Statistical Analysis Plan for Study 3110-304-002

A Phase 3, Multicenter, Randomized, Double-blind, Placebo-controlled, Crossover Study to Evaluate the Efficacy, Safety, and Tolerability of Oral Ubrogepant in the Acute Treatment of Migraine When Administered During the Prodrome

Date: 10 May 2022

Version 3.0

Table of Contents

List of Tables

List of Figures

List of Appendices

1.0 Introduction

This Statistical Analysis Plan (SAP) provides a technical and detailed elaboration of the statistical analyses of the efficacy and safety data as outlined and specified in the protocol of Study 3110-304-002. Study 3110-304-002 examines the efficacy, safety, and tolerability of ubrogepant in the acute treatment of migraine when administered during the prodrome. Specifications of tables, figures and data listings are contained in a separate document. The pharmacokinetics (PK) analyses will be described in a separate plan.

In general, statistical analyses will be performed using SAS version 9.4 (SAS Institute Inc., Cary, NC 27513) or higher.

2.0 Study Design and Objectives

2.1 Objectives and Endpoints

The overall study objective is to evaluate the efficacy, safety, and tolerability of ubrogepant 100 mg compared to placebo for the acute treatment of migraine when administered during the prodrome.

Table 1 provides primary, secondary, additional efficacy and additional health economics outcomes research (HEOR) objectives, safety objective and corresponding endpoints.

Table 1. Objectives and Endpoints

Objectives	Endpoints
Primary Efficacy	
To evaluate the effect of a single dose of ubrogepant (100 mg) versus placebo, administered during the prodrome, on attenuation of the headache phase	Absence of a headache of moderate/severe intensity within 24 hours after taking double-blind study intervention during the prodrome
Secondary Efficacy	
1: To evaluate the effect of a single dose of ubrogepant (100 mg) versus placebo, administered during the prodrome, on prevention of the headache phase	Absence of a headache of moderate/severe intensity within 48 hours after taking double-blind study intervention during the prodrome

Objectives	Endpoints
2: To evaluate the effect of a single dose of ubrogepant (100 mg) versus placebo, administered during the prodrome, on attenuation of the headache phase	Ability to function normally over 24 hours after taking double-blind study intervention during the prodrome
3: To evaluate the effect of a single dose of ubrogepant (100 mg) versus placebo, administered during the prodrome, on ability to function normally	Absence of a headache of any intensity within 24 hours after taking double-blind study intervention during the prodrome
Additional Efficacy	
To evaluate the effect of a single dose of ubrogepant (100 mg) versus placebo, administered during the prodrome, on attenuation of the headache phase.	• Absence of a headache of any intensity by timepoint (excluding the endpoints that are already captured as primary and secondary endpoints) • Absence of moderate/severe headache by timepoint (excluding the endpoints that are already captured as primary and secondary endpoints) • Absence of severe headache by timepoint • Time to development of headache of any intensity within 48 hours after taking double-blind study intervention during the prodrome (Kaplan-Meier analysis) • Time to development of headache of moderate/severe intensity within 48 hours after taking double-blind study intervention during the prodrome (Kaplan-Meier analysis) • Time to development of headache of severe intensity within 48 hours after taking double-blind study intervention during the prodrome (Kaplan-Meier analysis)

Objectives	Endpoints
To evaluate the effect of a single dose of ubrogepant (100 mg) versus placebo, administered during the prodrome, on prodrome symptoms, nonheadache migraine symptoms (photophobia, phonophobia, nausea, and dizziness), and aura	For each of the 5 most common individual prodrome symptoms • Absence of any intensity at each timepoint • Absence of moderate/severe intensity at each timepoint • Absence of severe intensity at each timepoint • Time to absence of any intensity After a headache of any intensity is reported: • Absence of nonheadache migraine symptoms (photophobia, phonophobia, nausea, dizziness) of any intensity at each timepoint • Absence of nonheadache migraine symptoms (photophobia, phonophobia, nausea, dizziness) of moderate/severe intensity at each timepoint • Absence of nonheadache migraine symptoms (photophobia, phonophobia, nausea, dizziness) of severe intensity at each timepoint Other: • Absence of aura at each timepoint
To evaluate the effect of a single dose of ubrogepant (100 mg) versus placebo on use of rescue medication	• Rescue medication use within 24 and 48 hours after taking double-blind study intervention • Time to rescue medication use within 48 hours after taking double-blind study intervention (Kaplan-Meier curve analysis)
Additional HEOR	
To evaluate the effect of a single dose of ubrogepant (100 mg) versus placebo, administered during the prodrome, on satisfaction with study medication	Satisfaction with study medication at 8 and 24 hours after taking double-blind study intervention during the prodrome
To evaluate the effect of a single dose of ubrogepant (100 mg) versus placebo, administered during the prodrome, on Activity Limitation	Activity Limitation over 24 hours after taking double-blind study intervention during the prodrome

Objectives	Endpoints
Safety	
To evaluate the safety of ubrogepant versus placebo in participants with migraine	Adverse events (AEs), clinical laboratory tests, electrocardiograms (ECGs), vital signs, and the Columbia-Suicide Severity Rating Scale (C-SSRS)

2.2 Study Design Overview

This is a Phase 3, multicenter, randomized, double-blind, placebo-controlled, crossover study to compare the efficacy, safety, and tolerability of ubrogepant 100 mg to placebo in the acute treatment of migraine when administered during the prodrome.

To be eligible for study participation, participants must be 18 to 75 years of age (inclusive) at Visit 1 (screening), have at least a 1-year history of migraine with or without aura consistent with a diagnosis according to the International Classification of Headache Disorders criteria, 3rd edition[1], and experience 2 to 8 migraine attacks with moderate to severe headache per month by history in each of the 3 months prior to the Screening Visit (Visit 1). Participants must be able to identify their prodrome symptom(s) and demonstrate that they reliably experience headache after experiencing prodrome symptom(s).

The study includes a 60-day screening period (between Visit 1 and Visit 2) during which participants will demonstrate that they reliably develop headache after experiencing qualifying prodrome events. After meeting eligibility criteria, participants will be randomized at Visit 2 and dispensed study intervention to treat their first qualifying prodrome event. Four days after taking double-blind study intervention for their first qualifying prodrome event, participants will have Visit 3 at which time study intervention will be provided to treat a second qualifying prodrome event. Visit 4 will occur 4 days after taking double-blind study intervention for their second qualifying prodrome event. In summary, participants will have up to 60 days (double-blind treatment period between Visit 2 and Visit 4) to treat a total of 2 qualifying prodrome events with study intervention. Participants unable to treat 2 qualifying prodrome events during the double-blind treatment period will be discontinued from the study.

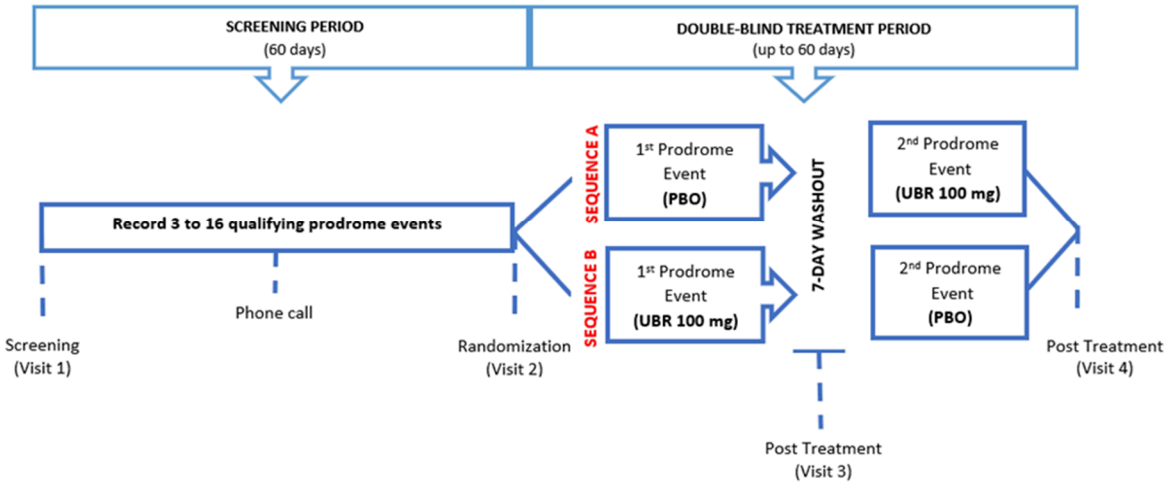
This is a crossover treatment study with 2 sequences of that participants and investigators are blinded.

Approximately 516 eligible participants will be randomized (1:1) to treatment sequences A or B in this crossover study. Participants randomized to Treatment Sequence A will receive placebo to treat their first qualifying prodrome event and ubrogepant 100 mg to treat their second qualifying prodrome event. For those randomized to Treatment Sequence B, they will receive the reverse: ubrogepant 100 mg to treat their first qualifying prodrome event and placebo to treat their second qualifying prodrome event.

No interim analysis of unblinded data is planned for this study.

The schematic of the study is shown in Figure 1.

Figure 1. Study Schematic



2.3 Treatment Assignment and Blinding

Subjects will be randomized to the following treatment sequences in a 1:1 ratio:

	First Qualifying Prodrome Event	Second Qualifying Prodrome Event
Treatment Sequence A	placebo	ubrogepant 100 mg
Treatment Sequence B	ubrogepant 100 mg	placebo

Participants randomized to Treatment Sequence A will receive placebo to treat their first qualifying prodrome event and ubrogepant 100 mg to treat their second qualifying prodrome event. For those randomized to Treatment Sequence B, they will receive the reverse: ubrogepant 100 mg to treat their first qualifying prodrome event and placebo to treat their second qualifying prodrome event.

Each blister card containing study intervention will be labeled with medication kit numbers. An automated Interactive Web-Response System (IWRS) will provide the site with the specific medication kit number(s) for each randomized participant at the time of randomization (Visit 2) and at Visit 3. Sites will dispense study intervention according to the IWRS instructions at these 2 visits. Sites will receive the IWRS confirmation notifications for each transaction. All notifications are to be maintained with the study source documents.

All study interventions will be provided in identical blister cards to maintain masking of the study. Tablets of ubrogepant 50 mg and placebo will be identical in appearance.

2.4 Sample Size Determination

The primary efficacy parameter is the absence of a headache of moderate/severe intensity within 24 hours after taking double-blind study intervention during the prodrome. The original sample size of 600 participants randomized is based on the assumption of a response rate of 64% for the placebo group and 80% for the ubrogepant 100 mg group, 240 participants in each study intervention will provide at least 95% power to detect the above intervention difference at the two-sided 5% significance level. The nQuery

Advisor 7.0 was used for the power calculation. Assuming 20% of randomized participants will not experience a qualified prodrome event during the double-blind treatment period, 300 participants will be randomized to each treatment sequence.

A blinded sample size re-estimation has been performed as planned. Given that only 7% of participants, rather than the 20% originally assumed, had no determinable primary endpoint as observed based on the data cut of July 05, 2021, it was re-estimated that approximately 516 participants will need to be randomized to maintain the effective sample size of 480 participants.

The actual power will be higher with the crossover design as some participants will contribute 2 qualifying prodrome events during the double-blind treatment period.

3.0 Endpoints

3.1 Primary Endpoint

The primary efficacy endpoint is the absence of a headache of moderate or severe (moderate/severe) intensity within 24 hours after taking double-blind study intervention during the prodrome.

3.2 Secondary Endpoints

Three secondary endpoints evaluate the efficacy of ubrogepant 100 mg to prevent and attenuate the headache phase, and to assess the ability to function normally within 24 hours after taking double-blind study intervention during the prodrome:

- Absence of a headache of moderate/severe intensity within 48 hours after taking double-blind study intervention during the prodrome.
- Ability to function normally within 24 hours after taking double-blind study intervention during the prodrome.
- Absence of a headache of any intensity within 24 hours after taking double-blind study intervention during the prodrome.

3.3 Other Efficacy Endpoints

Additional efficacy endpoints along with their respective clinical objectives are listed below in bullets in respect of the purposes.

