Title:

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

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Statistical Analysis Plan

Protocol No. K-645-P003-00, 03 June 2025

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

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Table of Contents

Table of Contents 4
List of Tables 6
Glossary and Abbreviations 7
1 Introduction 10
2 Study Objectives and Endpoints 11
2.1 Study Objectives 11
2.1.1 Primary Objective 11
2.1.2 Secondary Objectives 11
2.1.3 Exploratory Objectives 11
2.2 Study Endpoints 12
2.2.1 Primary Endpoints 12
2.2.2 Secondary Endpoints 12
2.2.3 Exploratory Endpoints 13
3 Study Design 14
3.1 Overall Study Design 14
3.2 Randomization 16
3.3 Blinding and Unblinding 17
3.3.1 Unblinded Personnel and /or Procedures 17
3.4 Sample Size Justification 20
4 Analysis Sets 20
4.1 Enrolled Set 20
4.2 Randomized Set 20
4.3 Modified Intent-to-Treat (mITT) Analysis Set 20
4.4 Per-Protocol (PP) Analysis Set 21
4.5 Safety Analysis Set 21
5 Statistical Methods 21
5.1 General Considerations 21
5.1.1 Data Summary 21
5.1.2 Baseline 22
5.1.3 Study Day 22
5.1.4 Unscheduled Visits 22
5.1.5 Handling of Missing or Incomplete Data 23
5.2 Subject Disposition 24
5.3 Protocol Deviations 25
5.4 Demographics and Baseline Disease Characteristics 25
5.4.1 Demographics 25

5.4.2 Migraine Characteristics at Onset of Qualifying Migraine....26
5.5 Medical History....26
5.5.1 Migraine Disease History....26
5.5.2 General Medical History....27
5.6 Prior and Concomitant Therapies....27
5.6.1 Prior and Concomitant Medications....27
5.6.2 History of Resistance to Migraine Medications....28
5.7 Treatment Exposure and Compliance....28
5.7.1 Treatment Exposure....28
5.7.2 Treatment Compliance....28
5.8 Efficacy Analyses....29
5.8.1 Missing Data Handling....29
5.8.2 Primary Efficacy Endpoint....29
5.8.3 Secondary Efficacy Endpoints....32
5.8.4 Subgroup Analyses....32
5.8.5 Exploratory Endpoints....33
5.9 Safety Analyses....38
5.9.1 Adverse Events....38
5.9.2 Clinical laboratory Assessments....39
5.9.3 Vital Signs....40
5.9.4 Twelve-Lead Electrocardiogram....40
5.9.5 Physical Examination....41
5.9.6 Columbia Suicidality Severity Rating Scale (C-SSRS)....41
5.10 Timing of Analyses....41
8 Changes from Pre-specified Analyses in the Protocol....42
6 Revision History....43
7 Programming Specifications and Considerations....44
8 Table, Figure, and Listing (TFL) Shells....45
9 References....46
APPENDIX 1 Schedule of Events....47
APPANDIX 2 Clinical Laboratory Assessments....51

List of Tables

Table 1: Study Schedule of Events 47
Table 2: Subject Treatment Period Schedule of eDiary Assessments by Hour 50
Table 3: Protocol-Required Laboratory Assessments 51
Table 4: Pre-Defined Limits of Change for Laboratory Parameters 53

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
LOCF	last observation carried forward
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

Abbreviation	Term
ULOQ	upper limit of quantification
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 K-645-P003-00 dated June 03, 2025 (A Phase IIa, Multicenter, Randomized, Double-Blind, Placebo-Controlled Crossover Study of K-645 in the Treatment of Multiple Migraine Attacks). 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 K-645 100 mg 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 K-645 100 mg compared to placebo on freedom from the most bothersome symptom (MBS), associated with migraine, at two hours post-dose.
- To evaluate the efficacy of K-645 100 mg compared to placebo on pain relief at 2 hours post-dose.
- To evaluate the safety and tolerability of K-645 100 mg and 10 mg in the treatment of acute migraine.

2.1.3 Exploratory Objectives

The study exploratory objectives are:

- To evaluate the efficacy of K-645 100 mg compared to placebo on freedom from photophobia at 2 hours post-dose.
- To evaluate the efficacy of K-645 100 mg compared to placebo on freedom from phonophobia at 2 hours post-dose.
- To evaluate the efficacy of K-645 100 mg compared to placebo on freedom from nausea at 2 hours post-dose.
- 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.
- To evaluate the efficacy of K-645 100 mg compared to placebo on sustained pain freedom from 2 to 24 hours post-dose.

