

H8H-CD-LAHK

A Study of Three Doses of Lasmiditan (50 mg, 100 mg and 200 mg) Compared to Placebo in the Acute TReATment of MigrAiNe: A randomized, double-blind, placebo-controlled parallel group study (**SPARTAN**)

NCT02605174

Approval Date: July 18, 2017

STATISTICAL ANALYSIS PLAN

A Study of Three Doses of Lasmiditan (50 mg, 100 mg and 200 mg) Compared to
Placebo in The Acute TReaTment of MigrAiNe: A Randomized, Double-blind,
Placebo-controlled Parallel Group Study (SPARTAN)

Code: COL MIG-302

Final 18 July 2017

Sponsor: CoLucid Pharmaceuticals, Inc.

Version: 2.0

The content of this Statistical Analysis Plan is confidential and may not be passed to any third party without permission of CoLucid Pharmaceuticals, Inc.

Output Templates Signature Page

Output Templates V2.0 (Dated 18JUL2017) for Protocol COL MIG-302

	Name	Signature	Date
Author:	PPD	PPD	
Position:	Biostatistician		
Company:	Quintiles		

Upon review of this document, the undersigned approves this version of the Output Templates, authorizing that the content is acceptable for the reporting of this study.

	Name	Signature	Date
Approved By:	PPD		
Position:	PPD	PPD	
Company:	CoLucid Pharmaceuticals, Inc.		

Table of Contents

LIST OF ABBREVIATIONS	6
1 PURPOSE	8
2 SUMMARY OF THE CLINICAL TRIAL PROTOCOL.....	8
2.1 STUDY SUMMARY.....	8
2.2 SAMPLE SIZE.....	10
2.3 RANDOMIZATION	11
3 EFFICACY AND SAFETY ENDPOINTS	12
3.1 PRIMARY EFFICACY ENDPOINT	12
3.2 KEY SECONDARY EFFICACY ENDPOINT	12
3.3 EXPLORATORY EFFICACY ENDPOINTS.....	12
3.4 SAFETY ENDPOINTS	13
3.5 RESOURCE UTILIZATION ENDPOINTS	13
4 ANALYSIS POPULATIONS.....	13
4.1 SUBPOPULATIONS	14
4.2 EXCLUSIONS FROM PER-PROTOCOL POPULATION	14
4.3 EXAMINATION OF SUBGROUPS.....	15
5 GENERAL SPECIFICATIONS	15
5.1 CHANGES AND CLARIFICATIONS FROM THE PLANNED ANALYSIS	17
5.2 ANALYSIS OF FIRST AND SECOND DOSES.....	18
5.3 HANDLING OF MISSING VALUES.....	18
5.4 DERIVATION OF ELECTRONIC DIARY ASSESSMENT TIMES FOR EFFICACY AND EXPLORATORY ANALYSIS	19
6 DISPOSITION OF SUBJECTS AND DISCONTINUATIONS	21
7 PROTOCOL DEVIATIONS	23
8 DEMOGRAPHICS AND BASELINE CHARACTERISTICS	23
8.1 DEMOGRAPHICS.....	23
8.2 MIDAS	24
8.3 MEDICAL HISTORY	24
8.4 MIGRAINE TREATMENT HISTORY	24
8.5 CHARACTERISTICS OF TREATED MIGRAINE ATTACKS	24
9 PRIOR, CONCOMITANT, AND POST-DOSE MEDICATIONS.....	25
10 TREATMENT COMPLIANCE	26
11 EFFICACY ANALYSES.....	26
11.1 MULTIPLICITY ADJUSTMENT	26
11.2 PRIMARY EFFICACY ANALYSIS.....	27
11.3 KEY SECONDARY EFFICACY ANALYSIS.....	27
11.4 SENSITIVITY ANALYSIS OF PRIMARY AND KEY SECONDARY ENDPOINT FOR CORRECTED STRATUM	28
11.5 SENSITIVITY ANALYSIS OF PRIMARY AND KEY SECONDARY ENDPOINTS FOR	