To evaluate the effect of a single dose of ubrogepant (100 mg) versus placebo, administered during the prodrome, on attenuation of the headache phase:

- Absence of headache of any intensity by timepoint (1, 2, 3, 4, 6, 8, 48 hours postdose)
- Absence of moderate/severe headache by timepoint (1, 2, 3, 4, 6, 8 hours postdose)
- Absence of severe headache by timepoint (1, 2, 3, 4, 6, 8, 24, 48 hours postdose)
- Time to development of headache of any intensity within 48 hours after taking double-blind study intervention during the prodrome (Kaplan-Meier analysis)
- Time to development of headache of moderate/severe intensity within 48 hours after taking double-blind study intervention during the prodrome (Kaplan-Meier analysis)
- Time to development of headache of severe intensity within 48 hours after taking double-blind study intervention during the prodrome (Kaplan-Meier analysis)

To evaluate the effect of a single dose of ubrogepant (100 mg) versus placebo, administered during the prodrome, on prodrome symptoms, nonheadache migraine symptoms (photophobia, phonophobia, nausea, and dizziness), and aura:

- For each of the 5 most common individual prodrome symptoms:
  - Absence of any intensity at each timepoint
  - Absence of moderate/severe intensity at each timepoint
  - Absence of severe intensity at each timepoint
  - Time to absence of any intensity
- After a headache of any intensity is reported:

  - Absence of nonheadache migraine symptoms (photophobia, phonophobia, nausea, dizziness) at each timepoint
  - Absence of nonheadache migraine symptoms (photophobia, phonophobia, nausea, dizziness) of moderate/severe intensity at each timepoint
  - Absence of nonheadache migraine symptoms (photophobia, phonophobia, nausea, dizziness) of severe at each timepoint
- Absence of aura at each timepoint

To evaluate the effect of a single dose of ubrogepant (100 mg) versus placebo on use of rescue medication:

- Rescue medication use within 24 and 48 hours after taking double-blind study intervention
- Time to rescue medication use within 48 hours after taking double-blind study intervention (Kaplan-Meier analysis)

3.4 Safety Endpoints

The safety parameters include AEs, clinical laboratory, ECG, vital signs, physical examinations, and C-SSRS. For clinical laboratory, vital signs, and ECG parameters, the last non-missing safety assessment before the first dose of double-blind study intervention will be used as the baseline for all analyses of that safety parameter.

3.5 Additional HEOR Endpoint(s)

To evaluate the effect of a single dose of ubrogepant (100 mg) versus placebo, administered during the prodrome, on satisfaction and Activity Limitation:

- Satisfaction with study medication at 8 and 24 hours after taking double-blind study intervention during the prodrome
- Activity Limitation within 24 hours after taking double-blind study intervention during the prodrome.

4.0 Analysis Populations

The analysis populations will consist of participants as defined below:

Table 2. Analysis Populations

Population	Definition	Study Intervention
Intent-to-treat (ITT)	All randomized participants. Participants will be summarized according to the randomized study sequence intervention.	Randomized
Safety	All treated participants who take ≥1 administration of study intervention. Participants will be summarized according to the study intervention they actually received.	Actual received
Modified Intent-to-treat (mITT)	All randomized participants with ≥1 assessment of headache occurrence within 24 hours after taking double-blind study intervention for at least 1 qualifying prodrome event during the double-blind treatment period. Participants will be summarized according to the randomized study intervention.	Randomized

For efficacy analyses, data will be analyzed according to participants' randomization assignments, regardless of actual study intervention received.

For safety data analyses, data will be analyzed according to participants' actual study intervention received (rather than as randomized).

5.0 Subject Disposition

Participant disposition encompasses the distribution of participants who enter, complete, and discontinue in the screening and double-blind treatment periods. Specifically, the number and percentage of participants with each disposition status in the screened, ITT, safety, and mITT populations will be summarized by treatment sequence and treatment. For participants who discontinue, the number and percentage of participants discontinued with one qualifying prodrome event, and with no qualifying prodrome event will be summarized.

6.0 Study Drug Duration and Compliance

Study treatment compliance will be provided for the safety population. A summary of treatment compliance to the dose of each study medication in terms of the number and percentage of participants who took two tablets or only one tablet will be provided by study intervention.

7.0 Demographics, Baseline Characteristics, Medical History, and Prior/Concomitant Medications

7.1 Demographics and Baseline Characteristics

Demographic parameters (age; age group [<20, 20 to 29, 30 to 39, 40 to 49, 50 to 59, 60 to 69, ≥70]; sex; race; ethnicity, weight; height; and body mass index, calculated as weight [kg] / (height [m])2) will be summarized descriptively by treatment sequence and treatment for the safety population. In general, unless otherwise specified, continuous variables will be summarized by number of participants with observed values (n), mean, standard deviation (SD), median, 1st and 3rd quartiles (Q1, Q3), minimum (min), and maximum (max). Categorical variables will be summarized by number of participants with observed values or events (n), frequency count (N1), and percentage of participants with observed values or events.

7.2 Medical and Migraine History

Medical history data will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). The number and percentage of participants with abnormalities in medical and surgical history in each system organ class (SOC) and preferred term (PT) will be summarized by treatment sequence and treatment for the safety population.

Migraine history (diagnosis, duration of migraines, whether migraine prescription medications have been taken currently or in the past, acute migraine medications that were taken, and whether prescription preventive migraine medications have been taken currently or in the past), prodrome symptom history (percentage of migraine headaches that are preceded by prodrome symptoms, symptoms, and time until headache onset for

each symptom), cardiovascular disease and risk (presence of cardiovascular disease and risk factors), historical triptan response (whether triptan was taken; reason if not taken; If taken, whether triptan relieve pain completely within 2 hours more than half the time and whether triptan was stopped in the past and the reasons), failed prevention therapy (medication currently taken and medication used in the past for migraine prophylaxis, whether the medication met failure definition and the primary reason, and whether the medication is 'not suitable' and the primary reason), and allodynia (ASC-12) questionnaire (allodynia score for each of the 12 questions and the severity based on ASC total score range: none [0-2], mild [3-5], moderate [6-8], severe [9 or more], and total score) will be summarized by treatment sequence and treatment in the safety population.

7.3 Prior and Concomitant Medications

The medication data will be coded using the World Health Organization (WHO) Drug Dictionary Enhanced Version. Prior medication is defined as any medication taken prior to the start of first study intervention regardless of stop date of the medication. Concomitant medication by treatment is defined as any medication taken after the start of study intervention (and before the next intervention if any) regardless of the start date of the medication. Prior and concomitant medications will be summarized using the Anatomical Therapeutic Chemical code (4th level, or most specific level available if 4th level is unavailable).

Prior and concomitant medications will be summarized by treatment for the safety population. The number and percentage of participants reporting prior or concomitant medications will be summarized further by ATC class and code, and preferred drug name. If more than one medication is coded to the same preferred drug name for the same participant, the participant will be counted only once for that preferred drug name.

8.0 Efficacy Analyses

8.1 General Considerations

Efficacy measurement assessments are based on information recorded by the participant in an eDiary.

- Absence/Presence of and Rating of Intensity of Prodrome Symptom(s)

After experiencing each qualifying prodrome event, the absence or presence of each identified prodrome symptom(s) will be followed (up to 48 hours) and the intensity subjectively rated (mild, moderate, or severe) for those that are present.

- Absence/Presence of Headache and Rating of Headache Intensity

After the prodrome symptoms have started, the participant will be alerted to record the presence of a headache when it occurs or record the absence/presence at various timepoints (up to 48 hours) following the dose of double-blind study intervention (during the double-blind treatment period). If a headache is reported as present, the intensity will be subjectively rated (mild, moderate, or severe).

- Absence/Presence of and Rating of Intensity of Nonheadache Symptoms

The participant will record whether nonheadache symptoms (photophobia, phonophobia, nausea, and/or dizziness) were absent or present as well as the intensity (mild, moderate, or severe) of the present nonheadache symptom (up to 48 hours).

- Absence/Presence of Aura

The participant will record whether aura was present or absent (up to 48 hours).

- Health outcome assessments

The functional disability scale (FDS), a single item used to measure the participant's level of functional disability, will be used to rate the performance of daily activities using 4 response options ranging from 0 (no disability, able to function normally) to 3 (severely impaired, cannot do all or most things, bed rest may be necessary). The measure will be taken at predose (baseline) and 1, 2, 3, 4, 6, 8, 24, and 48 hours after double-blind study intervention for treating the first and second qualifying prodrome events.

Overall satisfaction with study medication for migraine will be assessed using a single-item 7-point rating scale ranging from extremely satisfied (0) to extremely dissatisfied (6). The question will be answered by the participants in their eDiary at 8 hours and 24 hours after taking double-blind study intervention for treating the first and second qualifying prodrome events.

A single-item measure assessing activity limitation based on a 24-hour recall will be administered as an additional health outcome measure. The measure will be used to evaluate activity limitation with a 5-level response ranging from "Not at all limited – I could do everything" to "Extremely limited." The measure will be administered at 24 hours after taking double-blind study intervention.

The following are general considerations for efficacy analyses:

- Efficacy analyses will be performed based on mITT population.
- Continuous variables will be summarized by number of participants with observed values (n), mean, standard deviation (SD), median, 1st and 3rd quartiles (Q1, Q3), minimum (min), and maximum (max).
- Categorical variables will be summarized by number of participants with observed values or events and percentages based on the specified population.
- The efficacy analyses will be performed using a GLMM in the observed binary response variable unless an imputation method is specified.
- The least squares mean (LSMEAN) estimates of the treatment effects for the primary and secondary endpoints alongside its 95% CI will be presented.

- All statistical hypothesis tests will be performed at the 2-sided 5% significance level.
- Efficacy analyses will be presented by treatment or study intervention randomized (placebo or ubrogepant 100 mg).

8.2 Handling of Missing Data

Participants are expected to treat two qualifying prodrome events in the double-blinded treatment period. For each prodrome event, endpoints are derived based on all assessments recorded in the prodrome event. Missing data at prodrome event level and within prodrome event level (indeterminable endpoints within prodrome event level) will be handled using the following methods for the sensitivity analyses: non-responder imputation (NRI) for indeterminable endpoints, imputation under missing at random (MAR) for indeterminable endpoints, imputation under missing not at random (MNAR) for missing prodrome events and under MAR for indeterminable endpoints, and Period 1 data only.

Table 3. Missing data handling at prodrome level and within prodrome level

Analyses	Missing prodrome event	Indeterminable endpoints within prodrome event level
Primary analysis	Ignore and no imputation	Set as missing and no imputation
Sensitivity analysis 1: NRI for indeterminable endpoints	Ignore and no imputation	Set as non-responder
Sensitivity analysis 2: imputation under MAR for indeterminable endpoints	Ignore and no imputation	Sequential multiple imputation
Sensitivity analysis 3: imputation under MNAR for missing prodrome events and under MAR for indeterminable endpoints	MNAR	Sequential multiple imputation
Sensitivity analysis 4: Period 1 only	Ignore and no imputation	Set as missing and no imputation

For sensitivity analysis 2, indeterminable endpoints will be imputed using multiple imputation under MAR. The determinations of the efficacy endpoints are described in the corresponding endpoints sections. Specifically for the primary endpoint, for a participant who has not experienced headache of moderate/severe intensity by time t_j after study intervention and has missing headache severity assessment at the next timepoint t_{j+1}, whether the participant will experience headache of moderate/severe intensity at t_{j+1} will be imputed based on other participants on the same treatment who have not experienced headache of moderate/severe intensity by time t_j but have observed headache severity assessment at t_{j+1}. Base will be used in the imputation logistic model. Base is a continuous variable denoting the percentage of absence of moderate/severe headache within time t_{j+1} during the screening period. So firstly, the missing headache severity assessment by time t_1 will be imputed. The missing headache by the following timepoints (2, 3, 4, 6, 8, 24, and 48 hours) will be imputed step by step similarly. One hundred datasets will be imputed.

For sensitivity analysis 3, indeterminable endpoints will be imputed using multiple imputation under MAR, and endpoints in missing prodrome events will be imputed under MNAR. One hundred datasets will be imputed.

- For participants who go through the 60-day double-blind treatment period with only one qualifying prodrome event due to lack of qualifying event or having an event but with no headache assessment, the missing data for the missing qualifying prodrome event will be considered as missing at random using multiple imputation.
- For participants who discontinued the double-blind treatment period with only one qualifying prodrome event for other reasons, the missing data for the qualifying prodrome event will be imputed based on the observed data for the second qualifying prodrome event from participants who use placebo to treat the second qualifying prodrome event.

