Title:

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

Statistical Analysis Plan Date:

21-August-2025

NCT:

06848075

KALLYOPE

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Statistical Analysis Plan

Protocol No. K304-P001, 06 November 2024

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

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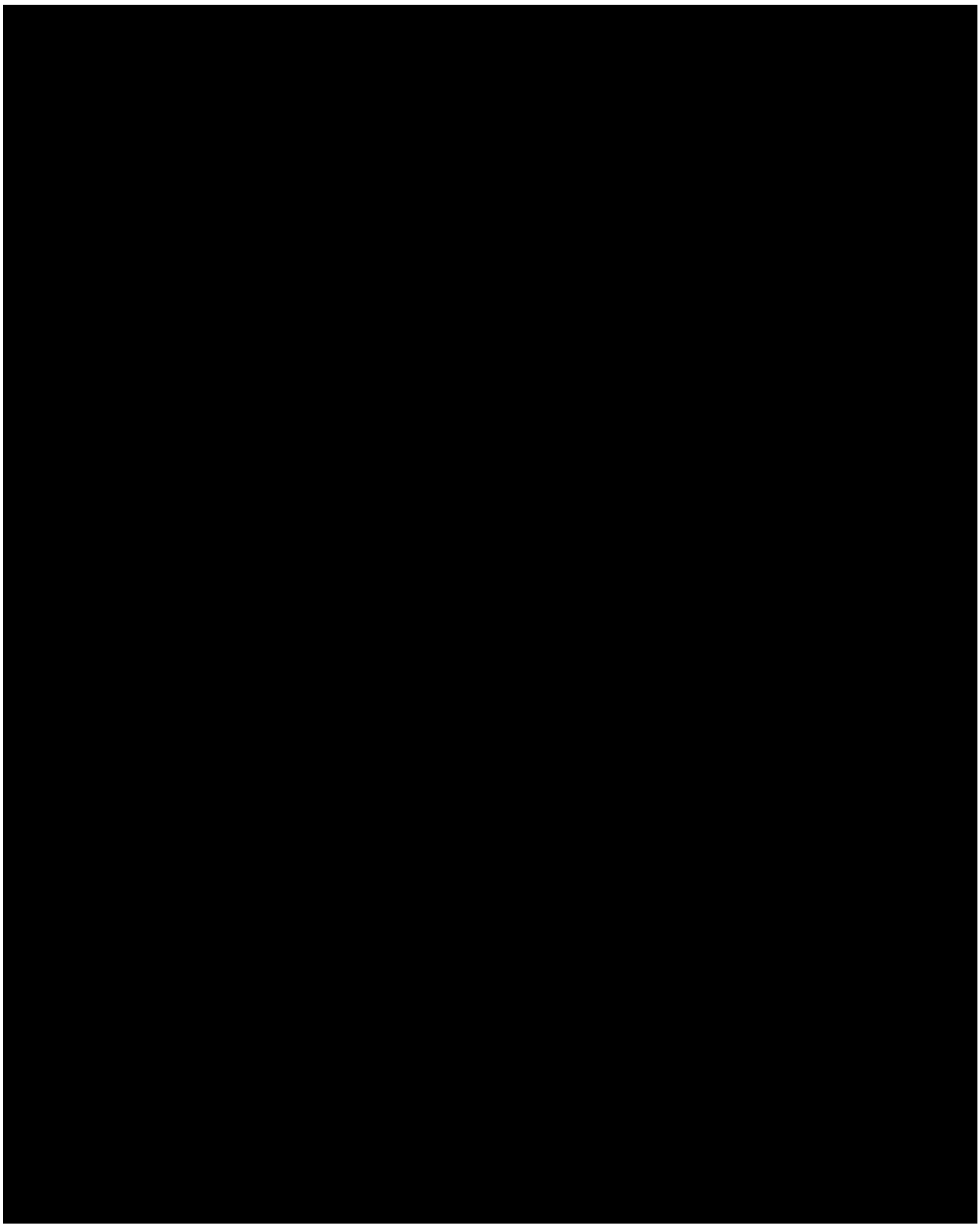
SAP Version:	V1.1
SAP Date:	21 August 2025



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History of Changes

Version Number	Description
1.0	New Document
1.1	Update TEAE definition in section 5.9.1 and analysis period of Sponsor's pre-defined limits of change in section 5.9.2 Add Per-Protocol Analysis Set in section 4 and analysis using per-protocol analysis set in section 5.8.2

List of Tables

Glossary and Abbreviations

Abbreviation	Term
AE(s)	adverse event(s)
ALP	alkaline phosphatase
ALT	alanine aminotransferase
AST	aspartate aminotransferase
ATC	anatomical therapeutic chemical
BMI	body mass index
BUN	blood urea nitrogen
CI	confidence interval
CMH	Cochran-Mantel-Haenszel
CRO	contract research organization
CSP	clinical study protocol
CSR	clinical study report
CTCAE	Common Terminology Criteria for Adverse Events
ECG	electrocardiogram
FDA	Food and Drug Administration
eCRF	electronic case report form
eGFR	estimated glomerular filtration rate
ET	early termination
FSH	follicle stimulating hormone
GGT	gamma-glutamyl transferase
HA	headache
IA	interim analysis
ICH	International Council for Harmonisation
IRT	Interactive Response Technology
IWRS	Interactive Web Response Systems

Abbreviation	Term
KM	Kaplan-Meier
LLOQ	lower limit of quantification
Max	maximum
MBS	most bothersome symptom
MedDRA	Medical Dictionary for Regulatory Activities
Min	minimum
n	number of subjects
NE	not evaluable
PE	Physical Examination
PT	preferred term
QTc	QT interval
QTcF	QT interval corrected by Fridericia's formula
RBC	red blood cell
SAE(s)	serious adverse event(s)
SAP	statistical analysis plan
SAS	Statistical Analysis System
SD	standard deviation
SE	standard error
SI	International System of Units
SOA	schedule of assessment
SOC	system organ class
SUSAR	Suspected Unexpected Serious Adverse Reaction
TEAE(s)	treatment-emergent adverse event(s)
TFL	table, figure, and listing
TMF	trial master file
ULOQ	upper limit of quantification

Abbreviation	Term
WBC	white blood cell
WHO	World Health Organization

1 Introduction

This statistical analysis plan (SAP) is a comprehensive and detailed description of strategy and statistical techniques to be used for the analyses of trial data from study protocol K304-P001 dated November 06, 2024 (A Phase IIb, Multicenter, Randomized, Double-Blind, Placebo-Controlled, Dose-Finding Study of Elismetrep (K-304) in the Treatment of Acute Migraine). This SAP will be finalized prior to database lock to ensure the credibility of the study results by pre-specifying the statistical methods for analyses.