MISSING DATA	28
11.6 SENSITIVITY ANALYSIS OF PRIMARY AND KEY SECONDARY ENDPOINT BY REMOVAL OF SUBJECTS DUE TO COMPLEX E-DIARY DATA	32
11.7 EXPLORATORY EFFICACY ANALYSES	32
11.7.1 HEADACHE PAIN-FREE	32
11.7.2 SUSTAINED HEADACHE PAIN-FREE	32
11.7.3 MBS-FREE	32
11.7.4 PRESENCE OF MIGRAINE SYMPTOMS	32
11.7.5 HEADACHE RELIEF	33
11.7.6 TIME TO HEADACHE PAIN-FREE	33
11.7.7 TIME TO HEADACHE RELIEF	33
11.7.8 TIME TO MBS-FREE	34
11.7.9 DISABILITY	34
11.7.10 INCIDENCE OF RESCUE OR RECURRENCE MEDICATION USE	35
11.7.11 INCIDENCE OF HEADACHE RECURRENCE	35
11.7.12 PATIENT GLOBAL IMPRESSION OF CHANGE	35
11.7.13 HEADACHE PAIN-FREE AFTER SECOND DOSE	36
11.7.14 TIME TO HEADACHE PAIN-FREE AFTER SECOND DOSE	36
11.7.15 HEADACHE RELIEF AFTER SECOND DOSE	37
11.7.16 TIME TO HEADACHE RELIEF AFTER SECOND DOSE	37
11.7.17 MBS-FREE AFTER SECOND DOSE	38
11.7.18 TIME TO MBS-FREE AFTER SECOND DOSE	38
11.8 SUBGROUP ANALYSIS	39
11.8.1 SUBJECTS WITH ANYTRIPTAN USE WITHIN THREE MONTHS OF SCREENING:	39
11.8.2 SUBJECTS THAT DOSED GREATER THAN 4 HOURS AFTER MIGRAINE START:	39
11.8.3 SUBJECTS WITH EITHER TOPAMAX OR PROPRANOLOL USE WHILE ON STUDY:	39
11.8.4 SUBJECTS WITH TOPAMAX USE WHILE ON STUDY:	39
11.8.5 SUBJECTS WITH PROPRANOLOL USE WHILE ON STUDY:	39
11.8.6 SUBJECTS WITH ONE OR MORE CVRFs	40
12 SAFETY ANALYSIS	40
12.1 ADVERSE EVENTS	40
12.1.1 RELATIONSHIP TO STUDY DRUG	41
12.1.2 ADVERSE EVENT SEVERITY	41
12.1.3 ADVERSE EVENTS LEADING TO DISCONTINUATION	42
12.1.4 SERIOUS ADVERSE EVENTS	42
12.2 CLINICAL LABORATORY EVALUATION	42
12.3 VITAL SIGNS	43
12.4 12-LEAD ELECTROCARDIOGRAMS (ECGs)	43
12.5 PHYSICAL EXAMINATION	44
12.6 COLUMBIA-SUICIDE SEVERITY RATING SCALE (C-SSRS)	44
13 RESOURCE UTILIZATION	45
14 INTERIM ANALYSIS AND DMC	45

15	REFERENCES.....	45
16	APPENDIX.....	45
16.1	PARTIAL DATE IMPUTATION: ALGORITHM FOR PRIOR/CONCOMITANT MEDICATIONS	45
16.2	PARTIAL DATE IMPUTATION: ALGORITHM FOR TREATMENT EMERGENCE OF ADVERSE EVENTS.....	47
16.3	DATA HANDLING RULES OF EFFICACY AND EXPLORATORY ANALYSIS FOR E-E-DIARY AND CRF DATES AND TIMES	49

LIST OF ABBREVIATIONS

The following abbreviations are listed as used within this statistical analysis plan or which might occur within the tables, listings and figures outputs:

>	Greater than
≥	Greater than or equal to
<	Less than
5-HT	5-Hydroxytryptamine
βHCG	Beta human chorionic gonadotropin
AE(s)	Adverse event(s)
ALT	Alanine aminotransferase
AMPP	American Migraine Prevalence and Prevention
AP	Alkaline phosphatase
AST	Aspartate aminotransferase
BP	Blood pressure
bpm	Beats per minute
BPPV	Benign paroxysmal positional vertigo
BUN	Blood urea nitrogen
CAD	Coronary artery disease
CBC	Complete blood count
CD	Compact disc
CFR	Code of Federal Regulations
CRF	Case Report Form
CRO	Contract research organization
CS	Clinically significant
C-SSRS	Columbia Suicide Severity Rating Scale
DBP	Diastolic blood pressure
DVD	Digital video disc
e-diary	Electronic diary
ECG	Electrocardiogram
EoS	End of study
FDA	Food and Drug Administration
GCP	Good Clinical Practice
HEENT	Head, eyes, ears, nose, and throat
HIPAA	Health Insurance Portability and Accountability Act
HIV	Human immunodeficiency virus
HR	Heart rate
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Conference on Harmonization
ICHHD	International Headache Classification
IHS	International Headache Society
IUD	Intrauterine Device
IV	Intravenous
ITT	Intent-to-treat
IVRS	Interactive Voice Response System
IWR	Interactive Web Response
L	Lasmiditan
MBS	Most Bothersome Symptom
MedDRA	Medical Dictionary for Regulatory Activities