8.3 Primary Efficacy Endpoint(s) and Analyses

8.3.1 Primary Efficacy Endpoint

The primary efficacy endpoint is the absence of a headache of moderate/severe intensity within 24 hours after taking double-blind study intervention during the prodrome.

8.3.2 Handling of Missing Data for the Primary Efficacy Endpoint(s)

Handling of missing data for the primary endpoint is described in Section 8.2.

8.3.3 Primary Efficacy Analysis

The primary hypothesis is stated as follows:

Primary Null hypothesis: Ubrogepant 100 mg is the same as placebo in the acute treatment of migraine when administered during the prodrome, as measured by the proportion of participants who do not develop headache of moderate/severe intensity within 24 hours after taking double-blind study intervention during the prodrome.

Primary Alternative hypothesis: Ubrogepant 100 mg is different from placebo in the acute treatment of migraine when administered during the prodrome, as measured by the proportion of participants who do not develop headache of moderate/severe intensity within 24 hours after taking double blind study intervention during the prodrome.

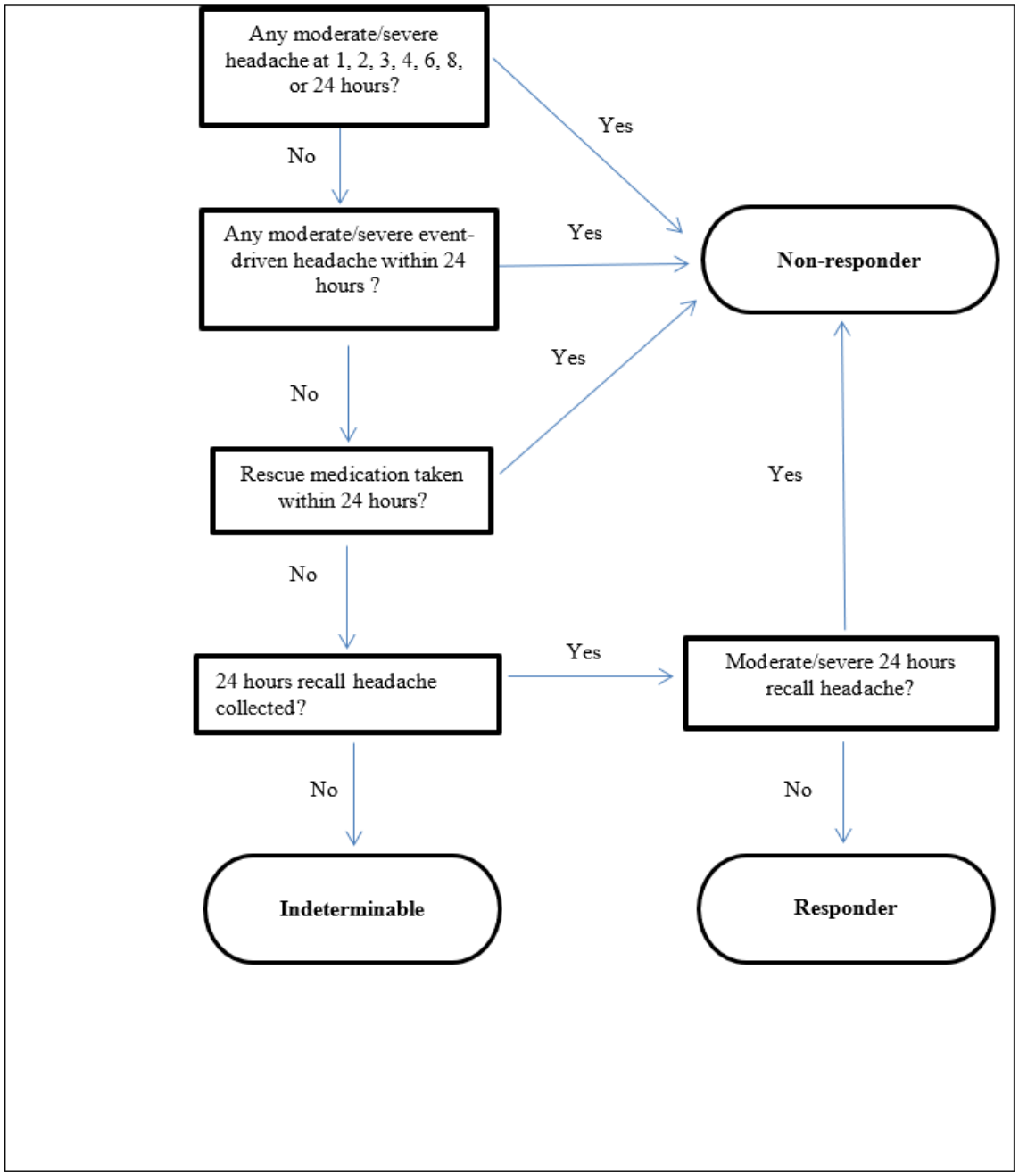
The main attributes of the primary estimand are summarized in Table 4.

Table 4. Summary of the Primary Estimand Attributes of the Primary Efficacy Endpoint

Estimand Label	Attributes of the Estimand				
	Treatment	**Endpoint**	**Population**	**Handling of Intercurrent Events**	**Statistical Summary**
Primary	Treatment A: placebo Treatment B: ubrogepant 100 mg Placebo or ubrogepant 100 mg are assigned based on the 2x2 crossover to treat two qualifying prodrome events (Sequence A: placebo/ubrogepant 100mg, Sequence B: ubrogepant 100mg/placebo).	Absence of a headache of moderate/severe intensity within 24 hours after taking double-blind study intervention during the prodrome	mITT population (randomized participants with ≥1 assessment of headache occurrence within 24 hours after taking double-blind study intervention for at least 1 qualifying prodrome event during the double-blind treatment period)	IE 1 at prodrome event level: data after the discontinuation will be handled by hypothetical strategy and assumed MAR. IE2 within prodrome event level: participants who took rescue medication within 24 hours will be counted as non-responder for the prodrome. IE3 within prodrome event level: indeterminable primary endpoint due to missing data during the prodrome will be set as missing and assumed MAR.	Treatment comparison (odds ratio) of percentages of absence of moderate/severe headache within 24 hours after taking ubrogepant 100mg vs placebo during the prodrome

The status of the primary endpoint will be determined as shown in Figure 2.

Figure 2. Determination of absence of moderate/severe headache within 24 hours (responder)



The primary comparison between study intervention groups will be analyzed using a GLMM model with repeated measurements based on determinable data on the primary efficacy endpoint data. The GLMM model assumes a binary distribution for the response and uses a logit link. The analysis model will include study intervention period, and treatment as categorical fixed effects. An unstructured covariance matrix will be selected for the covariance matrix of the residual effect for the repeated measurements (corresponding to the two qualifying prodrome events) within a participant. The treatment difference in terms of odds ratio between ubrogepant 100 mg and placebo will be estimated from the GLMM model.

The carryover effect will be tested although no or very minimum carryover effect is expected as the minimum 7-day washout period is much longer than the 5 times of half-life. A similar GLMM model will be fitted to examine the carryover effect. The model includes period and treatment as categorical fixed effects, and period by treatment as interaction effect. The carryover effect will be tested using the confounded period by treatment interaction at 0.05 significance level. If the carryover effect is significant, the analysis will use the first period only data for the primary efficacy analysis. For sensitivity analysis purpose, first period only data analysis will be performed regardless of the significance level of the carryover effect using logistic regression model with treatment effect.

8.3.4 Sensitivity Analyses

As alternative estimands for the primary study objective, the treatment condition, population, variable, and population-level summary will be the same as those in the primary estimand. However, the way to handle the discontinued participants with only one qualifying prodrome event and the approach to handle missing data within a prodrome event will be different. For participants who discontinued the double-blind treatment period with only one qualifying prodrome event, the missing data for the second qualifying prodrome event will be handled same as the primary analysis or imputed under MNAR. For indeterminable primary endpoint due to missing data within a prodrome

event, the primary endpoint will be set as missing, non-responder, or imputed using sequential multiple imputation. Missing data handling is described in Section 8.2.

A sensitivity analysis will impute participants with indeterminable status or missing headache occurrence within 24-hours recall as non-responders for the qualifying prodrome event. Data will be analyzed using the same primary GLMM model.

An additional sensitivity analysis will use multiple imputation approaches to impute the missing headache occurrence status within 24 hours under MAR for each qualifying prodrome event with indeterminable endpoints. Another sensitivity analysis will assume missing prodrome events as missing MNAR. The treatment difference between ubrogepant 100 mg and placebo will be estimated from the GLMM model for each imputed data set and combined across imputations to obtain the multiple imputation estimate using standard multiple imputation techniques applied to log odds ratio.

Analyses using only first period data will also be performed as a sensitivity analysis as mentioned in the previous section.

8.4 Secondary Efficacy Analyses

8.4.1 Secondary Efficacy Analyses

The secondary hypotheses are stated as follows:

Secondary null hypothesis 1: Ubrogepant 100 mg is the same as placebo in the acute treatment of migraine when administered during the prodrome, as measured by the proportion of participants who do not develop headache of moderate/severe intensity within 48 hours after taking the double-blind study intervention during the prodrome.

Secondary alternative hypothesis 1: Ubrogepant 100 mg is different from placebo in the acute treatment of migraine when administered during the prodrome, as measured by the proportion of participants who do not develop headache of moderate/severe intensity within 48 hours after taking the double-blind study intervention during the prodrome.

Secondary null hypothesis 2: Ubrogepant 100 mg is the same as placebo in the acute treatment of migraine when administered during the prodrome, as measured by the proportion of participants who are able to function normally over 24 hours after taking the double-blind study intervention during the prodrome.

Secondary alternative hypothesis 2: Ubrogepant 100 mg is different from placebo in the acute treatment of migraine when administered during the prodrome, as measured by the proportion of participants who are able to function normally over 24 hours after taking the double-blind study intervention during the prodrome.

Secondary null hypothesis 3: Ubrogepant 100 mg is the same as placebo in the acute treatment of migraine when administered during the prodrome, as measured by the proportion of participants who do not develop headache of any intensity within 24 hours after taking the double-blind study intervention during the prodrome.

Secondary alternative hypothesis 3: Ubrogepant 100 mg is different from placebo in the acute treatment of migraine when administered during the prodrome, as measured by the proportion of participants who do not develop headache of any intensity within 24 hours after taking the double-blind study intervention during the prodrome.

Estimands for the secondary objective will be assessed using three secondary endpoints. The population and population-level summary, as well as the approach to handle intercurrent events will be the same as those for the primary endpoint except that rescue medication is part of the treatment condition such that it is not an intercurrent event for FDS. The determination of the first and third secondary endpoints are shown in Figure 3 and Figure 4.

