suspected unexpected serious adverse reaction
SQ	subcutaneous
TAC3R	Tachykinin receptor 3
TEAE	Treatment emergent adverse event
THC	Tetrahydrocannabinol

Abbreviation or Specialist Term	Explanation
TIA	Transient ischemic attack
T_{max}	Time of maximum concentration
TRPM8	Transient receptor potential melastatin 8
ULN	Upper limit of normal
USPI	United States Package Insert
VMS	Vasomotor symptoms
WBC	White blood cells
WOCBP	Women of child bearing potential
β-hCG	β-human chorionic gonadotropin
μM	Micromolar

5. INTRODUCTION

5.1. Program and Study Rationale

Migraine is a common, often disabling disorder characterized by severe headaches associated with typical symptoms including nausea/vomiting, photophobia, and/or phonophobia. Treatment options for acute migraine attacks have long included non-prescription analgesics (e.g. nonsteroidal anti-inflammatory drugs (NSAIDs), acetaminophen) and triptans (5-$HT_{1B/1D}$ agonists, e.g. sumatriptan), and have expanded in recent years with approvals of small-molecule calcitonin gene-related peptide (CGRP) antagonists (rimegepant and ubrogepant), and the 5-HT_{1F} agonist lasmiditan. However, for many migraineurs, the available agents are ineffective, poorly tolerated, or contraindicated [1]. Therefore, there continues to be a significant unmet need for many migraine patients.



[redacted]

5.5. Rationale for Study Population

Review to Section 10.1 for discussion of prohibited and allowed concomitant medications.

Full inclusion and exclusion criteria are provided in Section 8.1 and Section 8.2, respectively.

Entry criteria are consistent with FDA guidance for acute migraine studies [16].

[redacted]

[redacted]

6. TRIAL OBJECTIVES, HYPOTHESES

6.1. Primary Objectives

1. To evaluate the efficacy of K-645 100 mg compared with placebo in the acute treatment of migraine as measured by pain freedom at two hours post-dose.

6.2. Secondary Objectives

1. To evaluate the efficacy of K-645 100 mg compared to placebo on freedom from the most bothersome symptom (MBS), associated with migraine, at two hours post-dose.
2. To evaluate the efficacy of K-645 100 mg compared to placebo on pain relief at 2 hours post-dose.
3. To evaluate the safety and tolerability of K-645 100 mg and 10 mg in the treatment of acute migraine.

6.3. Exploratory Objectives

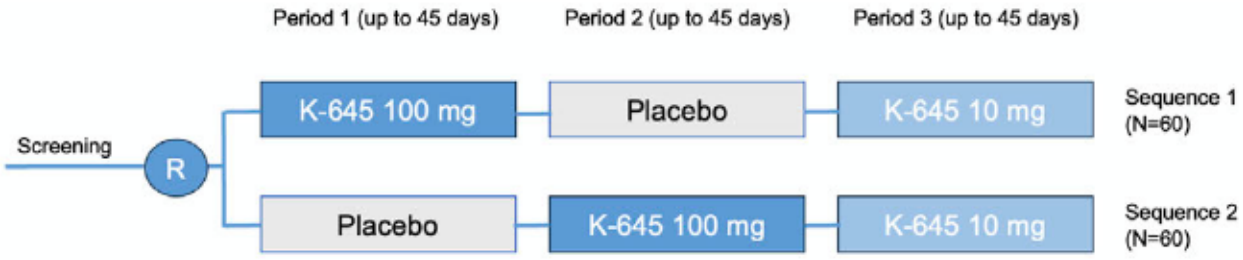
1. To evaluate the efficacy of K-645 100 mg compared to placebo on freedom from photophobia at 2 hours post-dose.
2. To evaluate the efficacy of K-645 100 mg compared to placebo on freedom from phonophobia at 2 hours post-dose.
3. To evaluate the efficacy of K-645 100 mg compared to placebo on freedom from nausea at 2 hours post-dose.
4. To evaluate the efficacy of K-645 100 mg compared to placebo on the probability of requiring rescue medication within 24 hours of initial treatment.
5. To evaluate the efficacy of K-645 100 mg compared to placebo on sustained pain freedom from 2 to 24 hours post-dose.
6. To evaluate the efficacy of K-645 100 mg compared to placebo on sustained pain relief from 2 to 24 hours post-dose.
7. To evaluate the efficacy of K-645 100 mg compared to placebo on sustained pain freedom from 2 to 48 hours post-dose.
8. To evaluate the efficacy of K-645 100 mg compared to placebo on sustained pain relief from 2 to 48 hours post-dose.
9. To evaluate the efficacy of K-645 100 mg 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.
10. To evaluate the efficacy of K-645 100 mg compared to placebo for the incidence of pain relapse from 2 to 48 hours post-dose.
11. To evaluate the efficacy of K-645 10 mg compared to placebo in the above primary, secondary, and exploratory objectives.

7. INVESTIGATIONAL PLAN

7.1. Overall Study Design

This is a multi-center, randomized, double-blind, placebo-controlled, 3 period crossover study to evaluate the safety, tolerability, and efficacy of two dose levels of K-645 in the treatment of patients with acute migraine. Up to approximately 120 patients will be randomized to one of two treatment sequences comprised of three successive treatment periods each for treatment of distinct migraine attacks. Each patient will eventually receive each of the three treatments, one in each treatment period. Patients will receive K-645 100 mg or placebo in a random order (double-blind) in the first two periods. All patients will receive K-645 10 mg in Period 3 (single-blind). The interactive web response system (IWRS) will be used to randomly assign patients to one of two sequences. In one sequence patients will be randomized to receive K-645 100 mg, placebo, and then K-645 10 mg in Periods 1, 2, and 3, respectively. In the other sequence patients will be randomized to receive placebo, K-645 100 mg, and then K-645 10 mg in Periods 1, 2, and 3, respectively. See Figure 6.