mg	milligram
MIDAS	Migraine disability assessment
mITT	modified Intent-to-treat
mL	milliliter
mmHg	millimeters of mercury
NCS	Not clinically significant
P	Placebo
PP	Per protocol
RR	Respiratory rate
SAE	Serious adverse event
SBP	Systolic blood pressure
SD	Standard deviation
TEAE	Treatment emergent adverse events
WBC	White blood cells
WHO	World Health Organization
WOCBP	Women of child-bearing potential
WNL	Within normal limits

1 PURPOSE

This Statistical Analysis Plan was defined by the Sponsor and the responsible statistician without knowledge of the randomization code. It is based on the Study Protocol (Final Version 1.0, November 30, 2015). It contains an actualization and specification of the statistical methods described therein.

2 SUMMARY OF THE CLINICAL TRIAL PROTOCOL

2.1 Study Summary

This is a prospective, randomized, double-blind, placebo-controlled study in subjects with disabling migraine (MIDAS score ≥ 11). Approximately 2968 subjects will be screened and randomized (742 per treatment group based on the first dose) to ensure that approximately 2280 subjects (570 per treatment group based on the first dose) treat a migraine attack and complete the Treatment Period.

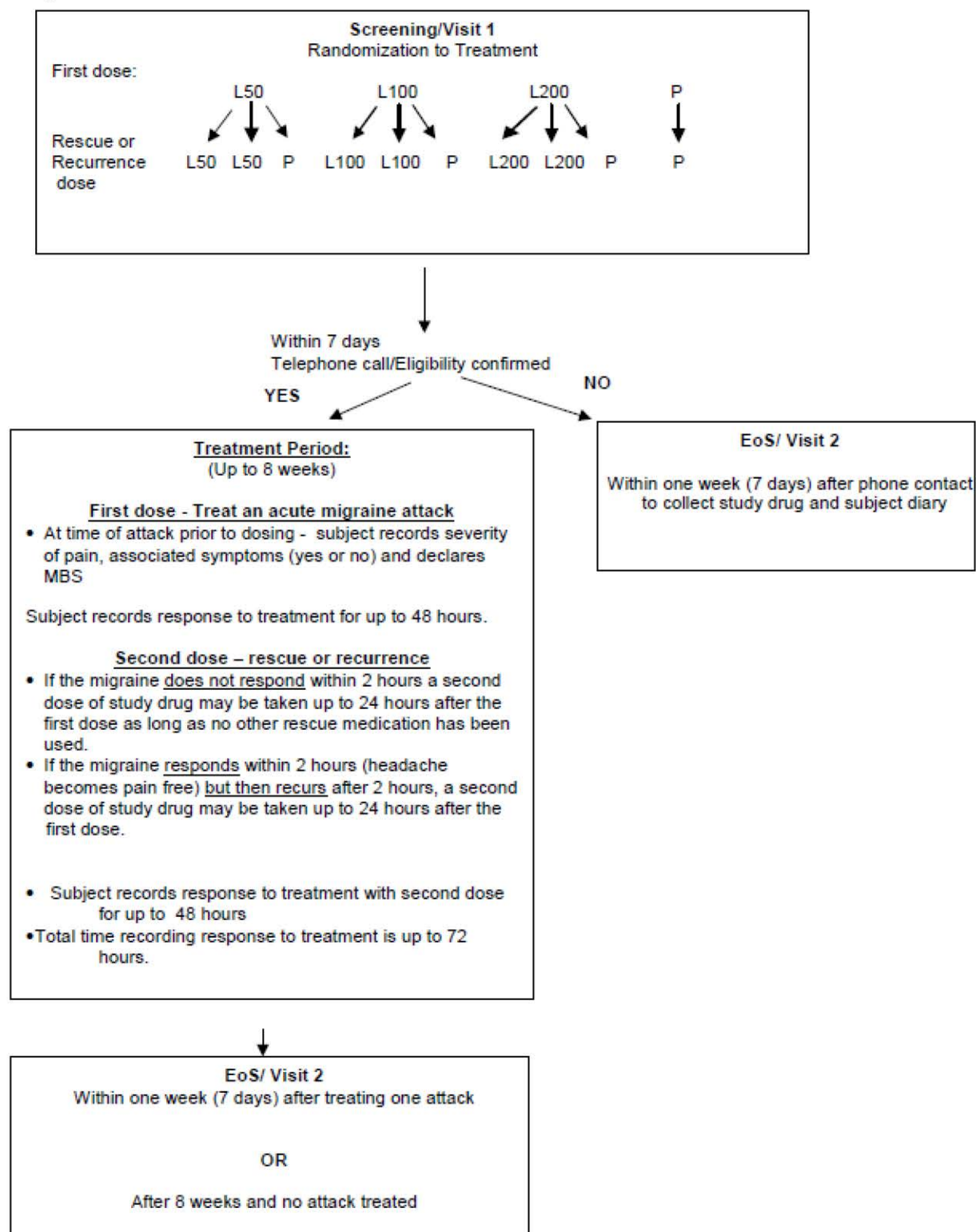
Subjects will be asked to treat a migraine attack with study drug on an outpatient basis. Subjects will be provided with a dosing card containing a dose for initial treatment and a second dose to be used for rescue or recurrence of migraine. Each dose consists of two tablets. Each subject's study participation will consist of a screening visit (Visit 1) with a telephone contact within 7 days to confirm eligibility, a Treatment Period of up to 8 weeks, and an EoS visit (Visit 2) within one week (7 days) of treating a migraine attack. The total time on study will be approximately 11 weeks. Subjects will be randomly assigned treatment as described in Section 2.3.