- To evaluate the efficacy of K-645 100 mg compared to placebo on sustained pain relief from 2 to 24 hours post-dose.
- To evaluate the efficacy of K-645 100 mg compared to placebo on sustained pain freedom from 2 to 48 hours post-dose.
- To evaluate the efficacy of K-645 100 mg compared to placebo on sustained pain relief from 2 to 48 hours post-dose.
- 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.
- 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.
- To evaluate the efficacy of K-645 10 mg compared to placebo in the above primary, secondary, and exploratory objectives.

2.2 Study Endpoints

2.2.1 Primary Endpoints

The study primary endpoint is pain freedom at 2 hours post-dose. 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.

2.2.3 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 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.
- 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.

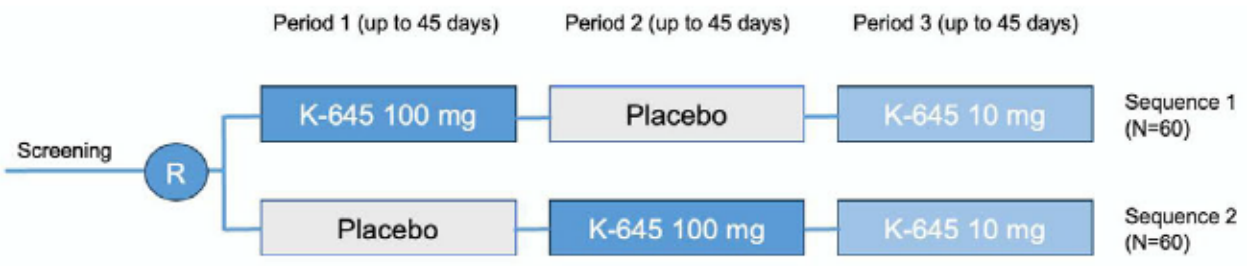
- Pain relapse will be assessed using the proportion of subjects with pain freedom at 2hrs who (a) have mild, moderate, or severe pain (response of 1, 2 or 3 on the 4-point scale) at any time point after 2 hours post-dose; (b) have missing pain data at 24 or 48 hours time point after 2 hours post-dose; (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, 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 1.

Figure 1: 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 in protocol.

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 1), 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

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.

The schedule of assessments are shown in Table 1. Schedule of eDiary assessments are shown in Table 2.

3.2 Randomization

Signant Health (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 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. Participants who meet all criteria for enrollment will be assigned a randomization number and randomized at Visit 2. The randomization number encodes the subject assignment to either of the treatment sequence 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 1:1 ratio to one of the following treatment sequence: placebo, K-645 100 mg, K-645 10 mg or K-645 100 mg, placebo, K-645 10 mg.

3.3 Blinding and Unblinding

This is a double-blind (Period 1 and 2) study where the Sponsor, relevant sponsor vendor designees and consultants, site staff, and study participants will be blinded to the treatment assignment. Due to the fixed sequence of the 10mg dose of K-645, Period 3 will be single-blind (participants will be blinded).

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 the 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

[redacted]

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).





[redacted]

3.4 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.

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 of each period consist of randomized subjects that take study therapy, have a qualifying migraine (as defined in Section 3.1) 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) for that specific period. The mITT analysis set will be used for demographic, baseline characteristic and efficacy analysis. Subjects are analyzed as randomized.

4.4 Per-Protocol (PP) Analysis Set

The PP analysis set consist of all mITT subjects and provided baseline and 2-hour pain assessment in ePRO 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 for selected efficacy analyses.

4.5 Safety Analysis Set

The Safety Analysis Set of each period consists of all randomized participants who took the study medication at that specific period. 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, K-645 100 mg, K-645 10 mg) and/or overall K-645, 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 of each treatment period for all efficacy endpoints. For laboratory data, vital sign and 12-lead electrocardiogram, baseline is defined as last available observation prior to first dose during study.