This SAP may be revised during the course of the study to accommodate protocol amendments and to adapt to revisions in the analysis approaches. Any changes made to the SAP after database lock will be documented and detailed in the Clinical Study Report (CSR) for this study.

The statistical principles applied in the design and planned analyses of this study will be consistent with the International Council on Harmonisation (ICH) guidelines E9 (Statistical Principles for Clinical Trials) (ICH 1998).

2 Study Objectives and Endpoints

2.1 Study Objectives

2.1.1 Primary Objective

The study primary objective is:

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

2.1.2 Secondary Objectives

The study secondary objectives are:

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

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

2.1.3 Exploratory Objectives

The study exploratory objectives are:

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

2.2 Study Endpoints

2.2.1 Primary Endpoints

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

2.2.2 Secondary Endpoints

- Proportion with 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 specified by subjects at pre-treatment baseline and 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) at 2h post-dose.
- 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 use any rescue medications, and 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 use any rescue medications, and 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.

2.2.3 Exploratory Endpoints

- The proportion of subjects able to function normally, at 2 hours, will be assessed using the number of subjects that self-report as "normal" on the functional disability scale (functional disability: four-point scale: normal (0), mildly impaired (1), moderately impaired (2), severely impaired, requires bedrest (3) in the subset of subjects who reported any level of disability at the migraine baseline.
- Pain relapse will be assessed using the proportion of subjects with pain freedom at 2hrs who (a) have 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) have missing pain data at 24 or 48 hours time point after 2 hours post-dose; (c) no intervening rescue medication taken at or before 48 hours post-dose evaluated for subjects with pain freedom at 2 hours post-dose within 48 hours after administration of study medication.

3 Study Design

3.1 Overall Study Design

This is a multi-center, randomized, double-blind, placebo-controlled, parallel-group study to evaluate the safety, tolerability, and efficacy of various doses of elismetrep in the treatment of patients with an acute migraine attack. Approximately four hundred (400) subjects will be randomized in a 2:1:2:2:1 ratio to one of the following treatment groups: placebo or 2, 5, 10, or 20 mg of elismetrep. Randomization will be stratified according to use of background prophylactic medications for migraine (yes/no).

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

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

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

- The migraine headache severity is moderate or severe (Grade 2 or 3).
- The migraine headache started less than four hours ago.

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

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

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

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

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

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

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

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

The schedule of assessments is shown in Table 1.

3.2 Randomization

Suvoda (IWRS vendor) will generate the randomization schedule. All randomization information will be stored in a secured area, accessible only by authorized personnel.

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

3.3 Blinding and Unblinding

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

Any intentional or accidental unintentional unblinding will be documented and filed as per relevant study operating procedures and/or plan, filed in the relevant study TMF folder(s), and summarized in the Clinical Study Report (CSR).

Certain personnel from the sponsor and/or Kallyope designees (i.e., vendor or consultant designees) within the study infrastructure are or may become unblinded to perform their respective accountabilities. The unblinded personnel and procedures are summarized below. Please refer to functional area and/or vendor specific relevant processes plans or operating procedures for further details.

3.3.1 Unblinded Personnel and /or Procedures

3.3.1.1 Clinical Supplies Related Personnel

Personnel who manage and oversee (i.e., Kallyope designees) drug inventory levels within the study interactive response technology system (IRT) and who are accountable for the quality assurance review/approval processes including but not limited to the review of documentation related to the manufacture, packaging, labeling and release stages will see unblinded information. These individuals will not have access or be informed as to subject level treatment allocations during the study. Additionally, these personnel will not be:

- attendees to study team meetings following study initiation,
- included on study team meeting minute distribution,
- included in study team communications through the duration of the study through database lock and unblinding.

The clinical supplies related personnel who are unblinded during the study:

- [redacted], Clinical Supplies Consultant

3.3.1.2 Pharmacovigilance Personnel

Designated safety management personnel (at Kallyope designated Pharmacovigilance vendor [redacted]) have the capability to unblind individual subject treatment assignment to determine the causality of potential SUSAR events upon approval of the Kallyope Medical Monitor. Unblinding for these circumstances is performed and recorded within the study randomization platform [i.e. IRT system supported by the Kallyope's designated [redacted]] (Refer to the IRT specifications and user manual for additional details). Sites, central IRB, and study team members will receive blinded SUSAR reports for all potential SUSARs. Designated Kallyope personnel [redacted], Head of Pharmacovigilance) may be unblinded for SUSARs that require submission to the regulatory agencies. The FDA submission vendor (Veristat) will receive unblinded MedWatch forms from [redacted] for submission of relevant SUSARs to FDA. (See [redacted] Safety Management Plan for unblinding details). Kallyope's internal Safety Review Committee will perform sponsor due diligence pharmacovigilance oversight of blinded safety data per SOPs.

3.3.1.3 Investigator Unblinding in Case of Medical Emergency at the Site

The site investigator (maybe in conjunction with the sponsor medical monitor lead) may exercise the option to unblind an individual subject in case of medical emergency. The unblinding by the investigator is performed, documented, and maintained within the context of the IRT system. Subject unblinding in these circumstances by the investigator and/or sponsor medical monitor will be documented by the site within the study medical records, IRT, and described in clinical study report. (Refer to the study medical monitoring plan for additional medical monitoring process requirements).

3.3.1.4 Biometrics

All biometrics personnel from the sponsor and CRO (including Data management, Biostatistics and Statistical programming) will remain blinded during the study before database lock, unless otherwise specified.

- ***Randomization System/Process Personnel***

[redacted] LLC, whose function is to generate/confirm/upload the study randomization schedule (as per the vendor established SOPs), will be unblinded. These unblinded personnel will not engage in study team meetings where any facets of the trial are being discussed. (Refer to the[redacted] standard operations procedures and respective IRT specifications for further details).