Figure 3. Determination of absence of moderate/severe headache within 48 hours (responder)

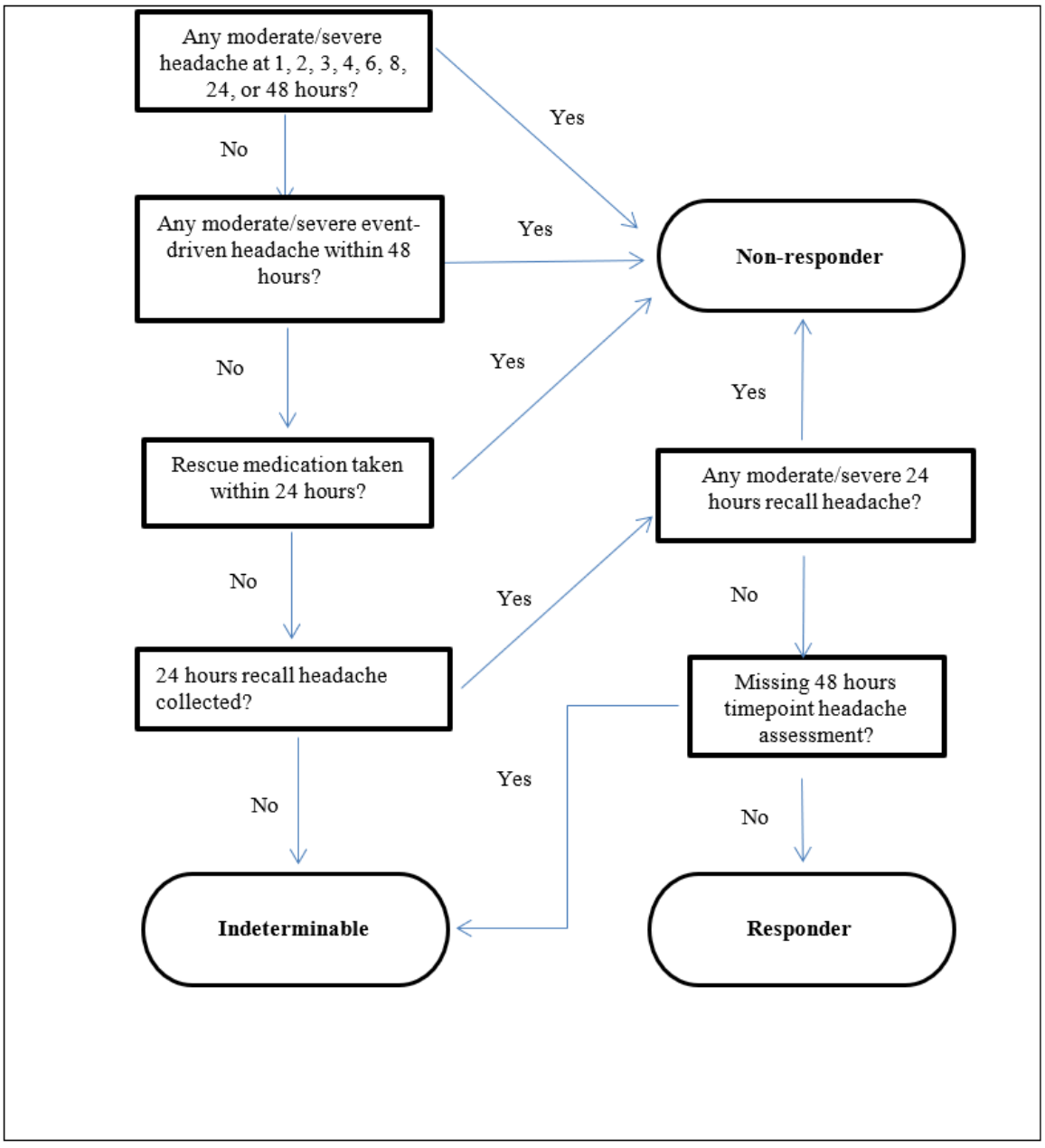
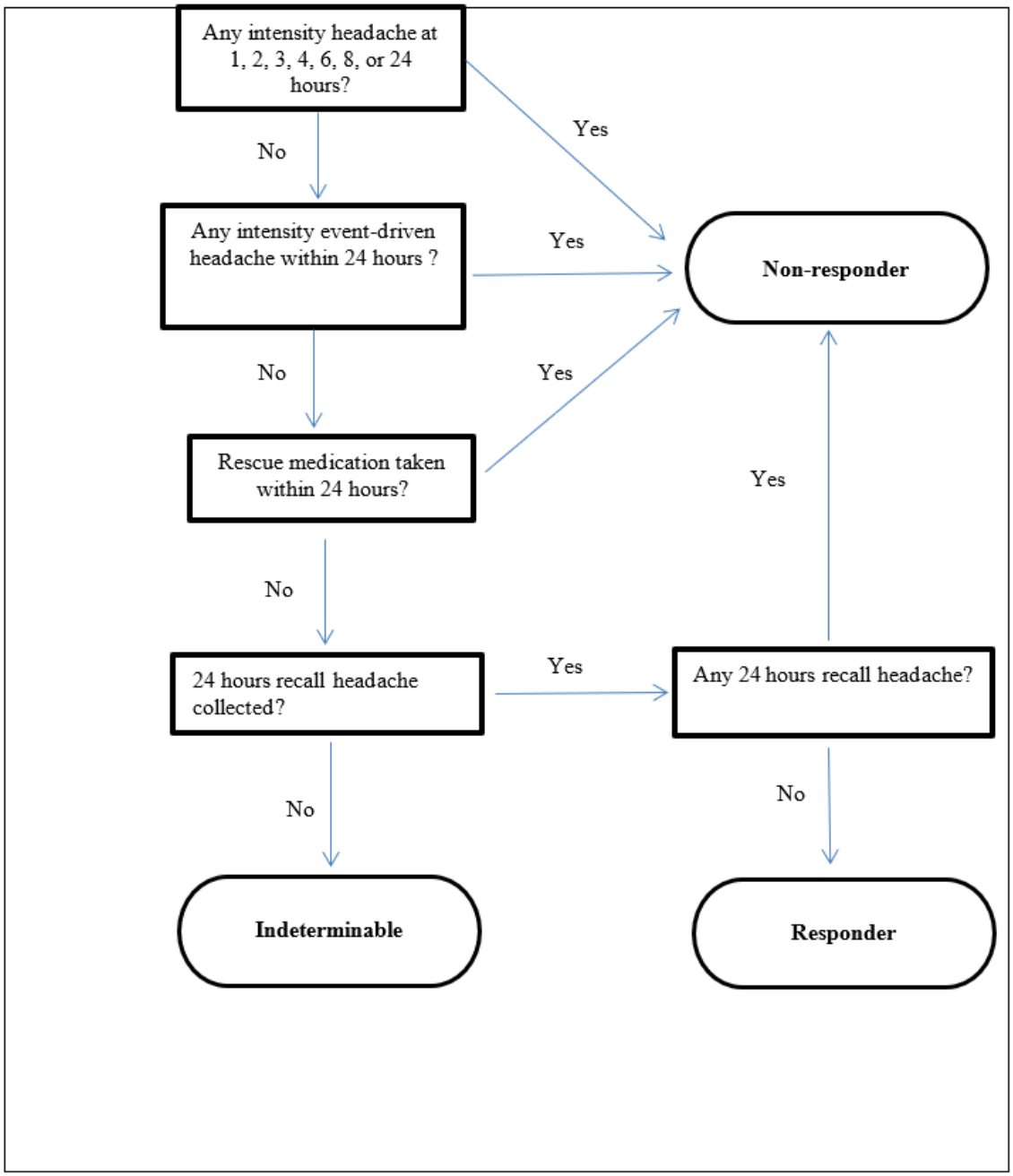


Figure 4. Determination of absence of any intensity headache within 24 hours (responder)



The first and third secondary endpoints (i.e., the absence of a headache of moderate/severe intensity within 48 hours and absence of a headache of any intensity within 24 hours after taking double-blind study intervention during the prodrome) will be analyzed using a GLMM model based on observed data similar to the one used for the analysis of the primary endpoint.

A sensitivity analysis will impute participants with indeterminable status as non-responders. An additional sensitivity analysis will use the multiple imputation approach described for the primary endpoint to impute the missing headache occurrence status within 24 hours/48 hours for the participant for each qualifying prodrome event with an unknown status of headache occurrence within 24 hours/48 hours after taking double-blind study intervention.

Another sensitivity analysis will assume missing prodrome events as MNAR. Analyses using only first period data will also be performed as a sensitivity analysis using logistic regression model.

The second secondary endpoint, i.e., ability to function normally over 24 hours after taking double-blind study intervention during the prodrome, includes the repeated measures of dichotomized FDS response at each postdose timepoint over 24 hours. The dichotomized response takes value 1 if the participant records no disability, able to function normally on the FDS, and takes value 0 otherwise. The repeated binary responses will be analyzed using a GEE model with a logit link. The GEE model will include period, treatment, time, treatment-by-time interaction as categorical fixed effects, predose baseline FDS score for the period, and predose baseline-by-time interaction as covariates. An unstructured working correlation matrix will be used for the repeated measures within each participant. If the unstructured correlation matrix does not converge, an unstructured correlation matrix or a working m-dependent (m=6) correlation matrix (if unstructured correlation matrix failed) will be used within each prodrome event and the two prodrome events will be assumed to be independent. The treatment effect will be expressed in terms of the geometric mean of the odds ratios of ubrogepant 100 mg

relative to placebo estimated at the scheduled timepoints within 24 hours after taking double-blind study intervention.

As described in Section 12.0, a serial gatekeeping procedure will be used to control the overall type I error rate at the 0.05 level for multiple comparisons across the primary and three secondary efficacy endpoints.

8.5 Additional Efficacy Analyses

The determination of absence of a headache of any intensity, moderate/severe and severe headache by each timepoint are shown in Figure 5, Figure 6, and Figure 7. When a headache is collected in a 24-hour recall, the missing headache intensity at prespecified hours before the recalled headache time is assumed to be less severe than the recalled headache intensity.

Figure 5. Determination of absence of any intensity headache by T hours (1, 2, 3, 4, 6, 8, 48 hours) (responder)

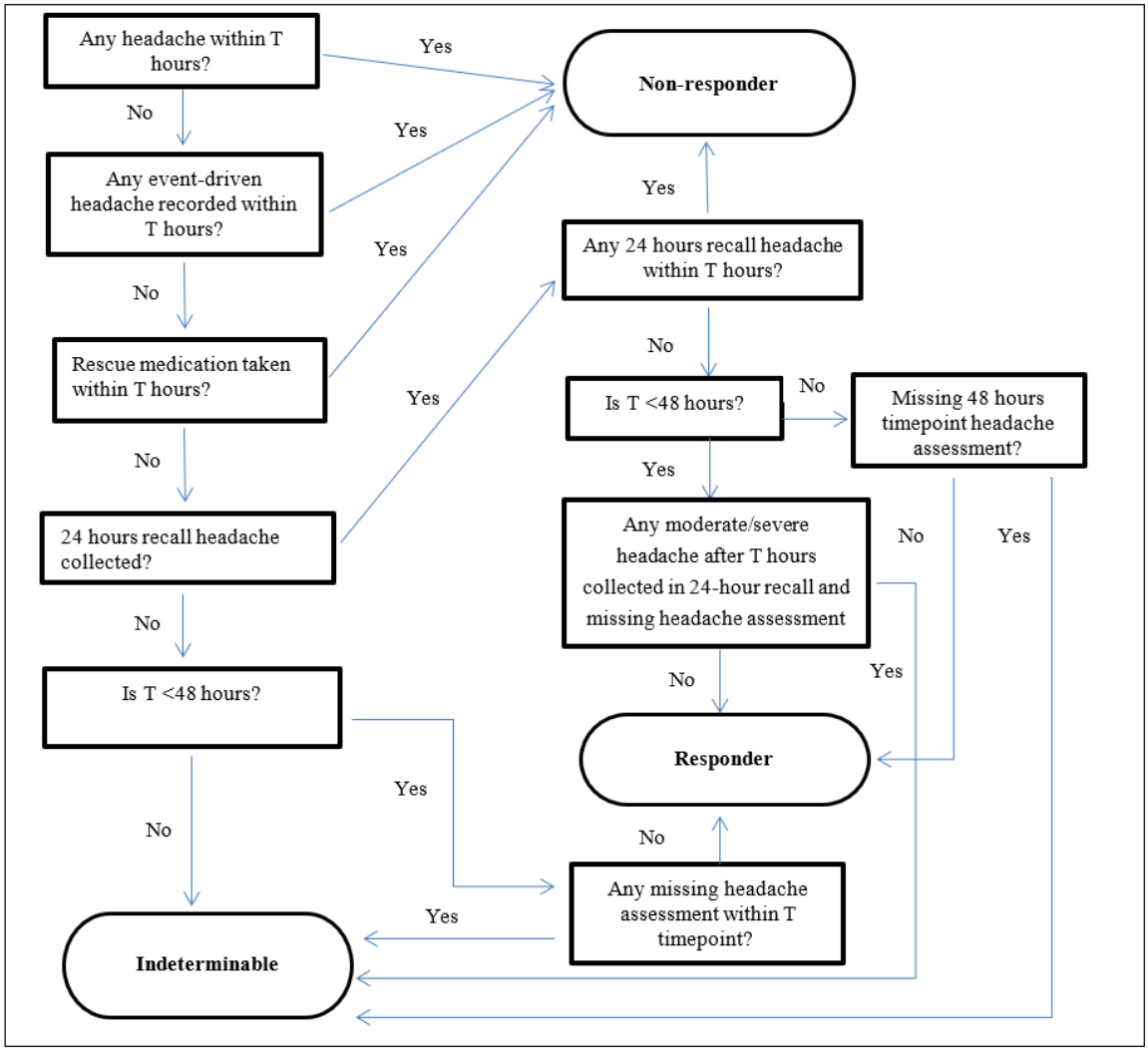


Figure 6. Determination of absence of moderate/severe headache by T hours (1, 2, 3, 4, 6, 8 hours) (responder)