Figure 6: K-645 P003 Study Design Schematic



The study will be comprised of a screening phase (up to approximately 4 weeks), a treatment phase, which will be comprised of three treatment periods of 45 days. The duration of the study for a participant is up to approximately 23 weeks.

In each treatment period, patients will be provided with a single dose of study medication to be taken on an outpatient basis as soon as they experience a qualifying headache that meets the criteria specified below.

In each treatment period, patients will have up to 45 days to treat a qualifying migraine. If a patient does not have a qualifying migraine in any particular 45-day treatment period, he/she should come to the end of period visit at the specified time window, undergo procedures for that visit (Table 2), and return the unused study medication assigned to the respective treatment period. Patients should continue into the subsequent treatment period and will be issued the appropriate study medication for the next period according to their treatment sequence.

Patients will use an eDiary to record migraine-related information. Upon experiencing a potentially qualifying headache, patients 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). Patients should proceed to take study medication only after it is confirmed via the eDiary that they are experiencing a qualifying migraine.

During the 48 hours following the dose of study medication, patients will record various measures in an eDiary at specified times. 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). In each period, subjects must return to the clinical research unit between Day 4 (minimum of 72 hours after study medication administration) and Day 7 for study procedures. Note: the day study medication is taken is considered Day 1 in each treatment period.

In each treatment period, 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 of any kind 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).

Patients should take study medication after answering eDiary 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 and subsequently in the eCRF.

After dosing with study medication, all other headache or migraine medication is prohibited during the 2 hours post-dose period. Once the eDiary assessments at the 2-hour post-dose timepoint have been fully 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/or for headache recurrence. Use of rescue medication must conform to the prescribing information of the product and the restrictions of this protocol.

In all circumstances, in all treatment periods, the patient will continue to complete the eDiary entries through 48 hours after taking study medication.

The schedule of assessments is shown in Table 2 and Table 3.

7.2. Number of Participants

Approximately up to 120 participants will be enrolled.

7.3. Treatment Assignment

7.3.1. Assignment of Screening and Randomization Numbers

All consented patients will be given a unique screening number that will be used to identify the patient for all procedures that occur before randomization or allocation. Each patient will be assigned only one screening number. Screening numbers must not be reused for different patients. Patients who meet all criteria for enrollment will be assigned a randomization number.

7.3.2. Study Drug Assignment

Patients will be randomized to one of 2 treatment sequences (Table 13) according to the randomization schedule generated before the study and uploaded into the IWRS. Each patient will be dispensed study drug in a double-blinded manner and assigned IMP according to their respective treatment sequence and dose assignment. The IWRS will direct site staff to assign the respective IMP (via Med ID number) associated with the assigned treatment sequence and dose level.

Table 13: Treatment Sequence

	Period 1	Period 2	Period 3
Sequence 1 (N=60)	100 mg	Placebo	10 mg
Sequence 2 (N=60)	Placebo	100 mg	10 mg

7.3.3. Subject Replacement

No patients 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, 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 65 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 who agrees to **all** of the following:
      - If partner is a non-pregnant female of child-bearing potential: To use an appropriate method of contraception, including a condom with spermicidal cream or jelly, from the first dose of study drug until ≥72 hours after the last dose of study drug (i.e. Period 3). A male participant who has had a vasectomy procedure must use a condom but is not required to use spermicidal cream or jelly.
      - If partner is pregnant: To use a condom from the first dose of study drug until ≥72 hours after the last dose of study drug.

      Note: Contraception/condom requirements are waived if partner is NOT of child-bearing potential (i.e. is male or is a female who is post-menopausal or surgically sterile [post-hysterectomy or bilateral salpingectomy]).

      - To not donate sperm from the first dose of study drug until ≥ 72 hours after the last dose of study drug.

   OR

   b. Is a female who is of non-childbearing potential defined by at least 1 of the following criteria:
      - Postmenopausal defined as **one** of the following: a minimum of 12 months of spontaneous amenorrhea **OR** a minimum of 6 months of spontaneous amenorrhea with a Screening serum follicle-stimulating hormone (FSH) level >40 mIU/mL **OR** at least 6 weeks post-bilateral oophorectomy (with or without hysterectomy).
      - Post hysterectomy or bilateral salpingectomy, based on the subject's recall of their medical history.
      - If pre-menopausal, they must agree to not donate eggs from the first dose of study drug until 30 days after the last dose study drug.

OR

c. Is a female of reproductive potential and:

- agrees to not donate eggs from the first dose of study drug until 30 days after the last dose study drug.

AND

- agrees to remain abstinent from heterosexual activity[a,b] **or**
- agrees to use (or have their partner use) a birth control method that is highly effective[b]. Acceptable methods of birth control are:
  - Combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation
  - Progestogen-only contraception (e.g. oral, injectable, implant) associated with inhibition of ovulation
  - Intrauterine device (IUD)
  - Intrauterine hormone-releasing system (IUS)
  - Bilateral tubal occlusion
  - Vasectomized partner

[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.

[b] **Note**: Participants must agree that they will **not** attempt to become pregnant during the cycles of study drug administration or the menstrual cycle following the last dose of study medication.