3.3.1.5 Interim Analysis

After approximately 200 subjects have completed the primary endpoint, an interim analysis (IA) of efficacy data will be conducted for internal decision making. An external contractor statistician will be unblinded to the randomization schedule. The external statistician will provide group level summary efficacy data on the primary endpoint only to selected sponsor personnel. The selected 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 on the study team will remain blinded to treatment assignments and summary efficacy results until after the end of the study.

[redacted]

The timing of the unblinding will be documented in the unblinding tracking sheet.

3.4 Sample Size Justification

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

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

4 Analysis Sets

The following analysis sets are defined and used for this study.

4.1 Enrolled Set

The Enrolled Set includes all subjects who sign an informed consent form and were assigned a subject identification number.

4.2 Randomized Set

The Randomized Set includes all enrolled subjects who received a randomized treatment assignment from the IWRS.

4.3 Modified Intent-to-Treat (mITT) Analysis Set

The mITT analysis set consist of all randomized participants who took study therapy, had a qualifying migraine of moderate or severe pain intensity at baseline (as defined in Section 3.1), and provided baseline and at least one post-baseline efficacy data point (i.e. non-missing pain level, phonophobia status, photophobia status, nausea status etc). The participants will be analyzed as randomized. The mITT analysis set will be used for demographic, baseline characteristics and efficacy analyses.

4.4 Per-Protocol (PP) Analysis Set

The PP analysis set consist of all randomized participants who took study therapy, had a qualifying migraine of moderate or severe pain intensity at baseline (as defined in Section 3.1), provided baseline and 2-hour pain assessment in ePRO and excluding subjects with major PD in "Prohibited Medications" and "Improper Study Medication Dose" categories. The participants will be analyzed as randomized. The PP analysis set will be used selected efficacy analyses.

4.5 Safety Analysis Set

The Safety Analysis Set consists of all randomized participants who took the study medication. The Safety Analysis Set will be used for safety analysis and analyzed as treated.

5 Statistical Methods

5.1 General Considerations

Unless otherwise specified, all statistical analyses of the study will be performed using the statistical software Statistical Analysis System (SAS) for Windows Version 9.4 or later (SAS Institute, Inc., Cary, NC). All by-subject data used in the analyses will be displayed in listings.

5.1.1 Data Summary

All summary tables will be presented by treatment group (placebo, elismetrep 2mg, 5mg, 10mg, and 20 mg) and/or overall elismetrep, as needed.

Unless otherwise specified, continuous variables will be summarized using descriptive statistics, the number of participants (n), mean, standard deviation (SD), minimum (min), first quartile (Q1), median, third quartile (Q3) and maximum (max). The min and max values will be

presented to the same number of decimal places as the raw data. If the raw data has 3 decimal places or more, 3 decimal places will be presented for the mean and SD; 2 decimal places will be presented for median, Q1, Q3, min, and max. Otherwise the mean and median will be presented to one more decimal place than the raw data. The SD will be presented to two more decimal places than the raw data.

Summaries for categorical (discrete or dichotomous) variables will include the number and/or percentage of subjects in a particular category. Percentages will be presented to one decimal place, unless otherwise specified. Population counts (either number of subjects or number of time points at the assessment) for each treatment group will be used as the denominator in the calculation of percentages unless otherwise specified.

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

5.1.2 Baseline

Unless otherwise specified, baseline is defined as the last available observation prior to dosing during the double-blind treatment period.

Change from baseline is defined as the difference between the post-baseline assessment value and the baseline value, i.e.,

Post-baseline Assessment Value – Baseline Value.

Percent change from baseline is defined as

(Change from baseline value/Baseline value) × 100%

5.1.3 Study Day

Study day is relative to the day of first dose of study drug. Day 1 is defined as the day of the first dose of study drug. Study day after Day 1 is calculated as:

Assessment date – date of Day 1 + 1.

Study day prior to Day 1 is calculated as:

Assessment date – date of Day 1.

The day prior to Day 1 is Day -1.

5.1.4 Unscheduled Visits

An unscheduled visit value may be used to provide a measurement for a scheduled visit, a baseline, a last or a worst value, if appropriate according to their definitions.

5.1.5 Handling of Missing or Incomplete Data

For Efficacy endpoints handling of missing data is described in Section 5.8.

Unless otherwise specified, missing or incomplete dates for prior/concomitant medications, AEs, and laboratory data will be imputed as follows:

Adverse Events

The following imputation rules for missing or partial AE start dates are used:

- If only Day is missing, the start day will be the first day of the month or the date of study drug first dose if the AE end date is on/after the date of study drug first dose or is missing/partial AND the start year and month of the AE are the same as year and month of the study drug first dose date;
- If Day and Month are both missing, the start date will be the date of study drug first dose if the AE end date is on/after the date of study drug first dose or is missing/partial AND the start year of the AE is the same as year of the study drug first dose date; the start date will be imputed to January 1 of the year otherwise.
- If Day, Month, and Year are all missing, the date will not be imputed. However, if the AE end date is on/after the date of study drug first dose, then the AE will be considered a treatment emergent adverse event (TEAE).

Missing or partial AE stop dates will not be imputed.

If the severity of an AE is missing, it will be classified as “severe” in the summary tables. If the assessment of relationship of study medication is missing, it will be classified as “related” to the study drug.

Prior or Concomitant Medications

The same imputation rule as applied to missing or partial AE start date will be used for missing or partial medication start dates.

Missing or partial medication stop dates will not be imputed.

Safety Laboratory Data

For the analysis/summary of laboratory data, lab values preceded by a "<" or a ">" sign (i.e., those below the lower limit of quantification [LLOQ] or above the upper limit of quantification [ULOQ]) will be considered equal to the LLOQ or ULOQ, respectively. The original values preceded by a "<" or a ">" sign will be presented in the listings.

5.2 Subject Disposition

The number and percentage of participants in the following categories will be summarized by treatment group:

- Participants who were randomized
- Participants who had a qualifying migraine
- Participants with a qualifying migraine and took the study drug
- Participants with a qualifying migraine and did not take the study drug
- Participants who mistakenly took the study drug without having a qualifying migraine
- Participants who completed the study (requires completion of Visit 3 'end of treatment' regardless of whether subject had a qualifying migraine or took the study drug).
- Participants who prematurely discontinued the study
- The primary reasons for premature discontinuation

A separate summary will be provided for the number and/or percentage of subjects that were screened, enrolled and screened failed and reason for screen failure.

Subject disposition will be listed for all randomized participants. Also, the eligibility status for the study will be listed for all screened participants.