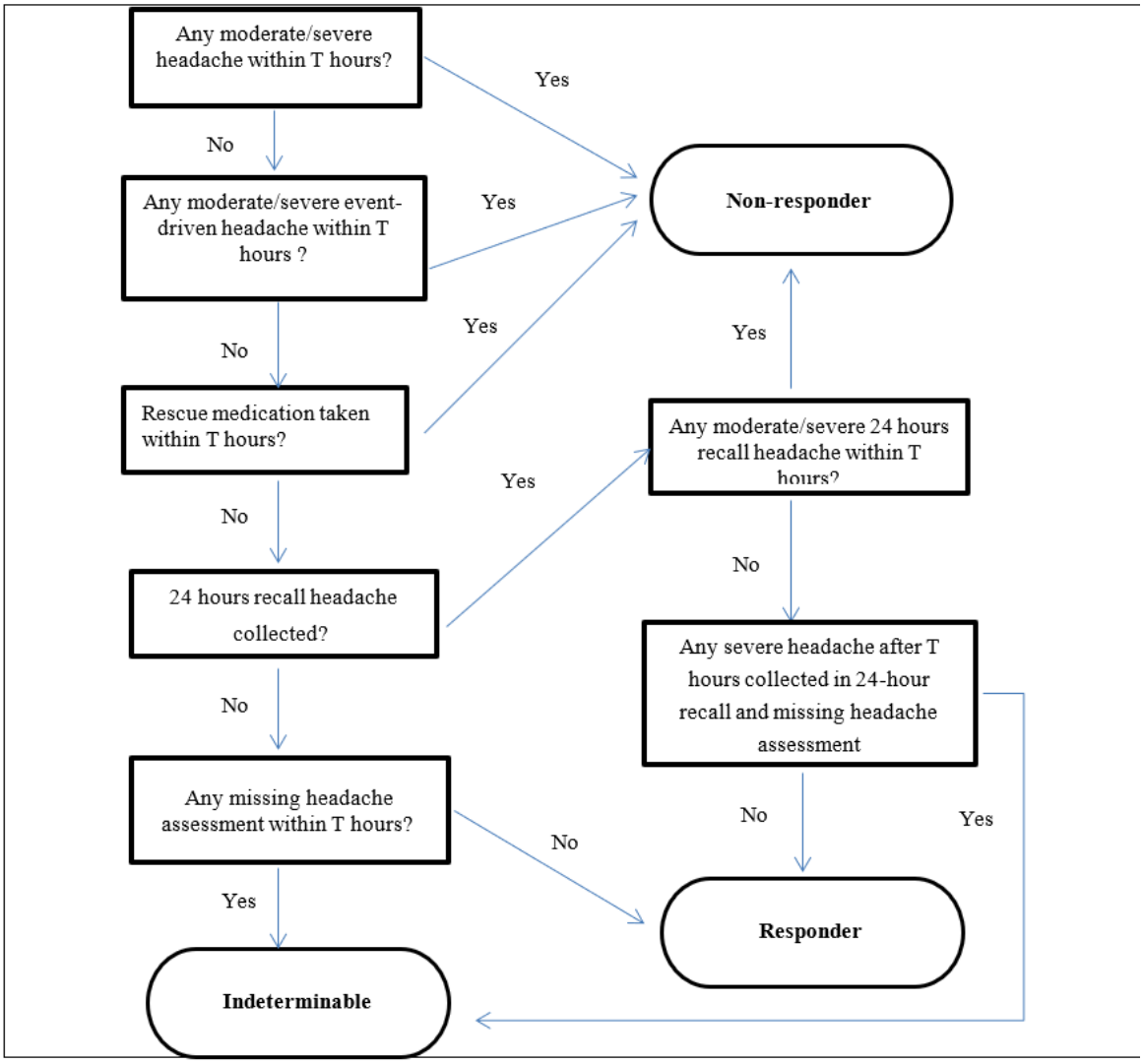
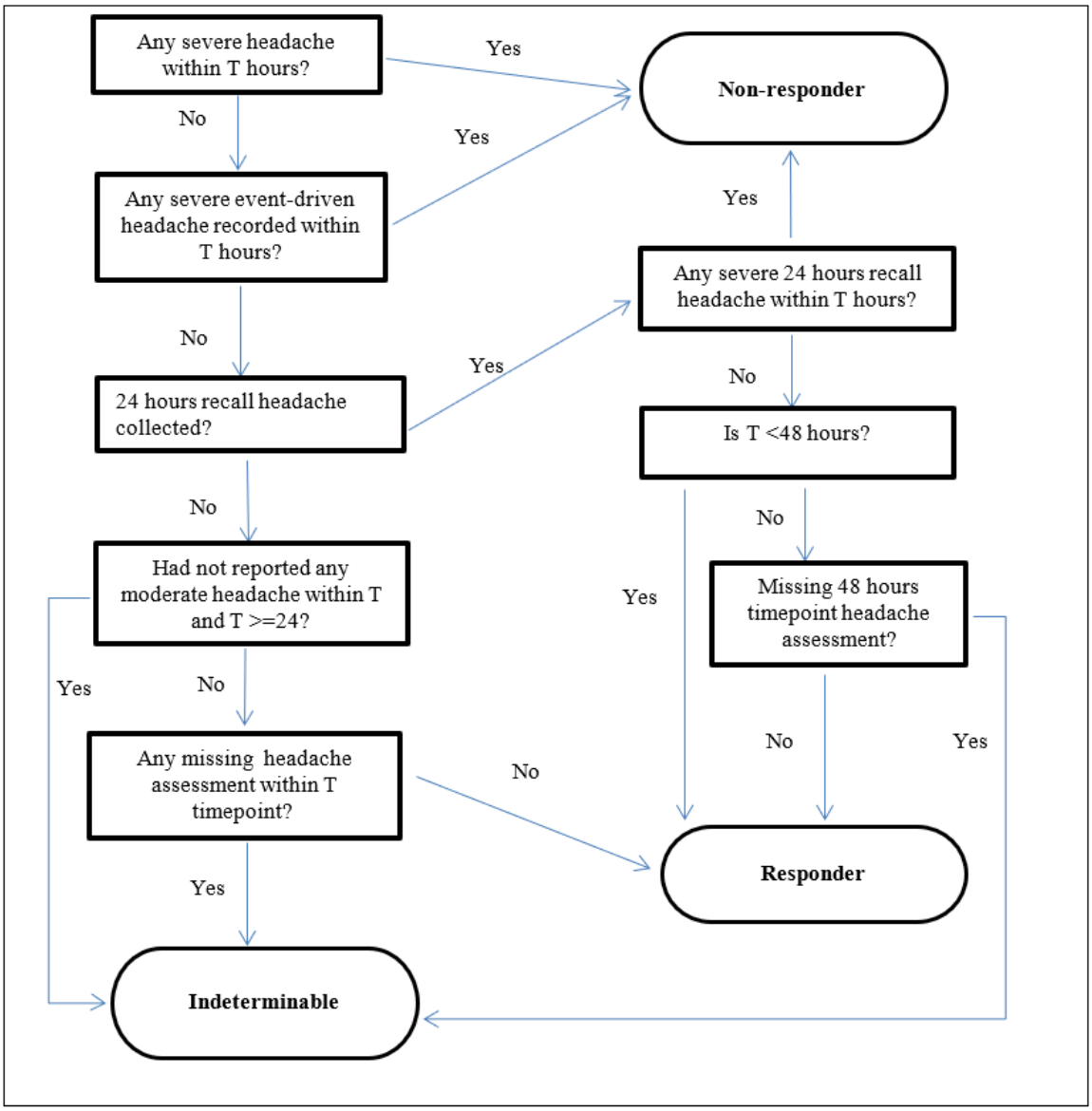


Figure 7. Determination of absence of severe headache by T hours (1, 2, 3, 4, 6, 8, 24, 48 hrs) (responder)



The absence of a headache of any intensity by each timepoint after taking double-blind study intervention will be analyzed using the same GLMM model as primary endpoint.

Similar analyses will be performed for the absence of a headache of moderate/severe intensity and absence of severe headache by timepoint. Kaplan-Meier curves for time to development of any intensity headache (or rescue medication taken), time to development of moderate/severe headache, time to development of severe headache within 48 hours will be produced by treatment and compared between treatment using the log-rank test. In addition, Kaplan-Meier curves for time to development of moderate/severe headache (or rescue medication taken) and time to development of severe headache within 48 hours (or rescue medication taken) will be produced. Hazard ratio will be estimated from cox proportional hazard model with treatment and period factors.

For each of the 5 most common individual prodrome symptoms, the absence of any intensity, absence of moderate/severe intensity, absence of severe intensity at each timepoint will be analyzed using GLMM with additional predose baseline prodrome symptom intensity category. In addition, prodrome symptoms will be summarized by descending frequency in ubrogepant group and by intensity at predose. Same GLMM model as the primary endpoint will be performed for the absence of any intensity, absence of moderate/severe intensity, absence of severe intensity nonheadache migraine symptom at each timepoint after a headache of any intensity is reported. The absence of aura at timepoint will be analyzed using GLMM model with additional predose baseline aura status. Kaplan-Meier curves for time to absence of each of the 5 most common individual prodrome symptoms will be produced by treatment and compared between treatment using the log-rank test. Kaplan-Meier curves will also be generated censoring data collected after rescue medication for migraine associated symptoms. Hazard ratio will be estimated from cox proportional hazard model with treatment and period factors.

The observed proportions of participants who used rescue medication within 24 and 48 hours after taking double-blind study intervention will be summarized and analyzed using the same GLMM model as primary endpoint. The treatment comparisons will be conducted using the primary model. Kaplan-Meier curves for time to rescue medication use within 48 hours after taking double-blind study intervention will also be produced by

treatment and compared by log rank test. Hazard ratio will be estimated from cox proportional hazard model with treatment and period factor.

8.6 Efficacy Subgroup Analyses

Subgroup analyses of the primary efficacy endpoint will be performed by current exposure (yes/no) to a migraine prevention medication with proven efficacy, and by allodynia status by history (absence/presence).

Additional subgroup categories that may be considered are:

- Exposure to a migraine prevention medication (current, past and none)
- Triptan therapy historical response (triptan responders, triptan naïve, and triptan non-responder)
- Optimization of triptan therapy historical response (triptan responder, triptan optimized, triptan unoptimized)
- Cardiovascular disease (presence or not)
- Cardiovascular risk (presence or not)
- Cardiovascular risk (none, only 1 risk factor, 2 and more risk factors)
- Failed prevention medication (yes or no)

9.0 Safety Analyses

9.1 General Considerations

- Safety analyses will be performed based on the safety population.
- Safety analysis will be presented by treatment or study intervention participants actually received (placebo or ubrogepant 100 mg) unless specified otherwise.
- The baseline for safety endpoints is defined as the last non-missing assessment prior to the first dose of the double-blind study intervention.

9.2 Adverse Events

9.2.1 Treatment-Emergent Adverse Events

An AE will be considered a treatment emergent adverse event (TEAE) if the AE began or worsened (increased in severity or became serious) on or after the date (and time, if known) of the study intervention. However, AEs that occurs more than 30 days after the Period 1 study intervention and before the date of the Period 2 study intervention and AEs that occurs more than 30 days after Period 2 study intervention will not be counted as a TEAE. A TEAE will be assigned to a study intervention if it occurred on or after the date of the study intervention and before the date of the next study intervention. An AE will be assigned to the last study intervention of the treatment sequence if it occurred on or after the date of the last study intervention. An AE will be considered a treatment-emergent serious AE (TESAE) if it is a TEAE that additionally meets any SAE criterion.

AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) version 23.1 or higher.

9.2.2 Adverse Event Overview

Overall summary of TEAEs will be provided on a per-participant level for TEAEs, treatment-related TEAEs, TESAEs, treatment-related TEAEs, deaths, and TEAEs leading to discontinuation.

9.2.3 Treatment-Emergent Adverse Events by SOC and/or PT

AEs will primarily be assessed through the analysis of AEs reported in the 48 hours following the administration of each study intervention. A supportive analysis will include AEs reported within 30 days after the study intervention (and before the next intervention if any). Unique participants reporting AEs will be summarized in the following AE categories by treatment and total for the safety population in double-blind treatment period.