5. Voluntarily agrees to participate in the study by giving written informed consent.
6. 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 and 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:** Female participants of child-bearing potential 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. Has difficulty distinguishing his/her migraine attacks from tension-type headaches.
3. Has a history of predominantly mild migraine attacks or migraines that usually resolve spontaneously in less than two hours.
4. 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. Has brainstem (a.k.a. basilar-type) or hemiplegic migraine headache, or retinal migraine.
6. Was >50 years old at age of first migraine onset.
7. 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.
8. Stopped preventive migraine medication(s) within 30 days prior to Screening for small molecules or 90 days for antibodies.

Medical history related

9. 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].
10. 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.
11. 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.
12. 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.
13. Has a history and/or 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.
14. 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.
15. Has any family history of congenital hypogonadotropic hypogonadism in a first-degree relative unless a specific genetic cause has been confirmed which does not involve mutation of tachykinin receptor 3 (TAC3R) (the NK3R gene) or tachykinin precursor 3 (TAC3) (the neurokinin B gene).

Laboratory, vital sign, and ECG related

16. Has a positive test result for hepatitis B surface antigen, hepatitis C virus antibody, or human immunodeficiency antibody, at the Screening Visit.
17. Has a Screening estimated Glomerular Filtration Rate (eGFR) estimated with the Modification of Diet in Renal Disease (MDRD) equation of <60 ml/min/1.73 m^2.
18. Has a Screening result for 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.
19. Has a mean of triplicate corrected QT interval to Fridericia's formula (QTcF) >450 milliseconds (msec) for males and >470 msec for females at Screening.
20. 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

21. Has known history of or suspected abuse of alcohol or recreational drugs at Screening.
22. 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.
23. Has a positive drug screen at Screening or Randomization. **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.
    - If amphetamines are detected on the drug screen, this is not exclusionary if the subject is taking a stimulant medication (e.g. Adderall) for a therapeutic purpose (e.g. for ADHD), confirmatory documentation is obtained from the prescribing physician, and the stimulant medication in question is known to be detected as amphetamine on the drug screen being used.

24. 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.
25. Has any use of prescription opiate medications within 14 days of Screening or any anticipated/potential use of opiates during study participation.
26. Has 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.
27. Has history of non-narcotic analgesic intake on greater than/equal 15 days per month for greater than/equal 3 months prior to Screening.

Other

28. Has known or suspected hypersensitivity to trial product(s) or related products.

29. 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.
30. Has any surgery scheduled for the duration of the trial.
31. 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).
32. Has previous participation in this trial. Participation is defined as signed informed consent.
33. 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.
34. 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.
35. Is an employee or immediate family member (e.g., spouse, parent, child, sibling) of the Sponsor or study site.
36. Is unable or unwilling to refrain from consumption of grapefruit, grapefruit juice, 2 weeks prior to administration of the first dose of study drug, throughout the study, and until the Follow-up Visit

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

8.3. Subject Withdrawal Criteria

8.3.1. Discontinuation from Study Medication/Trial Discontinuation

Discontinuation of trial product can be decided by either the investigator or the subject. A participant may discontinue his or her participation without giving a reason at any time during the trial.

If a subject does not take IMP in any treatment period due to lack of qualifying HA, this should not be considered as discontinuation of study medication.

Participants who discontinue trial product should have an EoP3/end of treatment (EoT) visit and undergo procedures (see Schedule of Assessments [SOA]).

If the subject who discontinues refuses to attend the end of treatment period (EoP3/EoT) visit (V5), efforts should be made to have the visits converted to phone contacts.

If the subject refuses to attend the 'end of treatment' visit, information about the attempts to follow up with the subject must be documented in the subject's medical record.

The subject must be discontinued from trial product if any of the following applies:

- Safety concern as judged by the investigator
- Pregnancy

- Liver function test (LFT) abnormalities meeting specified discontinuation criteria (refer to Appendix D for discontinuation criteria and instruction on management of LFT abnormalities
- If a subject experiences a treatment-emergent serious adverse event (SAE; see Section 15.2.3), they will undergo no further dosing until the investigator and Sponsor evaluate the relatedness to investigational medicinal product (IMP). If the Investigator and Sponsor agree that the SAE is not plausibly related to IMP and it is appropriate for the subject to proceed with scheduled dosing, they may do so. If the Investigator and/or Sponsor feels that the SAE is plausibly related to IMP, the subject will be discontinued from study medication (i.e. they will not participate in any further dosing).
- Participants who reply with yes to questions 4 or 5 in the suicidal ideation section indicating having suicidal ideation with intent (with or without plan) or yes to any question in the suicidal behavior section of the C-SSRS should be discontinued and receive appropriate follow-up as in routine clinical practice. The participant should return to the clinic for a EoP3/EoT.

The primary reason for discontinuation of trial product must be specified in the source data at the time of discontinuation, and the subject should continue to follow the visit and assessment schedule. The reasons for treatment discontinuations are:

- Adverse event (AE)
- Voluntary withdrawal by subject
- Lost to follow up
- Pregnancy
- Death
- Investigator decision
- Significant protocol deviation

Subjects who discontinue from study medication will also be considered to have discontinued from the trial. Subjects who participate in all three treatment periods and complete the final EOTP follow up visit (V5) in the trial regardless of whether study medication was taken in any or all periods (i.e., lack of dosing due to lack qualifying migraine in one or more periods does not constitute withdrawal from study medication) will be considered as trial completers. Subjects who took IMP in all 3 periods and do not return for a final visit will be considered as trial non-completers.