5.3 Protocol Deviations

Protocol deviations identified during the course of the study will be classified as major or minor.

A major protocol deviation (sometimes referred to as a protocol violation or a significant protocol deviation) is a deviation to the protocol that might significantly impact the

completeness, accuracy or reliability of the study data or that may significantly affect a participant's rights, safety or well-being.

Before the database lock, all protocol deviations will be reviewed by the Sponsor. Final determination of major deviations is the responsibility of the Sponsor. Major protocol deviations will be identified and listed in the CSR.

Major protocol deviations will be summarized by treatment group and overall, and by category and sub-category if there is a sufficient number of major protocol deviations using the mITT set.

All protocol deviations will be presented in a listing for randomized set. A by-subject listing will be provided for major protocol deviations for randomized set.

5.4 Demographics and Baseline Disease Characteristics

5.4.1 Demographics

Demographics and baseline characteristics will be summarized by treatment group and overall using the mITT set. Demographics and baseline characteristic include age, age group (< 65 years or ≥ 65 years), sex, childbearing potential if female, race, ethnicity, baseline height (cm), weight (kg) and body mass index (BMI; kg/m^2).

BMI, if not available, will be calculated as the ratio of subject's weight (kg) to the square of the subject's height (m):

$$BMI = \text{Weight (kg)}/(\text{Height [m]})^2.$$

Continuous variables (age, height, weight and BMI) will be summarized by n, mean, SD, median, min, and max. Number of subjects and percentages will be used to describe categorical variables (sex, race, ethnicity and age group.).

Demographic data will be listed.

5.4.2 Migraine Characteristics at Onset of Qualifying Migraine

Characteristics at onset of qualifying migraine will include the following, and will be summarized only for mITT subjects:

- Pain level: moderate, severe (pain score of 2 or 3).

- MBS: nausea, phonophobia, photophobia
- Nausea: present, absent
- Phonophobia: present, absent
- Photophobia: present, absent
- Functional disability level: normal, mildly impaired, moderately impaired, severely impaired

Data will be summarized using descriptive statistics frequency counts and percentages (for categorical variables) by treatment group and overall using the mITT set.

A by-subject listing will be provided for the migraine characteristics.

5.5 Medical History

5.5.1 Migraine Disease History

The migraine disease characteristics will include the following:

- Background prophylactic medications for migraine: Yes, No
- Duration of disease: Calculated as (date of informed consent – date of initial diagnosis + 1)/365.25 if full dates are available; (year of informed consent date - year of initial diagnosis date) + (month of informed consent date - month of initial diagnosis date)/12 if only month and year are available; calculated as (year of informed consent date – year of initial diagnosis date) if only year parts are available.
- Age (years) at first migraine onset
- Migraine criteria: Migraine with aura, Migraine without aura
- Average number of migraine attacks per month

Data will be summarized using descriptive statistics (for continuous variables - n, mean, SD, median, minimum, and maximum) or frequency counts and percentages (for categorical variables) by treatment group and overall using the mITT set.

A by-subject listing will be provided for the migraine disease history.

5.5.2 General Medical History

General medical history will be coded using the latest version of Medical Dictionary for Regulatory Activities (MedDRA).

Medical history will be summarized by system organ class (SOC) and preferred term (PT) using the mITT set. A by-subject listing will be provided for medical history.

5.6 Prior and Concomitant Therapies

5.6.1 Prior and Concomitant Medications

Any medication or vaccine that the subject is receiving at the time of enrollment or receives during the study will be recorded in the subject's source documentation and the eCRF.

Medications will be classified into prior medications and concomitant medications.

- Prior medications are defined as medications that started and stopped prior to the first dose of study drug.
- Concomitant medications are defined as any medications that were ongoing or started on or after the first dose of study drug.

A given medication can be classified as a prior medication or a concomitant medication.

Medications will be recorded and coded using the latest version of World Health Organization (WHO) Drug Enhanced Dictionary. Prior and concomitant medications will be summarized separately by Anatomical Therapeutic Chemical (ATC) classification pharmacological or therapeutic subgroup (Level 2) and preferred drug name for the Safety Analysis Set. At each level of summarization, a subject is counted once if he/she reported 1 or more medications at that level. Medications will be listed by subject, including ATC classification, preferred drug name and reported drug name, the start and end dates (or ongoing status), dose, unit, frequency, route, and indication.

5.6.2 History of Resistance to Migraine Medications

Number and percentage of subject with history of resistance to prior migraine medications will be summarized using mITT set. Migraine resistance medications will be summarized by drug

name and reason for stopping. A by-subject listing will be provided for history of resistance to migraine medications.

5.7 Treatment Exposure and Compliance

5.7.1 Treatment Exposure

Subjects report study drug exposure in the eDiary, whereas sites report study drug accountability on the Study Drug Accountability CRF. eDiary study drug exposure will be summarized by as-randomized treatment group for randomized set.

Number and percent of subjects will be summarized in the following categories:

- Study drug taken
    - Study drug taken by mistake (i.e. no qualifying migraine)
    - Study drug actually received different from randomized treatment assignment
- Study drug not taken

5.7.2 Treatment Compliance

Number and percent of subjects with and without administering full dose will be summarized by treatment group in the mITT set. Number of capsules taken will be summarized for subjects without administering full dose. If the Safety Analysis Set is not the same as the mITT Set, summarization of treatment compliance will be repeated using the Safety Analysis Set.

Compliance will be calculated as follows:

Treatment compliance = Total number of capsules taken / 4 * 100

A by-subject listing will be presented for drug administration and compliance in the Safety Analysis set.

5.8 Efficacy Analyses

All efficacy analyses will be performed using the mITT Set unless otherwise specified.

5.8.1 Missing Data Handling

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

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

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

5.8.2 Primary Efficacy Endpoint

The primary efficacy endpoint is pain freedom which 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). The primary analysis will be based on data collected in the eDiary only. Additional data collected in the eCRF may be used for exploratory analysis.

5.8.2.1 Primary Estimand

Primary trial objective: To assess percentages of subjects with pain freedom at 2 hours post dose compared between treatment with 2, 5, 10, or 20 mg of elismetrep in comparison to placebo.

Estimand Scientific Question of Interest: What is the effect on pain freedom of assigning subjects to 2, 5, 10, or 20 mg of elismetrep, in comparison to placebo on treatment?