- TEAEs by SOC and PT.
- TEAEs by SOC, PT and severity. If more than 1 AE is coded to the same PT for the same participant, the participant will be counted only once for that PT using the maximum severity for the summarization by severity. If the severity of a TEAE is missing, the maximum severity will be assigned to the event for the summarization by severity. The value will be displayed as missing in the data listing.
- Treatment-related TEAEs by SOC and PT. If more than 1 AE is coded to the same PT for the same participant, the participant will be counted only once for that PT using the closest causal relationship to treatment for the summarization by causal relationship. If the relationship to the study intervention is missing for a TEAE, the event will be considered related to the study intervention for the summarization. The value will be displayed as missing in the data listing.
- The incidence of common (≥ 2% [after rounding] of participants in either study intervention) TEAEs will be summarized by descending frequency in the ubrogepant group.

9.2.4 SAEs (Including Deaths) and Adverse Events Leading to Study Drug Discontinuation

TEAEs leading to discontinuation and TESAEs will be summarized by SOC and PT. Listings of all TEAEs, SAEs, and AEs leading to discontinuation will be provided.

9.2.5 Adverse Events of Special Interest

Adverse events of special interest will be summarized by SOC and PT recorded on case report form (CRF) as of special interest.

9.3 Analysis of Laboratory Data

9.3.1 Clinical Laboratory Parameters

Descriptive statistics for clinical laboratory values (in SI units) at baseline and changes from baseline at each assessment time point will be presented by study intervention for

each clinical laboratory assessment. An assessment will be assigned to the most recently administered study intervention.

- Hematology: Hemoglobin; hematocrit; red blood cell count; red blood cell indices (mean corpuscular volume, mean corpuscular hemoglobin, mean corpuscular hemoglobin concentration); white blood cell count, including differential (neutrophils, lymphocytes, monocytes, eosinophils, and basophils); platelet count
- Chemistry: Sodium, potassium, chloride, bicarbonate, glucose, blood urea nitrogen, creatinine, total bilirubin, alkaline phosphatase, aspartate aminotransferase, alanine aminotransferase, lactate dehydrogenase, creatine kinase, total protein, albumin, calcium, phosphorus, uric acid, total cholesterol, HDL, LDL, total triglycerides, eGFR (calculated by the central lab)
- Urinalysis: Specific gravity, pH.

Shift tables from baseline to end of study for these clinical laboratory parameters will be presented by study intervention for the following categories: low, normal, and high, which are categorized by the laboratory vendor based on reference ranges.

9.3.2 Potentially Clinically Significant Laboratory Findings

Clinical laboratory test values will be considered potentially clinically significant (PCS) if they meet either the lower-limit or higher-limit PCS criteria listed in Table C-1.

The number and percentage of participants who have at least one PCS post-baseline clinical laboratory value will be tabulated by study intervention. The percentages will be calculated based on the denominator of the number of participants with available non-PCS baseline values and at least one post-baseline value and the numerator of the number of participants with non-PCS baseline value and at least one PCS post-baseline value. In addition, a listing of all AEs occurring in participants who have PCS clinical laboratory test values will be provided.

A listing of participants with PCS postbaseline values will be provided for the safety population.

9.3.3 Hepatic Laboratory Abnormities

The number and percentage of participants meeting each of the criteria provided in Table C-2 for postbaseline hepatic laboratory abnormalities will be summarized by study intervention group. The percentages will be calculated relative to the number of participants with at least 1 available postbaseline assessment. The numerator will be the total number of participants having at least 1 postbaseline value that meets the specific category.

A listing of participants with hepatic laboratory abnormalities will be provided for the safety population.

9.4 Analysis of Vital Signs

Descriptive statistics for vital signs (systolic and diastolic blood pressures, pulse rate, respiratory rate, and temperature) at baseline, postbaseline, and changes from baseline values at each postbaseline timepoint will be presented by study intervention. An assessment will be assigned to the most recently administered study intervention. Vital sign values will be considered PCS if they meet both the observed value criterion and the change from baseline value criterion, if both criteria are available, or meet either the observed value criterion or the change from baseline value criterion that will be detailed in Table C-3.

The number and percentage of participants who have PCS postbaseline vital sign values will be calculated relative to the number of participants who have available baseline or non-PCS baseline (for parameters with only the observed value criterion) values and at least 1 postbaseline assessment. The numerator will be the total number of participants with at least 1 PCS postbaseline value during the qualifying prodrome event.

A supportive listing of participants with PCS postbaseline values will be provided.

9.5 Safety Subgroup Analyses

No safety subgroup analyses are planned.

9.6 Other Safety Analyses

COVID-19 impact on participants' disposition, protocol deviation, site visits and missed assessments and COVID-19 vaccine will be summarized. A summary of AEs related to COVID-19 will also be provided.

9.6.1 Electrocardiogram

Descriptive statistics for 12-lead ECG parameters (heart rate, PR interval, QRS interval, QT interval, and QTc interval) at baseline, postbaseline, and changes from baseline values at each postbaseline timepoint will be presented by study intervention. An assessment will be assigned to the most recently administered study intervention.

ECG parameter values are considered PCS if ECG values meet either the actual value or change from baseline PCS high criteria listed in Table C-4. The number and percentage of participants with PCS postbaseline values will be tabulated by study intervention. The percentages will be calculated relative to the number of participants with an available non-PCS baseline value and at least 1 postbaseline assessment. The numerator will be the total number of participants with an available non-PCS baseline value and at least 1 PCS postbaseline ECG value.

A supportive listing of participants with PCS postbaseline values will be provided. A listing of all AEs for participants with PCS ECG values will also be provided.

9.6.2 Suicidality Assessment

For the C-SSRS, the number and percentage of participants with suicidal ideation and suicidal behavior in lifetime history, 6 months prior to screening, and post the study intervention will be summarized by study intervention for the safety population. An

assessment will be assigned to the most recently administered study intervention. The assessment collected at each visit will be summarized.

A supportive listing of participants with suicidal ideation or suicidal behavior will be provided for the safety population.

10.0 Other Analyses

10.1 Additional Health Economics Outcomes Research (HEOR) Analyses

Satisfaction with study medication responder is defined as response to the Satisfaction with Study Medication question of 'Satisfied' or 'Extremely Satisfied.' The same GLMM model for the primary endpoint will be performed at 8 hours and 24 hours, separately. Descriptive statistics at 8 hours and 24 hours after taking double-blind study intervention will be presented by study intervention.

The ordinal activity limitation will be analyzed using Cochran-Armitage trend test. In addition, responder analyses will be performed using the same GLMM model. A participant will be defined as a responder if the participant records not at all limited - I could do everything or a little limited, and a non-responder otherwise. Descriptive statistics at 24 hours taking double-blind study intervention will be presented by study intervention.

For FDS, by timepoint analysis will be performed using the same primary GLMM model with an additional covariate of predose baseline FDS score at 1, 2, 3, 4, 6, 8, and 24 hours. Additional endpoint will be defined as a responder if a participant records no disability, able to function normally at all the observed timepoints FDS (1, 2, 3, 4, 6, 8, and 24 hours postdose), and a non-responder otherwise. The data will be analyzed using the same primary GLMM model with an additional covariate of predose baseline FDS score.

10.2 Additional Analysis

Qualifying prodrome events and prodrome symptom data collected in the screening period will be analyzed for the screened population to understand the prodrome information in the general population.

For each participant, number of qualifying prodrome events and positive prodrome events will be summarized. The positive prodrome event rate will be calculated based on the denominator of the number of qualifying prodrome events and the numerator of the number of positive prodrome events. The positive prodrome event rate will be analyzed using a GLMM model with participant as a random effect. The LSMEAN of the positive prodrome rate with 95% CI will be reported.

Prodrome symptoms will be analyzed in individual prodrome symptom positive rate. The individual prodrome symptoms positive rate is to show how likely an individual qualifying prodrome event with this symptom at baseline will be positive. The individual prodrome symptom positive rate will be calculated based on the denominator of the numbers of qualifying prodrome events with this symptom and the numerator of the numbers of positive qualifying prodrome events preceded with this symptom. Individual prodrome symptom prevalence rate will be calculated based on the denominator of the numbers of qualifying prodrome events and the numerator of the numbers of qualifying prodrome events preceded with this symptom. These participant-specific variables will then be summarized in the screened population who have entered eDiary data in the screening period. The individual prodrome symptom positive rate in the screening period will also be analyzed in the mITT population. In addition, Kaplan-Meier curves for time to onset of a headache of any intensity and time to onset of a headache of moderate/severe intensity using all prodrome events and using the first prodrome event will be generated.

The derivation of the endpoints in the screening period are the same as double-blind period except for the absence of moderate/severe headache which are described in Figure 8, Figure 9, and Figure 10.

Figure 8. Determination of absence of moderate/severe headache within 24 hrs in the screening period (responder)

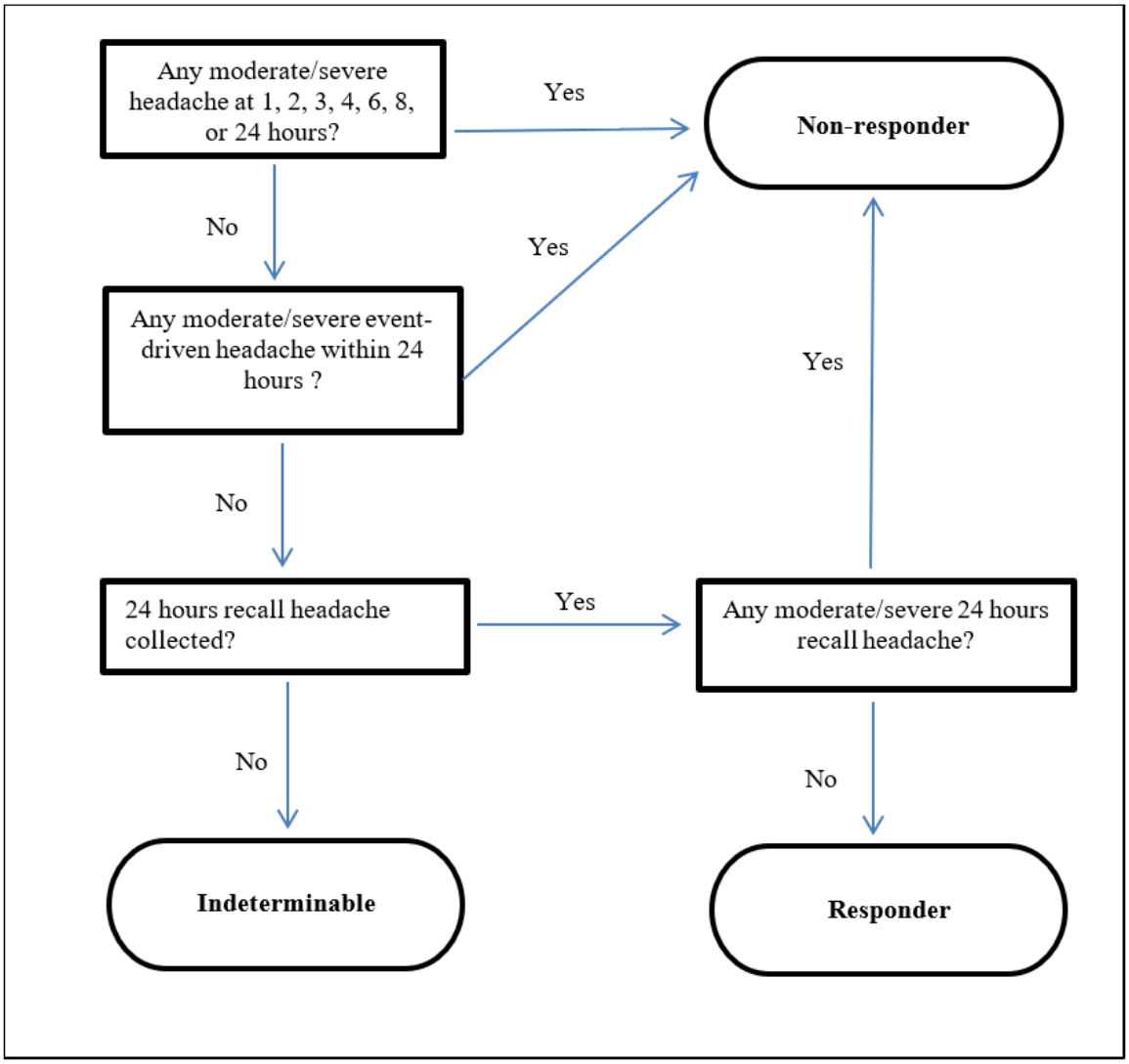


Figure 9. Determination of absence of moderate/severe headache within 48 hours in the screening period (responder)