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 during the study. Day 1 is defined as the day of the first dose of study drug in study. 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 sequence and overall:

- Participants who were randomized
- Participants did not take the study drug in period 1
- Participants took the study drug in period 1
    - For qualifying migraine (Confirmed by ePRO)
    - Not for qualifying migraine
- Participants did not take the study drug in period 2
- Participants took the study drug in period 2
    - For qualifying migraine (Confirmed by ePRO)
    - Not for qualifying migraine
- Participants did not take the study drug in period 3
- Participants took the study drug in period 3
    - For qualifying migraine (Confirmed by ePRO)
    - Not for qualifying migraine
- Participants who completed the study (requires completion of Visit 5 'end of treatment' regardless of whether subject had any qualifying migraines or took all study drug or not).
- Participants who prematurely discontinued the study
- The primary reasons for premature discontinuation from study

Subject disposition will be listed for all randomized 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 sequence and treatment period, 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 sequence and treatment group 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):

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

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 by treatment group:

- 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 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
- Time since diagnosis (years): 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 sequence and treatment group 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 by treatment sequence and treatment group. 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.

Prior medications will be summarized by treatment sequence and treatment group.

Concomitant medications will be further break down by treatment period and summarized by treatment group.

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 by treatment sequence and treatment group. 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 by as-randomized treatment group for safety set .

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

- Study drug taken by mistake (i.e. no qualifying migraine)
- Study drug actually received dsifferent from randomized treatment assignment

5.7.2 Treatment Compliance

Number and percent of subjects with and without administering full dose will be summarized by treatment group in the safety set.

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 by treatment group 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:

- Endpoints based on one timepoint: If data is missing at the timepoint of interest, the response at that timepoint will be imputed by Last Observation Carried Forward (LOCF) method using post-dose assessment values. 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).
- Endpoints based on more than 1 timepoints: 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.

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 100 mg of K-645 in comparison to placebo.

Estimand Scientific Question of Interest: What is the effect on pain freedom of assigning subjects to 100 mg of K-645, 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 100 mg relative to placebo
- Analysis methodology: 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).
- 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 imputed by LOCF using post-dose assessment values.

5.8.2.2 Primary Analysis

5.8.2.2.1 Primary Analysis using eDiary Data

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 in K645 100mg and Placebo groups with pain freedom at 2 hours post-dose will be compared using logistic regression with treatment group, treatment period, and the use of background prophylactic medications for migraine (yes/no) as covariates. In this analysis, intercurrent event of rescue medication = Failure and LOCF imputation will be applied.

In addition, as an exploratory analysis, the percentages of subjects in K645 10mg with pain freedom at 2 hours post-dose will also be compared with placebo using logistic regression with treatment group, and the use of background prophylactic medications for migraine (yes/no) as covariates.

Number of subjects with pain freedom, percentage of subjects with pain freedom for each treatment group, odds ratio and risk difference between K-645 100mg,10mg and placebo, the corresponding 90% CI and one-sided p-value will be provided.

5.8.2.2.2 Supportive Analysis

The only attributes that changes from the primary estimand is that both eDairy data and data collected in eCRF will be used in analysis.

5.8.2.3 Sensitivity Analysis

5.8.2.3.1 Missing as Failure 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 considered as non-responder.

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 categorized as non-responder. The same statistics as the primary analysis will be presented.

5.8.2.3.2 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.

5.8.2.3.3 Per-Protocol Analysis

The same analysis as section 5.8.2.2.1 will be repeated using Per-Protocol analysis set. As per-protocol analysis set consists of only subjects with 2-hour post dose assessments so missing data imputation 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 primary, supportive and sensitivity analyses described for the primary endpoint will be used to address the secondary endpoint.

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.

5.8.4 Subgroup Analyses

To assess the consistency in the treatment effect across different subgroups, subgroup analyses will be performed for the primary and key secondary 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
- Triptan resistance (yes/no)

5.8.5 Exploratory Endpoints

The exploratory endpoints are described in Section 2.2.3.

5.8.5.1 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.

5.8.5.2 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. Odds ratio between each K-645 100mg, 10mg and placebo, the corresponding 90% CI and the p-value based on logistic regression 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.

5.8.5.3 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.

5.8.5.4 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.

5.8.5.5 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.

5.8.5.6 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.

5.8.5.7 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.

5.8.5.8 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) after the dosing of study medication and before next dosing in each treatment period. If time is not available for an AE, TEAE is defined as an AE that starts or worsens after the time of dosing up to 7 days after the dosing date of study medication and before next dosing date in each treatment period.

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 effect 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 100mg K-645):

- 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 3 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 done after the time of dosing up to 7 days after last dosing of study medication that meet the Sponsor's pre-defined limits of change as presented in Table 4 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 conventional units.

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.