- Variable: report pain or no pain
- Analysis Set: Modified intent-to-treat set
- Analysis time point: 2 hours post dose
- Treatment: Average treatment effect of 2, 5, 10, or 20 mg of elismetrep relative to placebo
- Analysis methodology: Cochran-Mantel-Haenszel (CMH) test stratified by use of background prophylactic medications for migraine (yes/no)
- Intercurrent events: rescue medication taken at or before a data assessment at the time point of interest is considered an intercurrent event. The intercurrent event of rescue medication use will be handled using Rescue Medication = Failure, i.e, subjects who take rescue medications at or before 2 hours post dose are classified as failures.
- Missing data: Subjects with missing data at 2 hours post-dose will be classified as failures.

5.8.2.2 Primary Analysis

Subjects who meet both of the following criteria will be classified as responder with pain freedom:

- Pain level of none at 2 hours post-dose
- No intervening rescue medication taken at or before 2 hours post-dose, i.e., rescue medication start date/time missing or > eDiary finding date/time in the 2-hour post-dose date/time.

The percentages of subjects with pain freedom at 2 hours post-dose will be compared pairwise between each elismetrep treatment group (2, 5, 10, or 20 mg) and placebo using Cochran-Mantel-Haenszel (CMH) tests stratified by background prophylactic medications for migraine (yes/no). In this analysis, Non-Completer = Failure and intercurrent event of rescue medication = Failure will be applied.

Number of subjects with pain freedom, percentage of subjects with pain freedom for each treatment group, stratified percentage difference between each elismetrep and placebo, the corresponding 90% CI and the p-value will be provided.

5.8.2.3 All Observed Data Analysis

The only attributes that changes from the definition of the primary estimand is how the handling strategy is adopted for missing data. Subjects who have missing pain level at 2 hours post dose are excluded from analysis.

First, the intercurrent event of rescue medication = Failure method of handling intervening rescue medication use will be applied. Next, subjects with missing data at 2 hours post dose will be excluded. The same statistics as the primary analysis will be presented.

5.8.2.4 Multiple Imputation Analysis

The only attributes that changes from the definition of the primary estimand is how the handling strategy is adopted for missing data. Missing pain level data at 2 hours post dose will be imputed using the copy from reference multiple imputation approach 20 times.

The fully conditional specification (FCS) method is used with a generalized logit distribution. Covariates may include background prophylactic medications for migraine (yes/no), sex, pain level at the onset of qualifying migraine (moderate or severe), average number of headaches per month ($<$ median, $\geq$ median), and MBS at the onset of qualifying migraine (nausea, phonophobia, or photophobia).

First, the intercurrent event of rescue medication = Failure method of handling intervening rescue medication use will be applied. Next, missing data at 2 hours post-dose will be imputed for subjects who are not missing any of the covariates (subjects missing any of the covariates will be considered failures) for 20 times. Once imputations are made, 2 hours post-dose data (binary response) of each of the 20 complete datasets will be analyzed using CMH test. The SAS MIANALYZE procedure will be used to generate valid statistical inferences by combining results from the 20 analyses using Rubin's formula. An appropriate transformation (such as Wilson-Hilferty transformation) of CMH test statistics can be used in Rubin's formula (Ratitch et. al 2013).

The same statistics as the primary analysis will be presented.

5.8.2.5 Per-Protocol and Observed Analysis

The same analysis as section 5.8.2.2 will be repeated using Per-Protocol analysis set. As per-protocol analysis set consists of only subjects with 2-hour post dose assessments so non-complete=failure is not applicable in this analysis.

5.8.3 Secondary Efficacy Endpoints

The secondary efficacy endpoints are described in Section 2.2.2.

5.8.3.1 Freedom from the most bothersome symptom (MBS) at 2 hours post-dose

MBS freedom is defined as the MBS reported at the onset of qualifying migraine and being absent at a single time point post-dose. The same analysis described for the primary endpoint will be used to address the primary estimand.

5.8.3.2 Pain relief at 2 hours post-dose

Pain relief is defined as a pain level of none or mild at a single time point post-dose. Pain relief at each time point (30 min, 1 hour, 2 hours post-dose) will be analyzed in the same way as described for the primary endpoint in the primary estimand.

5.8.3.3 Freedom from Photophobia, Phonophobia, Nausea at 2 hours post-dose

Freedom from each symptom (nausea, phonophobia, photophobia) at 2 hours post-dose will be assessed separately.

Symptom freedom is defined as a symptom absent at a single time point post-dose for subjects with the symptom present at the onset of qualifying migraine. Thus, all analyses of symptom freedom will be based on mITT subjects with the symptom present at the onset of qualifying migraine), e.g., freedom from nausea at 2 hours post-dose time point will be based on subjects with nausea present at onset of qualifying migraine. Endpoints will be analyzed in the same way as described for the primary endpoint in the primary estimand.

5.8.3.4 Rescue medication use within 24-hour post-dose

Number and percentage of subjects that take rescue medication within 24 hours after administration of study medication will be displayed for each treatment group. Stratified percentage difference between each elismetrep and placebo, the corresponding 90% CI and the p-value based on Cochran-Mantel-Haenszel (CMH) test will be provided.

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.

5.8.3.5 Sustained pain freedom from 2 to 24 hours

Sustained pain freedom from 2 to 24 hours post-dose is defined as pain level of none at all time points from 2 to 24 hours post-dose (i.e 2, 3, 4, 6, 8 and 24 hours post-dose).
Subjects who meet all of the following criteria will be classified as responders of sustained pain freedom:

- Pain level is not missing and is reported as none at 2 hours and 24 hours post-dose
- Pain level is reported as none at all time points with non-missing data from 2 to 24 hours post-dose
- No intervening rescue medication taken at or before 24 hours post-dose

Sustained pain freedom from 2 to 24 hours outcomes will be summarized by treatment group as the number and percentage of subjects in the following categories:

- Responder: no pain at all time points from 2 to 24 hours post-dose, and no intervening rescue medication taken at or before 24 hours post-dose
- Failure
    - Rescue medication taken at or before 24 hours post-dose
    - Mild, moderate or severe pain at any time point from 2 to 24 hours post-dose
        - Severe Pain
        - Moderate Pain
        - Mild Pain
    - Missing pain level at 2 or 24 hours post-dose

Failure subcategories are mutually exclusive; subjects who meet more than one failure criterion will be classified according to the first failure criterion met; in case of ties, the first failure subcategory that is met in the hierarchy above will be chosen.
Treatment group comparisons of the percentage of subjects with sustained pain freedom from 2 to 24 hours post-dose will use analogous methods as the principal analysis of the primary endpoint of pain freedom.