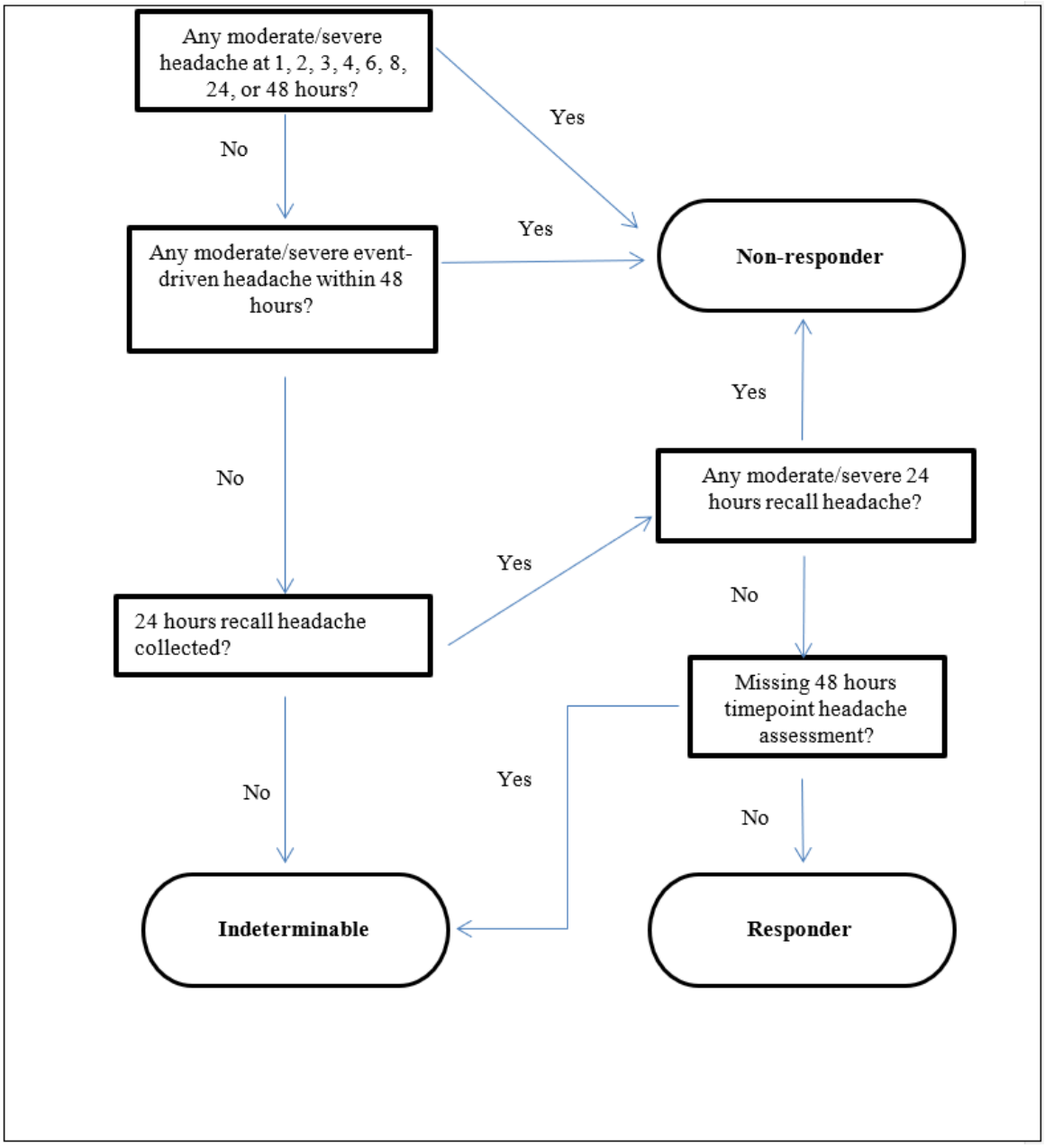
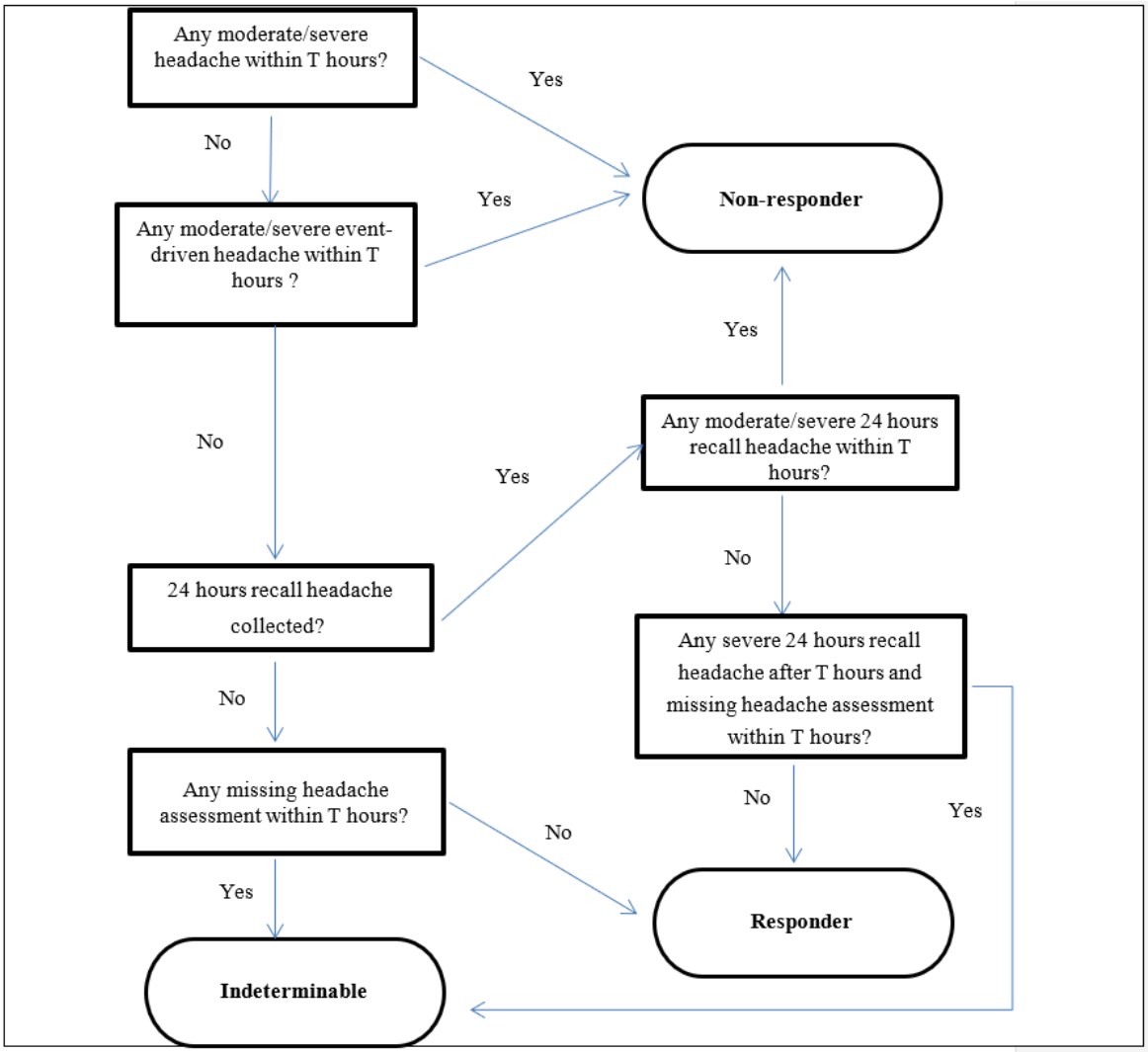


Figure 10. Determination of absence of moderate/severe headache by T hours (1, 2, 3, 4, 6, 8 hours) in the screening period (responder)



11.0 Interim Analyses

No interim analysis of unblinded data is planned for this study.

11.1 Data Monitoring Committee

Data monitoring committee is not required for this study.

12.0 Overall Type-I Error Control

To control the family-wise type I error rate at 0.05 for multiplicity across the hypothesis tests in the primary and secondary analyses, a hierarchical gatekeeping procedure will be followed.

Step 1: Test the primary hypothesis. If p-value <0.05, reject the primary hypothesis and go to the Step 2, otherwise stop.

Step 2: Test the first secondary hypothesis. If the first secondary hypothesis is rejected, go to Step 3, otherwise stop.

Step 3: Test the second secondary hypothesis. If 2nd secondary hypothesis is rejected, go to test third secondary hypothesis, otherwise stop.

Step 4: Test the third secondary hypothesis.

13.0 SAP Version History

This Statistical Analysis Plan (SAP) for Study 3110-304-002 is based on the Protocol Amendment 2 dated 02 May, 2020.

SAP Version History Summary			
SAP Version	**Approval Date**	**Change**	**Rationale**
1	01 February 2021	Not Applicable	Original version

SAP Version History Summary			
SAP Version	**Approval Date**	**Change**	**Rationale**
2	03 May 2022	Updated the additional prodrome endpoints as: • Absence of 5 most common individual prodrome symptoms of any intensity at each timepoint • Absence of 5 most common individual moderate/severe prodrome symptoms at each timepoint • Absence of 5 most common individual severe prodrome symptoms at each timepoint	Protocol Amendment 1. The 5 most common prodrome symptoms are mostly meaningful.
		Updated the additional nonheadache migraine symptom endpoints as: • Absence of nonheadache migraine symptoms (photophobia, phonophobia, nausea, dizziness) of any intensity on or after any intensity headache start at each timepoint • Absence of moderate/severe nonheadache migraine symptoms (photophobia, phonophobia, nausea, dizziness) on or after any intensity headache start at each timepoint • Absence of severe nonheadache migraine symptoms (photophobia, phonophobia, nausea, dizziness) on or after any intensity headache start at each timepoint	Protocol Amendment 1. Nonheadache migraine symptom is collected on or after any intensity headache collected in eDiary.
		Updated the additional time to prodrome symptom endpoint as: • Time to absence of 5 most common individual prodrome symptoms	Protocol Amendment 1. The 5 most common prodrome symptoms are mostly meaningful.

SAP Version History Summary			
SAP Version	**Approval Date**	**Change**	**Rationale**
		Updated the sensitivity analysis 3 so that the missing event due to lack of prodrome is imputed under MAR, and imputed under MNAR for other reasons	Discontinuation due to all other reasons is considered as MNAR except lack of prodrome
		Updated sample size from 600 randomized to 516 randomized	Protocol Amendment 1. Sample size is reduced due to lower percentage of participants who have indeterminable data
		Updated the secondary and additional headache endpoints derivation in Figure 4, Figure 5, Figure 6, and Figure 7	Updated based on the below assumptions: 1. Missing headache at 48 hours will lead to the endpoint within 48 hours indeterminable. 2. When 24 hours recall headache is collected, the missing headache intensity at prespecified hours before 24 hours recall headache time is assumed less severe than the 24 hours recall headache intensity.
		Added the derivation of absence of moderate/severe headache in the screening period in Figure 9 and Figure 10	The derivation of absence of moderate/severe headache in the screening period is difference from those in the DB period.
		Added analysis related COVID vaccine	COVID vaccine is collected in CRF
		Re-order secondary endpoints	Protocol Amendment 2
		Additional endpoint changed from absence of aura by timepoint to absence of aura at each timepoint	Protocol Amendment 2
3	10 May 2022	Clarified logistic regression model for period 1 data only analyses	Clarification
		Added predose baseline variable in the	Predose baseline effect

SAP Version History Summary			
SAP Version	**Approval Date**	**Change**	**Rationale**
		analysis models of absence of any intensity, moderate/severe intensity, severe intensity for the 5 most common individual prodrome symptom, and absence of aura at each timepoint	should be controlled in the analysis model

14.0 References

1. Headache Classification Committee of the International Headache Society (IHS). The international classification of headache disorders, 3rd edition (ICHD-3). Cephalalgia. 2018;38:1-211.