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 case report forms (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.

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 fails to attend the final visit (EoTP3 (V5)) and is unable to be contacted by the trial site for end of study assessments.

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 IMP 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 (see Section 14.1). 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.

9.3. Migraine Treatment Period

In each 45 Day period treatment will occur in the outpatient setting. Patients will complete the eDiary once they experience a qualifying headache and will take 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 and Table 3.

Sites are required to monitor subject eDiary compliance which may include daily migraine check-in and, most importantly, entry of the post-dose assessment. Sites will receive eDiary system notifications on subject dosing and missed timepoints. Sites are obligated to contact subjects to ensure entry of the post-dose assessments with greatest importance given to the 2-hour post-dose assessment. See Section 14 for detailed instruction related to eDiary compliance and monitoring.

9.4. End of Treatment Period Visit

Participants will return to the clinical research unit for EoP visit at the end of each treatment period. These will occur either within 4-7 days of dosing/treating a qualifying HA or once 45 days have passed in the treatment period without a qualifying migraine or without subject having taken study medication. The specific assessments to be performed are listed 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, EoP visit procedures will consist of return of study medication, collection of AEs, and collection of concomitant medications and issuing IMP for the next period (except Period 3) and pregnancy tests (for WOCBP). 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:

- Medication name
- Indication
- Dates of administration including start and stop dates
- 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.

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.

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's 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 subcutaneous (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 medications/drugs such as heroin, morphine, codeine, and oxycodone is prohibited.
4. Use of barbiturates is prohibited.

[redacted]

[redacted]

6. Neurokinin 3 receptor (NK3R) antagonists (other than blinded study medication). These include fezolinetant (Veoza™) and elinzanetant.

[redacted]

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 including acetaminophen/paracetamol and non-steroidal anti-inflammatory (NSAIDs) agents such as ibuprofen, naproxen, COX-2 inhibitors (e.g. celecoxib), and aspirin.
  - **Note:** This prohibition does **not** apply to daily aspirin being taking for cardiovascular (CV) prophylactic purposes at doses ≤81mg/day.
- any antiemetic agent
- any CGRP antagonist approved and used for acute migraine treatment (e.g. ubrogepant, zavegepant, rimegepant)
- any ditan (e.g. lasmiditan)

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 dose should not change) for at least three months prior to screening and throughout the study period.

Preventive medications for the treatment of migraine should be completed at least 30 days prior to screening for small molecules and 90 days for antibodies.

Note: Rimegepant (Nurtec™) is approved for both migraine prophylaxis and acute treatment. **Prophylactic use of rimegepant is exclusionary/prohibited in this study**. As-needed use of rimegepant for acute migraine treatment is not exclusionary/prohibited, but it must not be taken within 48 hours prior to study medication (see above).

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, CGRPs 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. Use of rescue medication (Y/N) in the eDiary will be reviewed. Sites are to record details of rescue medication taken in source documents and data enter onto Rescue Medication CRF.

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 in order to complete e-diary questions in a timely manner.

11.1.4. Dietary

Patients will be asked to refrain from grapefruit or grapefruit juice from randomization through end of the study.

11.2. Contraception Requirements

Requirements for contraception are outlined in the inclusion/exclusion criteria (Section 8).

Females of reproductive potential should be counseled that 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.

Females of reproductive potential should be counseled to **not** attempt to become pregnant during the cycles of study drug administration or the menstrual cycle following the last dose of study medication.

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 14.

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:

- K-645 10 mg and 100 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 14: K-645 Investigational Product

	Investigational Product
Product Name:	K-645
Dosage Form:	Dry filled capsules
Unit Dose	Capsules: placebo, 10-mg and 100-mg potencies
Route of Administration	Oral
[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.

K-645 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. Subjects are to take the specific IMP dose assigned to the respective treatment period.

13.4.1. Dose Timing

Subjects will be instructed to take study medication in the outpatient setting after answering eDiary 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 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 2 hr assessments, the subject should not take the study medication and should consider waiting to treat a subsequent headache within the 30-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.

NOTE: Subject who did not experience qualified headache within the protocol specified time window are required to return to their assigned treatment medication to the clinic. All used IMP packaging and unused IMP is to be returned to the clinic.

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 IMP.

14. EFFICACY ASSESSMENTS

14.1. eDiary Procedures

Sites are required to ensure that the patients complete all the electronic diary (eDiary) training PRIOR to leaving the clinic on Randomization Day (Visit 2). Sites are to confirm that every subject completed diary phone app training(s) and confirm the patient attestation has been completed in the clinic before being allowed to leave the clinical site at Visit 2. The initial patient attestation is required in order to enable the subject to receive the required daily check-in notifications.

Sites are to instruct subjects not to load the migraine diary app on any other device than the one used to load the app at the study clinic at Visit 2.

Patients will receive daily alerts and/or notifications related to whether they have experienced a migraine.

After onset of a qualifying migraine, patients will be required to complete eDiary entries at baseline (prior to taking IMP) and at the 10 timepoints over the 48 hours post-treatment that are specified in Table 3. The eDiary entries at baseline will record migraine characteristics and determine if the migraine is qualifying (ie, eligible for treatment with IMP), while postbaseline responses will address the efficacy assessments described in this section of the protocol (below).