5.8.3.6 Sustained pain relief from 2 to 24 hours

Sustained pain relief from 2 to 24 hours post-dose is defined as pain level of none or mild (pain score of 0 or 1) at all time points from 2 to 24 hours post-dose (i.e 2, 3, 4, 6, 8 and 24 hours post-dose).

Subjects who meet all of the following criteria will be classified as responders of sustained pain freedom:

- Pain level is not missing and reported as none or mild at 2 hours and 24 hours post-dose
- Pain level is reported as none or mild at all time points with non-missing data from 2 to 24 hours post-dose
- No intervening rescue medication taken at or before 24 hours post-dose

Sustained pain relief from 2 to 24 hours outcomes will be summarized by treatment group as the number and percentage of subjects in the following categories:

- Responder: no pain or mild pain at all time points from 2 to 24 hours post-dose, and no intervening rescue medication taken at or before 24 hours post-dose
- Failure
    - Rescue medication taken at or before 24 hours post-dose
    - Moderate or severe pain at any time point from 2 to 24 hours post-dose
        - Severe Pain
        - Moderate Pain
    - Missing pain level at 2 or 24 hours post-dose

Failure subcategories are mutually exclusive; subjects who meet more than one failure criterion will be classified according to the first failure criterion met; in case of ties, the first failure subcategory that is met in the hierarchy above will be chosen.

Treatment group comparisons of the percentage of subjects with sustained pain relief from 2 to 24 hours post-dose will use analogous methods as the principal analysis of the primary endpoint of pain freedom.

5.8.3.7 Sustained pain freedom from 2 to 48 hours

Sustained pain freedom from 2 to 48 hours post-dose is defined as pain level of none at all time points from 2 to 48 hours post-dose (i.e 2, 3, 4, 6, 8, 24 and 48 hours post-dose).

Subjects who meet all of the following criteria will be classified as responders of sustained pain freedom:

- Pain level is not missing and reported as none at 2 hours, 24 hours and 48 hours post-dose
- Pain level of none at all time points with non-missing data from 2 to 48 hours post-dose
- No intervening rescue medication taken at or before 48 hours post-dose

Sustained pain freedom from 2 to 48 hours outcomes will be summarized by treatment group as the number and percentage of subjects in the following categories:

- Responder: no pain at all time points from 2 to 48 hours post-dose, and no intervening rescue medication taken at or before 48 hours post-dose
- Failure
    - Rescue medication taken at or before 48 hours post-dose
    - Mild, moderate or severe pain at any time point from 2 to 48 hours post-dose
        - Severe Pain
        - Moderate Pain
        - Mild Pain
    - Missing pain level at 2 or 24 or 48 hours post-dose

Failure subcategories are mutually exclusive; subjects who meet more than one failure criterion will be classified according to the first failure criterion met; in case of ties, the first failure subcategory that is met in the hierarchy above will be chosen.

Treatment group comparisons of the percentage of subjects with sustained pain freedom from 2 to 48 hours post-dose will use analogous methods as the principal analysis of the primary endpoint of pain freedom.

5.8.3.8 Sustained pain relief from 2 to 48 hours

Sustained pain relief from 2 to 48 hours post-dose is defined as pain level of none or mild at all time points from 2 to 48 hours post-dose (i.e 2, 3, 4, 6, 8, 24 and 48 hours post-dose).

Subjects who meet all of the following criteria will be classified as responders of sustained pain freedom:

- Pain level is not missing and reported as none or mild at 2 hours, 24 hours and 48 hours post-dose

- Pain level of none or mild at all time points with non-missing data from 2 to 48 hours post-dose (i.e 2, 3, 4, 6, 8, 24 and 48 hours post-dose)
- No intervening rescue medication taken at or before 48 hours post-dose

Sustained pain relief from 2 to 48 hours outcomes will be summarized by treatment group as the number and percentage of subjects in the following categories:

- Responder: no pain or mild pain at all time points from 2 to 48 hours post-dose, and no intervening rescue medication taken at or before 24 hours post-dose
- Failure
    - Rescue medication taken at or before 48 hours post-dose
    - Moderate or severe pain at any time point from 2 to 48 hours post-dose
    - Missing pain level at 2 or 24 or 48 hours post-dose

Failure subcategories are mutually exclusive; subjects who meet more than one failure criterion will be classified according to the first failure criterion met; in case of ties, the first failure subcategory that is met in the hierarchy above will be chosen.

Treatment group comparisons of the percentage of subjects with sustained pain relief from 2 to 48 hours post-dose will use analogous methods as the principal analysis of the primary endpoint of pain freedom.

5.8.4 Subgroup Analyses

To assess the consistency in the treatment effect across different subgroups, subgroup analyses will be performed for the primary efficacy endpoint using same method as primary estimand without stratification, with respect to the following if sample sizes allow:

- Background prophylactic medications for migraine (yes/no)
- Gender (Male/Female)
- Migraine with or without aura

5.8.5 Exploratory Endpoints

The exploratory endpoints are described in Section 2.2.3.

5.8.5.1 Return to Normal Function at 2 Hours Post-Dose

Return to normal function is defined as a functional disability level of normal at a single time point post-dose for subjects with functional disability (mildly impaired, severely impaired, requires bedrest) at the onset of qualifying migraine. Return to normal function will be analyzed in the same way as described for the primary endpoint in the primary estimand.

5.8.5.2 Pain Relapse from 2 to 48 Hours Post-Dose

Pain relapse from 2 to 48 hours post-dose is defined as pain of mild, moderate, or severe at any time point post-dose after 2 hours post-dose for subjects with pain level of none at 2 hours post-dose. Thus, analyses of pain relapse will be based on mITT subjects with pain freedom at 2 hours post-dose (See Section 5.8.2.1).