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

5.9.6 Columbia Suicidality Severity Rating Scale (C-SSRS)

The C-SSRS will be performed at visits as indicated in the SOA (Table 1). 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.

A by-subject listing for the results of C-SSRS 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 K-645 100mg 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 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 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.

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 primary estimand and analysis of secondary endpoints, subjects with missing data will be classified as non-responder. In the SAP, missing data will be imputed using LOCF method first. Missing as non-responder imputation will be used as sensitivity analysis for selected primary and secondary endpoints.

6 Revision History

Version	Date	Description of Change and/or Rationale	Sections Affected

7 Programming Specifications and Considerations

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

8 Table, Figure, and Listing (TFL) Shells

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

9 References

ICH. 1998 Statistical principles for clinical trials, E9. International Council for Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use. https://database.ich.org/sites/default/files/E9_Guideline.pdf. Published 1998

APPENDIX 1 Schedule of Events

Table 1: Study Schedule of Events

SOA								
	Screening	Treatment Phase						
	Screening	Randomization	Treatment Period 1	EoP1 [i]	Treatment Period 2	EoP2[i]	Treatment Period 3	EoP3[i] EoT (ET Visit) [g]
Visit Number and Day Range	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						
Medical & Migraine Hx	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/weight	X	X		X		X		X

HR/BP	X	X		X		X		X
Respiratory Rate/Temperature	X	X		X		X		X
Triplicate 12-lead ECG	X							X
C-SSRS[d]	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
Laboratory and Safety Assessments								
General Safety Labs: chemistry, hematology, [e]	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[f]	X	X		X		X		X
AE Monitoring	X	X	X	X	X	X	X	X
Menstrual cycle history (premenopausal subjects only)[h]		X		X		X		X
Review & Record rescue medication				X		X		X
Study Drug Administration and Accountability								

IWR Study Drug Dispensing		X		X		X		
Drug Compliance and Accountability				X		X		X

[a] 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.

[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 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.

[d] The "Baseline C-SSRS" should be completed at Visit 1. The "Since Last Visit C-SSRS" should be completed at subsequent visits.

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

[f] 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).

[g] 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.

[h]. Complete menstrual history CRF.

[i] 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.

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

Table 2: 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

APPANDIX 2 Clinical Laboratory Assessments

Table 3: 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).

Table 4: Pre-Defined Limits of Change for Laboratory Parameters

Hematology	
Hemoglobin (g/dL)	1. Decrease ≥ 1.5 g/dL 2. Increase > 2.0 g/dL 3. Increase > 2.0 g/dL and value > ULN Both criteria 2 and 3 will be flagged.
WBC count (10^3/microL)	1. Decrease ≥50% and value < LLN 2. Increase ≥20% and value > ULN
Neutrophil count(10^3/microL)	1. Decrease ≥20% and value < LLN 2. Increase ≥20% and value > ULN
Lymphocyte count (10^3/microL)	1. Decrease ≥20% and value < LLN 2. Increase ≥20% and value > ULN
Platelet count (10^3/microL)	1. Decrease ≥25% and value < LLN 2. Increase ≥100% and value > ULN
Clinical Chemistry	
BUN mg/dL	Increase ≥ 50% and value > ULN
Total bilirubin mg/dL	Value > 2x ULN
AST (IU/L)	Value ≥ 3x ULN Value > 5x ULN Value > 10 x ULN Value > 20x ULN
ALT (IU/L)	Value ≥ 3x ULN Value > 5x ULN Value > 10 x ULN Value > 20x ULN
AST or ALT (IU/L)	Value ≥ 3x ULN Value > 5x ULN Value > 10 x ULN Value > 20x ULN
AST or ALT (IU/L) + Total bilirubin (mg/dL)	AST or ALT ≥3x ULN with concurrent bilirubin > 2x ULN
Alkaline phosphatase (IU/L)	Value > 1.5x ULN
Sodium (mmol/L)	1. Decrease ≥ 10 and value <LLN 2. Increase ≥ 10 and value >ULN 3. Value > 155

Potassium (mmol/L)	1. Decrease ≥ 1 and value <LLN 2. Increase ≥ 1 and value >ULN 3. Value > 5.4 and increased 15% above baseline 4. Value ≥ 6.0
Calcium (mg/dL)	1. Increase≥ 1 and value > ULN 2. Decrease≥ 1 and value < LLN
Magnesium (mg/dL)	1. Increase≥ 1 and value > ULN 2. Decrease≥ 1 and value < LLN