Please note:

- Sites must emphasize the importance of full compliance with eDiary post-dose assessments to subjects at all opportunities (i.e. at Screening/V1, V2, V3, and V4 and in any phone/email/text contacts).
- These communications/trainings must emphasize:
    - the **significant importance of all** of these timepoints for characterization of efficacy and the **critical necessity of the 2-hour responses**, which are required for assessment of the primary and secondary endpoints.
    - the need for **real-time data entry** enforced by time windows (Table 15), which are narrow at early timepoints; timely data entry will be prompted by alerts/alarms.
- If a subject experiences a qualifying migraine, but circumstances (i.e. work, other obligations, etc.) will preclude completing data entry at all post-dose timepoints, they should **not** proceed with taking IMP.

Table 15: Post-dose eDiary Timepoints and Data Entry Windows

All Timepoints are Relative to Dosing (T=0)			
Post-Dose Assessment timepoint	**Window**	**Entry Window Opens**	**Entry Window Closes**
0.5 hour	±10 min	20 min	40 min
1 hour	±10 min	50 min	1 hour 10 min
1.5 hour	±10 min	1 hour 20 min	1 hour 40 min
2 hour	±15 min	1 hour 45 min	2 hour 15 min
3 hour	±15 min	2 hour 45 min	3 hour 15 min
4 hour	±15 min	3 hour 45 min	4 hour 15 min
6 hour	±30 min	5 hour 30 min	6 hour 30 min
8 hour	±30 min	7 hour 30 min	8 hour 30 min
24 hour	±4 hrs	20 hour	28 hour
48 hour	±4 hrs	44 hour	52 hour

14.2. Site eDiary Compliance Monitoring

Sites are required to monitor each subject's daily check-in compliance and the entry of eDiary data/responses following treatment of qualifying migraines in each Period. Once a subject treats a qualifying migraine with IMP, he/she is to be compliant with complete entry of all eDiary data at all timepoints over 48 hours post-dose.

The eDiary system will send the site staff notifications to alert to events such when a subject has dosed or when a subject has missed eDiary data entry at a post-dose timepoint. In these circumstances, the sites should make every effort to contact subjects as quickly as possible after dosing to remind them to complete all diary timepoints with the 2-hour as being the most critical endpoint. If post-dose data entry has been missed at any timepoint(s), the site is to contact the subject to encourage compliance with data entry at all remaining post dose assessment timepoints.

Deviations arising from missing/incomplete eDiary data entry at the 2-hour post-dose timepoint are considered Important Protocol Deviations warranting Corrective and Preventative Action (CAPA) plans. Lack of entry of the 2-hour timepoint or repeated violations of eDiary entry requirements by subjects may necessitate closing off of screening and/or randomization for a given site.

Please Note: If a subject has missed eDiary data entry at the 2-hour post-dose timepoint, the site should contact the subject as soon as possible after the 2-hour timepoint to collect the 2-hour data by recall on a separate source document.

- Data collected by recall may include all 4 metrics noted below (i.e. pain, associated symptoms, rescue medication use, and functional disability)
- Data may only be collected by recall **if** the subject confirms that they are confident of accurate, time-specific recall. This may lead to partial collection (i.e. if they are confident for some, but not all responses).
- Recall collection of the 2-hour time point data may occur at any time through the EoP visit for that dosing period. However, to minimize the duration of the recall period **the**

site should make every reasonable effort to contact the subject as soon as they (the site) become aware that 2-hour data entry was missed.

- Data collected in this fashion are susceptible to recall bias. Therefore, there is no prospective intent to make use of these data for any purpose. However, they may be included in post-hoc, exploratory analyses if this is considered potentially informative.
- Successful collection of 2-hour data by recall will not alter the assessment of an Important Protocol Deviation or the need for a corrective and preventative action (CAPA) plan to address the lack of real-time data entry in the eDiary.

14.3. Pain

Subjects will use the eDiary to record their migraine pain score, on a 4-point numeric rating scale [0 no pain, 1- mild pain, 2-moderate pain, 3-severe pain].

14.4. Associated Symptoms (Nausea, Photophobia, Phonophobia)

The migraine associated symptoms of photophobia, phonophobia and nausea are measured on a binary scale (present or absent), using the eDiary.

At baseline (prior to taking IMP), the subjects will also be asked to identify their most bothersome symptom (MBS) (nausea, phonophobia or photophobia) in the eDiary.

14.5. Rescue Medication

Subjects must be instructed that rescue medication may not be taken until **after** the 2-hour post-dose time point (i.e. after they have **fully completed** all eDiary responses for the 2-hour timepoint).

Any use of rescue medication (yes/no) will be recorded by the subject in the eDiary. If rescue medication is used, the specific medication will not be recorded in the eDiary but should be captured/recorded by the site in the concomitant medication/rescue medication CRF at the subsequent EoP visit.

Refer to Section 10.1 for instructions regarding rescue medications.

14.6. Functional Disability

Functional disability will be assessed using a single-question scale (Appendix B)[22]. 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 eDiary, using a 4 point numeric rating scale with the following 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). BMI 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.

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) (Fredericia's).

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 SOA.

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 and Coagulation Tests

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
Coagulation Tests (PT and PTT)	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

Dipstick:	Microscopic:
Nitrite	white blood cells (WBC)
Protein	red blood cells (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. Subjects positive for the initial screening are to be excluded. No additional confirmatory testing will be required to exclude the subject.

15.1.5.5. Drug Screen

The urine drug screening assessment will include the following tests:

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

15.1.5.6. Pregnancy Monitoring

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 at EoP3/EoT (V5). Additionally, a urine hCG test will be conducted at V2 prior to randomization and at EoP1 (V3) and EoP 2 (V4).