Subjects who meet all of the following criteria will be classified as non-relapsers:

- Pain level of none at all time points with non-missing data after 2 hours post-dose (i.e 3, 4, 6, 8, 24 and 48 hours post-dose)
- No missing data at 24 or 48 hours post-dose
- No intervening rescue medication taken at or before 48 hours post-dose

Pain relapse from 2 to 48 hours outcomes will be summarized by treatment group as the number and percentage of subjects in the following categories:

- Non-relapser: as defined above
- Relapser
    - Rescue medication taken at or before 48 hours post-dose
    - Mild, moderate or severe pain at any time point after 2 hours post-dose
        - Severe Pain
        - Moderate Pain
        - Mild Pain
    - Missing pain level at 24, 48 hours post-dose

Relapser subcategories are mutually exclusive; subjects who meet more than one relapse criterion will be classified according to the first relapse criterion met; in case of ties, the first relapse subcategory that is met in the hierarchy above will be chosen.

Treatment group comparisons of the percentage of subjects with pain relapse from 2

to 48 hours post-dose will use analogous methods as the principal analysis of the primary endpoint of pain freedom.

5.9 Safety Analyses

The safety measurements include AEs, clinical laboratory assessments, vital signs, 12-lead ECG and physical examination. All summaries will be performed and reported by treatment group using the Safety Analysis Set.

No formal statistical tests or inference will be performed for safety analyses.

5.9.1 Adverse Events

An AE 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. All AEs will be recorded starting from the signing of informed consent form throughout the end of the follow-up or early study termination.

A TEAE is defined as an AE that starts or worsens after the time of dosing up to 168 hours or 7 days if start time of AE is not available after the dosing of study medication.

A SAE is defined as any untoward medical occurrence that:

- 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.

All AEs will be coded and classified using the version of the Medical Dictionary of Regulatory Activities (MedDRA) in affect at the start of the study. The severity/intensity of AE is assessed by the Investigator as mild, moderate or severe. The relationship to study drug is judged by the Investigator as related or not related.

Overall summary tables of TEAEs will be presented showing the number and percentages of subjects with any TEAEs, any study drug-related TEAEs, all SAE, TEAEs leading to study discontinuation.

The following AEs will be summarized by frequency and percentage of subjects by SOC (in alphabetical order) and PT (by decreasing frequency in overall elismetrep):

- TEAEs
- Study drug-related TEAEs
- SAEs if sufficient number of SAEs are reported

If the same AE (preferred term) is reported more than once for the same subject, it will be only counted once in the summary table.

The following by-subject listings will be provided:

- AEs
- SAEs

5.9.2 Clinical laboratory Assessments

The clinical laboratory parameters presented in Table 2 will be assessed at the specific times as outlined in the SOA (Table 1).

Observed values and change from baseline to end of treatment in the clinical laboratory parameters for hematology and clinical chemistry will be summarized by treatment group, using descriptive statistics.

In addition, hematology and clinical chemistry parameters that meet the Sponsor's pre-defined limits of change as presented in Table 3 from time of dosing up to 168 hours or 7 days if assessment time is not available after the dosing of study medication will be summarized by treatment group, using frequency and percentage.

Clinical laboratory test parameters for hematology, clinical chemistry and urinalysis along with the associated reference ranges will be listed for individual subjects; abnormal values will be flagged as high or low in the listings. Individual measurements of laboratory tests from hematology, chemistry, and urinalysis that meet the abnormal criteria will be categorized to and

listed by not clinical significant and clinical significant. Other clinical laboratory tests, such as, virus serology, drug screen, pregnancy, and follicle stimulating hormone (FSH) will be presented listings only.

Laboratory data will be summarized or listed in International System of Units (SI).

5.9.3 Vital Signs

Vital signs parameters include systolic and diastolic blood pressure, heart rate and temperature and are collected at the specified timepoints as outlined in the SOA (Table 1). Blood pressure and heart rate are measured in triplicate.

Descriptive statistics for observed values and the change from baseline in the vital sign parameters will be summarized and presented for each visit and time point by treatment group. For triplicate measurements, the average value will be summarized.

A by-subject listing for the vital signs results will be provided.

5.9.4 Twelve-Lead Electrocardiogram

A triplicate 12-lead ECG will be collected at all specified timepoints as outlined in the SOA (Table 1).

ECGs as interpreted by the Investigator to be within normal limits, abnormal but not clinically significant, or abnormal and clinically significant, will be listed.

A by-subject listing for the ECG results will be provided.

5.9.5 Physical Examination

Physical examination (PE) will include assessment of skin, head, ears, eyes, nose, throat, neck, thyroid, lungs, heart, cardiovascular, abdomen, lymph nodes, and musculoskeletal system/extremities, and will be performed at visits as indicated in the SOA (Table 1). Interim PEs will be performed at the discretion of the Investigator, if necessary, to evaluate AEs or clinical laboratory abnormalities.

The shift from baseline to post-baseline visit in the PE result (including normal; abnormal, not clinically significant; abnormal, clinically significant) by body system will be provided.

A by-subject listing for the results of physical examinations will be provided.

5.10 Timing of Analyses

A final analysis will be performed after all subjects complete the study and the database has been locked.

6. Multiplicity

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

7. Interim Analysis

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

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

8 Changes from Pre-specified Analyses in the Protocol

The SAP updates the missing data handling rules that deviate from the pre-specified analyses outlined in the protocol. Per the protocol, for sustained pain freedom, sustained pain relief (2 to 24 hours and 2 to 48 hours), and pain relapse (2 to 48 hours), subjects with missing data with >=1 missing data at more than one intermediate time point are to be classified as non-responders or relapsers. In the SAP, only missing data at the key time points (2, 24, or 48 hours) are considered when determining responder or relapser status, with missing intermediate time points no longer impacting classification.

This amendment of SAP updates definition of TEAE to an AE that starts or worsens after the time of dosing up to 7 days after the dosing of study medication while protocol defines TEAE as an AE that starts or worsens after the time of dosing up to 72 hours after the dosing of study medication.

9 Revision History

Version	Date	Description of Change and/or Rationale	Sections Affected

10 Programming Specifications and Considerations

The corresponding programming specifications for variables and programming validation will be provided in a separate document.

11 Table, Figure, and Listing (TFL) Shells

The corresponding TFL shells for this SAP will be provided in a separate document.

12 References

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Rubin DB. Multiple Imputation for Nonresponse in Surveys. New York, NY: John Wiley & Sons, Inc., 1987.