15.0 Appendices

Appendix A. Protocol Deviations

Protocol deviations will be defined in Protocol Deviation Requirement Specification, including importance classification. The number and percentage of participants with significant protocol deviations that occurred in the double-blind treatment period will be summarized by treatment sequence for the ITT population.

Appendix B. Definition of Adverse Events of Special Interest

The following AESI(s) have been specified in the protocol and will be reported:

- Treatment-emergent suicidal ideations with intent, with or without a plan, (i.e., Type 4 or 5 on the C-SSRS) or any suicidal behaviors.
- Potential Hy's law cases: elevated ALT or AST laboratory value that is ≥ 3 × ULN and an elevated total bilirubin laboratory value that is ≥ 2 × ULN and, at the same time, an alkaline phosphatase laboratory value that is < 2 × ULN.

Responses to the C-SSRS that meet the above criterion will be captured in the eTablet and monitored by the sponsor.

Appendix C. Potentially Clinically Important Criteria for Safety Endpoints

The potentially clinically significant criteria for clinical laboratory parameters, vital signs and ECG parameters are provided in the following tables.

Clinical laboratory parameters are provided in the following tables.

Table C-1. Potentially Clinically Significant Criteria for Clinical Laboratory Parameters

Category	Parameter	SI Unit	PCS Criteria	
			PCS Low	PCS High
Chemistry	Albumin	g/L	< 0.8 × LLN	> 1.2 × ULN
	Alanine aminotransferase	U/L	—	≥ 3.0 × ULN
	Alkaline phosphatase	U/L	—	≥ 3.0 × ULN
	Aspartate aminotransferase	U/L	—	≥ 3.0 × ULN
	Bicarbonate	mmol/L	< 0.9 × LLN	> 1.1 × ULN
	Bilirubin, total	µmol/L	—	≥ 1.5 × ULN
	Blood urea nitrogen	mmol/L	—	> 1.5 × ULN
	Calcium	mmol/L	< 0.9 × LLN	> 1.1 × ULN
	Chloride	mmol/L	< 0.9 × LLN	> 1.1 × ULN
	Cholesterol, total	mmol/L	—	> 1.6 × ULN
	Creatinine	µmol/L	—	> 1.5 × ULN
	Creatine kinase	U/L	—	> 2.0 × ULN
	Estimated glomerular filtration rate	mL/min/1.73m^2	< 0.8 × LLN	—
	Glucose, nonfasting	mmol/L	< 0.8 × LLN	> 2.0 × ULN
	Lactate dehydrogenase (LDH)	U/L	—	> 3.0 × ULN
	Phosphorus	mmol/L	< 0.9 × LLN	> 1.1 × ULN
	Potassium	mmol/L	< 0.9 × LLN	> 1.1 × ULN
	Protein, total	g/L	< 0.9 × LLN	> 1.1 × ULN
	Sodium	mmol/L	< 0.9 × LLN	> 1.1 × ULN
	Triglycerides	mmol/L	—	> 2.0 × ULN
	Uric acid	µmol/L	—	> 1.2 × ULN

Category	Parameter	SI Unit	PCS Criteria	
			PCS Low	PCS High
Hematology	Basophils, absolute cell count	10^9/L	—	> 2.0 × ULN
	Eosinophils, absolute cell count	10^9/L	—	> 2.0 × ULN
	Hematocrit	Ratio	< 0.9 × LLN	> 1.1 × ULN
	Hemoglobin	g/L	< 0.9 × LLN	> 1.1 × ULN
	Lymphocytes, absolute cell count	10^9/L	< 0.7 × LLN	> 1.3 × ULN
	Monocytes, absolute cell count	10^9/L	< 0.5 × LLN	> 2.0 × ULN
	Neutrophils, absolute cell count	10^9/L	< 0.7 × LLN	> 1.3 × ULN
	Platelet count	10^9/L	< 0.5 × LLN	> 1.5 × ULN
	Red blood cell count	10^{12}/L	< 0.9 × LLN	> 1.1 × ULN
	White blood cell count	10^9/L	< 0.9 × LLN	> 1.5 × ULN
Urinalysis	pH	pH	< 0.9 × LLN	> 1.1 × ULN
	Glucose	mmol/L	—	Positive[1]
	Protein	g/L	—	Positive[2]
	Specific gravity	—	—	> 1.1 × ULN

LLN = lower limit of normal value; ULN = upper limit of normal value; normal value provided by laboratory;
SI = Le Système International d'Unités (International System of Units)

1. Any results other than trace or normal will be considered as positive.
2. Any results other than trace or negative will be considered as positive.

Table C-2. Criteria for Hepatic Laboratory Abnormalities

Laboratory Parameter	Categories
ALT	≥ 1 × ULN
	≥ 1.5 × ULN
	≥ 2 × ULN
	≥ 3 × ULN
	≥ 5 × ULN
	≥ 10 × ULN
	≥ 20 × ULN

Laboratory Parameter	Categories
AST	≥ 1 × ULN
	≥ 1.5 × ULN
	≥ 2 × ULN
	≥ 3 × ULN
	≥ 5 × ULN
	≥ 10 × ULN
	≥ 20 × ULN
ALT or AST	≥ 1 × ULN
	≥ 1.5 × ULN
	≥ 2 × ULN
	≥ 3 × ULN
	≥ 5 × ULN
	≥ 10 × ULN
	≥ 20 × ULN
Bilirubin Total	≥ 1 × ULN
	≥ 1.5 × ULN
	≥ 2 × ULN
	≥ 3 × ULN
	≥ 5 × ULN
	≥ 10 × ULN
	≥ 20 × ULN
Alkaline Phosphatase	≥ 1 × ULN
	≥ 1.5 × ULN
	≥ 2 × ULN
	≥ 3 × ULN
	≥ 5 × ULN
	≥ 10 × ULN
	≥ 20 × ULN
Concurrent Elevations[1]	ALT or AST ≥ 3 × ULN and Bilirubin Total ≥ 1.5 × ULN
	ALT or AST ≥ 3 × ULN and Bilirubin Total ≥ 2 × ULN

Laboratory Parameter	Categories
Potential Hy's Law[1]	ALT or AST ≥ 3 × ULN and Bilirubin Total ≥ 2 × ULN and ALP < 2 × ULN

ALT = alanine aminotransferase; AST = aspartate aminotransferase; TBL = total bilirubin; ALP = alkaline phosphatase; ULN = upper limit of normal (value provided by the laboratory)

1. Elevations are from the same day.

Vital sign values will be considered PCS if they meet both the observed value criterion and the change from baseline value criterion, if both criteria are available, or meet either the observed value criterion or the change from baseline value criterion that is detailed in the following table.

Table C-3. Potentially Clinically Significant Criteria for Vital Signs Parameters

Parameter	Flag	Criteria	
		Observed Value	Change from Baseline
Systolic blood pressure, mm Hg	High	≥ 180	Increase of ≥ 20
	Low	≤ 90	Decrease of ≥ 20
Diastolic blood pressure, mm Hg	High	≥ 105	Increase of ≥ 15
	Low	≤ 50	Decrease of ≥ 15
Pulse rate, bpm	High	≥ 120	Increase of ≥ 15
	Low	≤ 50	Decrease of ≥ 15
Weight, kg	High	—	Increase of ≥ 7%
	Low	—	Decrease of ≥ 7%
Orthostatic SBP change, mm Hg	Low	≤ -20	—
Orthostatic DBP change, mm Hg	Low	≤ -15	—
Orthostatic Pulse rate change, bpm	High	≥ 25	—

SBP = Systolic blood pressure, DBP = Diastolic blood pressure, bpm = beats per minute

ECG parameter values are considered PCS if ECG values meet either the actual value or change from baseline PCS high criteria listed in the following table.

Table C-4. Potentially Clinically Significant Criteria for ECG Parameters

Parameter	Unit	Actual Value	Change from Baseline
QRS interval	msec	≥ 150	—
PR interval	msec	≥ 250	—
QTcB	msec	> 500	Increase > 60
QTcF	msec	> 500	Increase > 60

QTc = QT interval corrected for heart rate.

QTcB = QT interval corrected for heart rate using the Bazett formula.

QTcF = QT interval corrected for heart rate using the Fridericia formula.

Appendix D. Reporting Selected Laboratory Parameters in Conventional Unit

All clinical laboratory parameters will be reported in the International System (SI) units as standard practice. In addition, descriptive statistics for values and changes from baseline in conventional units at all assessed visits will be reported for selected laboratory parameters as listed in Table D-5 below.

Table D-5. List of Selected Parameters to be Reported in Conventional Units

Number	Laboratory Parameter	Conventional Unit	Decimal Places
1	Alanine Aminotransferase (SGPT)	U/L	0
2	Albumin	g/dL	1
3	Alkaline Phosphatase	U/L	0
4	Aspartate Aminotransferase (SGOT)	U/L	0
5	Bilirubin, Direct (Conjugated)	mg/dL	1
6	Bilirubin, Indirect (Unconjugated)	mg/dL	1
7	Bilirubin, Total	mg/dL	1
8	Blood Urea Nitrogen	mg/dL	0
9	Calcium	mg/dL	1
10	Cholesterol, HDL	mg/dL	0
11	Cholesterol, LDL	mg/dL	0
12	Cholesterol, LDL direct and calculated (combined) *(This lab parameter could be the same as #11)*	mg/dL	0
13	Cholesterol, Total	mg/dL	0
14	Creatine Kinase	U/L	0
15	Creatinine	mg/dL	1
16	Glucose	mg/dL	0
17	Insulin	uIU/mL	1
18	Triglycerides	mg/dL	0
19	Uric Acid	mg/dL	1
20	Hemoglobin	g/dL	1

Appendix E. List of Abbreviations

Abbreviation/Term	Definition
AE	adverse event
AESI	adverse event of special interest
ALP	alkaline phosphatase
ALT	alanine aminotransferase
ASC-12	12-item Allodynia Symptom Checklist
AST	aspartate aminotransferase
CI	confidence interval
C-SSRS	Columbia–Suicide Severity Rating Scale
ECG	electrocardiogram, electrocardiographic
EOS	end of study
ET	early termination
FDS	Functional Disability Scale
GEE	generalized estimating equation
GLMM	generalized linear mixed model
HEOR	Health Economics Outcomes Research
LLN	lower limit of normal value
LSMEAN	least squares mean
MedDRA	Medication Dictionary for Regulatory Activities
mITT	modified intent-to-treat
PCS	potentially clinically significant
PID	participant identification
PLS	population-level summary.
PT	preferred term
Q1	first quartile (25th percentile of the data)
Q3	third quartile (75th percentile of the data)
QTc	QT interval corrected for heart rate
QTcB	QT interval corrected for heart rate using the Bazett formula ($QTcB = QT/(RR)^{1/2}$)
QTcF	QT interval corrected for heart rate using the Fridericia formula ($QTcF = QT/(RR)^{1/3}$)
SAE	serious adverse event
SAP	statistical analysis plan

Abbreviation/Term	Definition
SD	standard deviation
SI	Le Système International d'Unités (International System of Units)
SOC	system organ class
TBL	total bilirubin
TEAE	treatment-emergent adverse event
TESAE	treatment-emergent serious adverse event
ULN	upper limit of normal value
WHO	World Health Organization

Appendix F. Changes to Protocol-planned Analyses

Below are the changes from the planned analyses in protocol version 1.

1. One sensitivity analysis uses the multiple imputation approach to impute the missing headache for the qualifying prodrome event. The missing headache severity assessment by 1 hour postdose will be imputed first. The missing headache by the following timepoints (2, 3, 4, 6, 8, 24 and 48 hours) will be imputed step by step similarly.
2. In the other efficacy analyses, Kaplan-Meier curves for time to development of any intensity headache within 48 hours will be produced with rescue medication taken as an event instead of censoring data collected after the rescue medication. Similar Kaplan-Meier curves will also be produced for time to development of moderate/severe, or severe headache within 48 hours.

Predose baseline variables will be added in the analysis models of absence of any intensity, moderate/severe intensity, severe intensity for the 5 most common individual prodrome symptoms, and absence of aura at each timepoint. These are made in SAP version 3.0 which are changes from planned analyses in protocol versions 1, 2, and 3.