15.1.5.7. Menstrual Cycle Monitoring

For pre-menopausal women, sites will record the date of the first day of each woman's menstrual cycle (collect date for last menstrual period before the study and then any menstrual periods during the study through V5). This information should be collected at V2, V3, V4, V5. Sites will also ask whether the subject generally has regular or irregular menstrual cycles.

15.1.6. C-SSRS

The C-SSRS will be completed as indicated in the SOA (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. Subjects 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.

15.2. Adverse Events and Serious Adverse Events

15.2.1. Definition of Adverse Events and Serious Adverse Events

15.2.1.1. Adverse Event

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.

15.2.1.2. Serious Adverse Event

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 will be collected as efficacy parameters and are not considered AEs/SAEs unless progression of the treatment indication or associated clinical symptoms are either new or worsening greater than anticipated in the natural course of the disease:

- Migraine
- Nausea
- Photophobia (light sensitivity)
- Phonophobia (noise sensitivity)

Note: If either of the following conditions applies, then the event must be recorded and reported as an AE/SAE:

- The event is, in the investigator's opinion, of greater intensity, frequency, or duration than expected for the individual participant or the natural course of the disease.

  OR

- The investigator considers that there is a reasonable possibility that the event was related to study intervention.

In addition, 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., Medical Dictionary for Regulatory Activities [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 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 the safety mailbox and the Kallyope, Inc. medical monitor, 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 suspected 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

An adverse event of special interest (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 EoT 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 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 (CI), 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

With 120 subjects randomized to two treatment sequences, it is anticipated that about 80% of subjects will have a qualifying headache in the first two periods, which would provide 96 qualifying migraine attacks in each of the placebo arm and high dose arm. Assuming a placebo response rate of 10% and the treatment response rate of 25% and a treatment difference of 15%, 96 qualifying migraine attacks in each treatment group provide approximately 87.4% power for the primary endpoint of pain freedom at 2 hours post-dose for the comparison between the high dose vs placebo respectively with a two-sided alpha of 0.10.

16.3. Analysis Populations

The following analysis sets will be evaluated and used for analysis of the data. The data for each treatment (i.e., high or low dose or placebo) from different periods are pooled for analysis.

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.

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. Efficacy Endpoints

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

Primary endpoint:

1. 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:

1. Freedom from the 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).
2. 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).

Exploratory endpoints:

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.
2. 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.
3. 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.

4. 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.
5. 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.
6. 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.
7. 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.
8. 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.

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 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) 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 Endpoints

The primary endpoint of pain freedom at 2 hours post-dose will be analyzed using the mITT analysis population. Subjects with missing data at 2 hours post-dose will be classified as failures. A logistic regression analysis will be conducted to evaluate the effect of treatment on pain freedom at 2 hours, adjusting for the following covariates: treatment group, treatment sequence, treatment period, and the use of background prophylactic medications for migraine (yes/no). The proportion of subjects achieving the endpoint response criteria will be reported by treatment group. Additionally, odds ratios with 90% confidence intervals will be presented to compare the likelihood of achieving pain freedom between the K-645 high dose, low dose, and placebo groups. Sensitivity analysis will be described in the SAP.

16.6.3. Secondary Endpoints

For secondary categorical endpoints, the same statistical analysis will be applied using logistic regression. Subjects with missing data or with measurements after using rescue medications will be classified as failure (for timepoints analyses using post-rescue observations).

16.6.4. Exploratory Endpoints

For exploratory endpoints, the same statistical analysis will be applied using logistic regression. Subjects with missing data or measurement after using rescue medications will be classified as failure.

For the probability of rescue medication use within 24-hour post-dose, logistic regression will be performed. Time to reschedule medication use through 24 hours post-dose will be assessed by treatment group using Kaplan-Meier (K-M) 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.

16.7. 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

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 adverse events (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 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.

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

Baseline, post baseline measurements and changes from baseline for electrocardiogram data will be summarized by treatment and timepoint. QTc values and changes form baseline that reach the threshold of clinical concern will be summarized. 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

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., endpoints at 2 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.

This missing data imputation method will be specified in the statistical analysis plan for 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). Additional sensitivity analysis will be defined in the statistical analysis plan.

16.9. Multiplicity

The study tests the primary hypothesis that at K-645 high dose is superior to the placebo arm in primary endpoint of pain freedom at 2 hours post-dose. 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 100 treated headaches assessments have been completed in the e-diaries for periods 1 or 2, an interim analysis (IA) of efficacy data will be conducted for internal decision making. An external independent contract 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.

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 an 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/ Independent Ethics Committee

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) and/or delegated staff 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/if required per regulatory requirements. Financial Disclosure requirements are outlined in the US Food and Drug Administration Regulations, Financial Disclosure by Clinical Investigators (21 Code of Federal Regulations [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.

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19. APPENDICES

Appendix A: HIS 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. HIS ICHD CRITERIA

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

The figure below gives an outline of the criteria.