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APPENDIX 1 Schedule of Events

Table 1 Schedule of Events

SOA														
	Screening	**Randomization**	**Treatment Period by Hour**											**End of Treatment/ Early Withdrawal[g]**
Visit Number	**1**	**2**	**0**	**0.5**	**1**	**1.5**	**2**	**3**	**4**	**6**	**8**	**24**	**48**	**3**
Study Day	**-28**	**0**	**1**											**4-7[a]**
Visit Window (days)	**N/A**													
Administrative														
Informed Consent	X													
Inclusion/ Exclusion[b]	X	X												
Migraine History[c] & Medical History/ Demographics	X													
Prior/Concomitant Med	X	X	X											X

SOA														
	Screening	**Randomization**	**Treatment Period by Hour**											**End of Treatment/ Early Withdrawal[5]**
Visit Number	**1**	**2**	**0**	**0.5**	**1**	**1.5**	**2**	**3**	**4**	**6**	**8**	**24**	**48**	**3**
Study Day	**-28**	**0**	**1**											**4-7[a]**
Visit Window (days)	**N/A**													
Patient Training on Diary/Dispense Diary, instructions		X												
IWRS/Randomization		X												
Clinical Assessment														
Physical Examination	X	X												X
Height/weight	X													

Table 1: Schedule of Events (continued)

SOA														
	Screening	**Randomization**	**Treatment Period by Hour**											**End of Treatment / Early Withdrawal[g]**
Visit Number	**1**	**2**	**0**	**0.5**	**1**	**1.5**	**2**	**3**	**4**	**6**	**8**	**24**	**48**	**3**
Study Day	**-28**		**1**											**4-7**
Visit Window (days)	**N/A**		**0**											
Heart Rate/Blood Pressure	X	X												X
Respiratory Rate/Temperature	X													X
Triplicate 12-lead ECG	X													
C-SSRS[d]	X	X												X
Laboratory and Safety Assessments														
General Safety Labs: chemistry,	X	X												X

SOA														
	Screening	**Randomization**	**Treatment Period by Hour**											**End of Treatment / Early Withdrawal[g]**
Visit Number	**1**	**2**	**0**	**0.5**	**1**	**1.5**	**2**	**3**	**4**	**6**	**8**	**24**	**48**	**3**
Study Day	**-28**		**1**											**4-7**
Visit Window (days)	**N/A**		**0**											
hematology, urinalysis [e,]														
Urine Drug Screen	X													

Table 1: Schedule of Events (continued)

SOA														
	Screening	**Randomization**	**Treatment Period by Hour**											**End of Treatment/ Early Withdrawal[g]**
Visit Number	**1**	**2**	**0**	**0.5**	**1**	**1.5**	**2**	**3**	**4**	**6**	**8**	**24**	**48**	**3**
Study Day			**1**											**4-7**
Visit Window (days)	**N/A**													
Hepatitis Screen	X													
hCG Pregnancy Test/FSH Test[f]	X (serum)	X (urine)												X (serum)
AE Monitoring	X	X	X											X[h]
Study Drug Administration and Compliance														
Study Drug Dispensing		X												
Thermometer and instruction card dispensing		X												
Drug Compliance Check														X

SOA														
	Screening	**Randomization**	**Treatment Period by Hour**											**End of Treatment/ Early Withdrawal[g]**
Visit Number	**1**	**2**	**0**	**0.5**	**1**	**1.5**	**2**	**3**	**4**	**6**	**8**	**24**	**48**	**3**
Study Day			**1**											**4-7**
Visit Window (days)	**N/A**													
Review use of rescue medication[i]														X
Patient doses with study medication			X											
Return study medication[g]														X

Table 1: Schedule of Events (continued)

	Screening	Randomization	Treatment Period by Hour										End of Treatment/Early Withdrawal[g]
Visit Number	**1**	**2**	**0**	**0.5**	**1.0**	**1.5**	**2.0**	**3**	**4**	**6**	**8**	**24**	**48**	**3**
Study Day			**1**											**4-7**
Visit Window (days)	**N/A**													
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	

[a] Day is relative to dosing day. Dosing Day is Day 1. Subjects should return for V3 between Day 4 and Day 7 and not sooner than 72 h post dose.

[b] 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.

[c] Migraine history is to be collected by obtaining documentation of subject's medical history from relevant treating physician and investigator should verify patient meets diagnostic and entry criteria related to migraine.

[d] The "Baseline C-SSRS" should be completed at Visit 1. The "Since Last Visit C-SSRS" should be completed at Visits 2 and 3.

[e] Urinalysis at Screening only. Safety labs need not be in fasted state.

[f] Serum hCG at screening (V1) and End of Treatment (V3); urine hCG at randomization visit (V2). FSH test at screening only for females of non-childbearing potential due to menopause. If screening FSH test is not consistent with menopausal status, subjects may return for a serum pregnancy test and participate under requirements for females of child-bearing potential (contraception and pregnancy testing).

[g] All subjects should attend the EoT/withdrawal visit. For subjects who did not take study medication, EoT/Withdrawal visit activities will consist only of return of study medication, collection of con-meds, collection of AEs (could be remote visit if study medication returned by mail). For patients who took study medication, all assessments listed in the SOA should be performed.

[h] Follow up of AEs ongoing at V3 is described in Section 14.6.5

[i] Use of rescue medication (Y/N) in the eDiary will be reviewed. Record details of rescue medication taken in source documents and data enter onto Rescue Medication CRF

Abbreviations: C-SSRS= Columbia Suicide Severity Rating Scale, FSH= follicle stimulating hormone, hCG = human chorionic gonadotropin

APPENDIX 2 Clinical Laboratory Assessments

Table 2: Protocol-Required Laboratory Assessments

Hematology	
White blood cell (WBC) count[a]	Hemoglobin
Red blood cell (RBC) count[b]	Hematocrit
Platelet count	
Clinical Chemistry	
Alanine aminotransferase (ALT)	Phosphorus
Albumin	Potassium
Alkaline phosphatase (ALP)	Sodium
Aspartate aminotransferase (AST)	Total bilirubin
Bicarbonate	Direct bilirubin
Chloride	Total Protein
Creatinine	Urea
Calcium	Gamma-glutamyl transferase (GGT)
Glucose	Magnesium
	Calculated eGFR (MDRD)
Urinalysis	
Dipstick:	Microscopic:
Nitrite	WBC
Protein	RBC
Glucose	Epithelial cells
pH	Casts (specify)
Specific gravity	
Ketones	

Bilirubin	
Urobilinogen	
Leucocyte Esterase	
Blood	

[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).