1. Migraine

- **1.1 Migraine without aura**
- **1.2 Migraine with aura**
  - 1.2.1 Migraine with typical aura
    - 1.2.1.1 Typical aura with headache
    - 1.2.1.2 Typical aura without headache
  - 1.2.2 Migraine with brainstem aura
  - 1.2.3 Hemiplegic migraine
    - 1.2.3.1 Familial hemiplegic migraine (FHM)
      - 1.2.3.1.1 Familial hemiplegic migraine type 1 (FHM1)
      - 1.2.3.1.2 Familial hemiplegic migraine type 2 (FHM2)
      - 1.2.3.1.3 Familial hemiplegic migraine type 3 (FHM3)
      - 1.2.3.1.4 Familial hemiplegic migraine, other loci
    - 1.2.3.2 Sporadic hemiplegic migraine (SHM)
  - 1.2.4 Retinal migraine
- **1.3 Chronic migraine**
- **1.4 Complications of migraine**
  - 1.4.1 Status migrainosus
  - 1.4.2 Persistent aura without infarction
  - 1.4.3 Migrainous infarction
  - 1.4.4 Migraine aura-triggered seizure
- **1.5 Probable migraine**
  - 1.5.1 Probable migraine without aura
  - 1.5.2 Probable migraine with aura
- **1.6 Episodic syndromes that may be associated with migraine**
  - 1.6.1 Recurrent gastrointestinal disturbance
    - 1.6.1.1 Cyclical vomiting syndrome
    - 1.6.1.2 Abdominal migraine
  - 1.6.2 Benign paroxysmal vertigo
  - 1.6.3 Benign paroxysmal torticollis

APPENDIX B. FUNCTIONAL DISABILITY SCALE – SINGLE QUESTION – EXAMPLE

Question:

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

Response Options:

Normal Function (0), Mild Impairment (1), Severe Impairment (2), Required Bedrest (3).

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

SUICIDAL IDEATION		
Ask questions 1 and 2. If both are negative, proceed to "Suicidal Behavior" section. If the answer to question 2 is "yes", ask questions 3, 4 and 5. If the answer to question 1 and/or 2 is "yes", complete "Intensity of Ideation" section below.	**Lifetime: Time He/She Felt Most Suicidal**	**Past __ Months**
1. Wish to be Dead Subject endorses thoughts about a wish to be dead or not alive anymore, or wish to fall asleep and not wake up. ***Have you wished you were dead or wished you could go to sleep and not wake up?*** If yes, describe:	Yes ☐ No ☐	Yes ☐ No ☐
2. Non-Specific Active Suicidal Thoughts General non-specific thoughts of wanting to end one's life/commit suicide (e.g., *"I've thought about killing myself"*) without thoughts of ways to kill oneself/associated methods, intent, or plan during the assessment period. ***Have you actually had any thoughts of killing yourself?*** If yes, describe:	Yes ☐ No ☐	Yes ☐ No ☐
3. Active Suicidal Ideation with Any Methods (Not Plan) without Intent to Act Subject endorses thoughts of suicide and has thought of at least one method during the assessment period. This is different than a specific plan with time, place or method details worked out (e.g. thought of method to kill self but not a specific plan). Includes person who would say, *"I thought about taking an overdose but I never made a specific plan as to when, where or how I would actually do it…and I would never go through with it."* ***Have you been thinking about how you might do this?*** If yes, describe:	Yes ☐ No ☐	Yes ☐ No ☐
4. Active Suicidal Ideation with Some Intent to Act, without Specific Plan Active suicidal thought of killing oneself and subject reports having some intent to act on such thoughts, as opposed to *"I have the thoughts but I definitely will not do anything about them."* ***Have you had these thoughts and had some intention of acting on them?*** If yes, describe:	Yes ☐ No ☐	Yes ☐ No ☐
5. Active Suicidal Ideation with Specific Plan and Intent Thoughts of killing oneself with details of plan fully or partially worked out and subject has some intent to carry it out. ***Have you started to work out or worked out the details of how to kill yourself? Do you intend to carry out this plan?*** If yes, describe:	Yes ☐ No ☐	Yes ☐ No ☐
INTENSITY OF IDEATION		
The following features should be rated with respect to the most severe type of ideation (i.e., 1-5 from above, with 1 being the least severe and 5 being the most severe). Ask about time he/she was feeling the most suicidal. Lifetime - ***Most Severe Ideation:*** ____ (*Type # (1-5)*) _____ (*Description of Ideation*) Past X Months - ***Most Severe Ideation:*** ____ (*Type # (1-5)*) _____ (*Description of Ideation*)	Most Severe	Most Severe
Frequency ***How many times have you had these thoughts?*** (1) Less than once a week (2) Once a week (3) 2-5 times in week (4) Daily or almost daily (5) Many times each day	____	____
Duration ***When you have the thoughts how long do they last?*** (1) Fleeting - few seconds or minutes (2) Less than 1 hour/some of the time (3) 1-4 hours/a lot of time (4) 4-8 hours/most of day (5) More than 8 hours/persistent or continuous	____	____
Controllability ***Could/can you stop thinking about killing yourself or wanting to die if you want to?*** (1) Easily able to control thoughts (2) Can control thoughts with little difficulty (3) Can control thoughts with some difficulty (4) Can control thoughts with a lot of difficulty (5) Unable to control thoughts (0) Does not attempt to control thoughts	____	____
Deterrents ***Are there things - anyone or anything (e.g., family, religion, pain of death) - that stopped you from wanting to die or acting on thoughts of committing suicide?*** (1) Deterrents definitely stopped you from attempting suicide (2) Deterrents probably stopped you (3) Uncertain that deterrents stopped you (4) Deterrents most likely did not stop you (5) Deterrents definitely did not stop you (0) Does not apply	____	____
Reasons for Ideation ***What sort of reasons did you have for thinking about wanting to die or killing yourself? Was it to end the pain or stop the way you were feeling (in other words you couldn't go on living with this pain or how you were feeling) or was it to get attention, revenge or a reaction from others? Or both?*** (1) Completely to get attention, revenge or a reaction from others (2) Mostly to get attention, revenge or a reaction from others (3) Equally to get attention, revenge or a reaction from others and to end/stop the pain (4) Mostly to end or stop the pain (you couldn't go on living with the pain or how you were feeling) (5) Completely to end or stop the pain (you couldn't go on living with the pain or how you were feeling) (0) Does not apply	____	____
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SUICIDAL BEHAVIOR *(Check all that apply, so long as these are separate events; must ask about all types)*	**Lifetime**	**Past __ Years**
Actual Attempt: A potentially self-injurious act committed with at least some wish to die, *as a result of act*. Behavior was in part thought of as method to kill oneself. Intent does not have to be 100%. If there is *any* intent/desire to die associated with the act, then it can be considered an actual suicide attempt. ***There does not have to be any injury or harm***, just the potential for injury or harm. If person pulls trigger while gun is in mouth but gun is broken so no injury results, this is considered an attempt. Inferring Intent: Even if an individual denies intent/wish to die, it may be inferred clinically from the behavior or circumstances. For example, a highly lethal act that is clearly not an accident so no other intent but suicide can be inferred (e.g., gunshot to head, jumping from window of a high floor/story). Also, if someone denies intent to die, but they thought that what they did could be lethal, intent may be inferred. ***Have you made a suicide attempt?*** ***Have you done anything to harm yourself?*** ***Have you done anything dangerous where you could have died?*** ***What did you do?*** ***Did you_____ as a way to end your life?*** ***Did you want to die (even a little) when you_____?*** ***Were you trying to end your life when you _____?*** ***Or Did you think it was possible you could have died from_____?*** ***Or did you do it purely for other reasons / without ANY intention of killing yourself (like to relieve stress, feel better, get sympathy, or get something else to happen)?*** (Self-Injurious Behavior without suicidal intent) If yes, describe:	Yes No ☐ ☐ Total # of Attempts _____	Yes No ☐ ☐ Total # of Attempts _____
Has subject engaged in Non-Suicidal Self-Injurious Behavior?	Yes No ☐ ☐	Yes No ☐ ☐
Interrupted Attempt: When the person is interrupted (by an outside circumstance) from starting the potentially self-injurious act *(if not for that, actual attempt would have occurred)*. Overdose: Person has pills in hand but is stopped from ingesting. Once they ingest any pills, this becomes an attempt rather than an interrupted attempt. Shooting: Person has gun pointed toward self, gun is taken away by someone else, or is somehow prevented from pulling trigger. Once they pull the trigger, even if the gun fails to fire, it is an attempt. Jumping: Person is poised to jump, is grabbed and taken down from ledge. Hanging: Person has noose around neck but has not yet started to hang - is stopped from doing so. ***Has there been a time when you started to do something to end your life but someone or something stopped you before you actually did anything?*** If yes, describe:	Yes No ☐ ☐ Total # of interrupted _____	Yes No ☐ ☐ Total # of interrupted _____
Aborted Attempt: When person begins to take steps toward making a suicide attempt, but stops themselves before they actually have engaged in any self-destructive behavior. Examples are similar to interrupted attempts, except that the individual stops him/herself, instead of being stopped by something else. ***Has there been a time when you started to do something to try to end your life but you stopped yourself before you actually did anything?*** If yes, describe:	Yes No ☐ ☐ Total # of aborted _____	Yes No ☐ ☐ Total # of aborted _____
Preparatory Acts or Behavior: Acts or preparation towards imminently making a suicide attempt. This can include anything beyond a verbalization or thought, such as: assembling a specific method (e.g., buying pills, purchasing a gun) or preparing for one's death by suicide (e.g., giving things away, writing a suicide note). ***Have you taken any steps towards making a suicide attempt or preparing to kill yourself (such as collecting pills, getting a gun, giving valuables away or writing a suicide note)?*** If yes, describe:	Yes No ☐ ☐	Yes No ☐ ☐
Suicidal Behavior: Suicidal behavior was present during the assessment period?	Yes No ☐ ☐	Yes No ☐ ☐

Answer for Actual Attempts Only	Most Recent Attempt Date:	Most Lethal Attempt Date:	Initial/First Attempt Date:
Actual Lethality/Medical Damage: 0. No physical damage or very minor physical damage (e.g., surface scratches). 1. Minor physical damage (e.g., lethargic speech; first-degree burns; mild bleeding; sprains). 2. Moderate physical damage; medical attention needed (e.g., conscious but sleepy, somewhat responsive; second-degree burns; bleeding of major vessel). 3. Moderately severe physical damage; *medical* hospitalization and likely intensive care required (e.g., comatose with reflexes intact; third-degree burns less than 20% of body; extensive blood loss but can recover; major fractures). 4. Severe physical damage; *medical* hospitalization with intensive care required (e.g., comatose without reflexes; third-degree burns over 20% of body; extensive blood loss with unstable vital signs; major damage to a vital area). 5. Death	*Enter Code* _____	*Enter Code* _____	*Enter Code* _____
Potential Lethality: Only Answer if Actual Lethality=0 Likely lethality of actual attempt if no medical damage (the following examples, while having no actual medical damage, had potential for very serious lethality: put gun in mouth and pulled the trigger but gun fails to fire so no medical damage; laying on train tracks with oncoming train but pulled away before run over). 0 = Behavior not likely to result in injury 1 = Behavior likely to result in injury but not likely to cause death 2 = Behavior likely to result in death despite available medical care	*Enter Code* _____	*Enter Code* _____	*Enter Code* _____

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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.