Subjects will be asked to treat their next migraine attack within 4 hours of onset provided that the headache severity is documented as being of mild, moderate, or severe intensity at that time and not improving. Subjects will record their response to the first dose over the next 48 hours using an electronic diary (e-diary). Subjects will be asked not to use rescue medication until at least 2 hours after dosing with study drug and completing the 2 hour assessments. If the migraine does not respond at 2 hours, a second dose of study drug may be taken up to 24 hours after the first dose as long as no other rescue medication has been used. If the migraine does respond within 2 hours (headache becomes pain-free) but then recurs after 2 hours a second dose of study drug may be taken up to 24 hours after the first dose. Subjects will record their response to a second dose, taken for either rescue or recurrence, for 48 hours in the e-diary. The total time for recording response to study drug is up to 72 hours depending on whether or not a second dose is used. Subjects are to contact the clinic to schedule EoS/Visit 2 within one week (7 days) after one attack has been treated, or after 8 weeks have passed without treating an attack. The total time on study is approximately 11 weeks.

This study is designed to evaluate the efficacy and safety of lasmiditan 50 mg, of lasmiditan 100 mg and of lasmiditan 200 mg, each compared with placebo, in the acute treatment of migraine based on the first dose.

The study will be conducted at up to 150 centers in the US, United Kingdom (UK) and Germany.

Study schema:



2.2 Sample Size

This Phase 3 study is designed to demonstrate that lasmiditan is effective in the treatment of acute migraine in adult subjects with and without aura. The sample size was estimated based on the 2-hour headache pain-free and associated symptoms-free response rates observed in the Phase 2 study COL MIG-202.

Dose	Pain-free	Nausea-free	Phonophobia-free	Photophobia-free
Placebo	7.4%	59.3%	51.9%	36.4%
50 mg	13.9%	68.4%	58.2%	53.2%
100 mg	13.6%	74.1%	75.3%	67.9%
200 mg	18.8%	63.8%	59.4%	58.0%

For the primary endpoint of subjects pain-free at 2 hours, a sample size of 570 evaluable subjects per arm provides power of >90% for the 50 mg dose, the 100 mg dose and the 200 mg dose.

In order to estimate sample size for the key secondary endpoint of subjects who were Most Bothersome Symptom (MBS)-free at 2 hours, simulation was performed in SAS on the conditional probability of being free from any one symptom defined as MBS under 4 different scenarios. For each symptom or combination of symptoms, the likelihood of an individual symptom being the MBS was estimated. In the most conservative scenario (Scenario 1) it was assumed that nausea would always be declared the MBS if it was present, regardless of the presence of other symptoms (phonophobia or photophobia). The other 3 scenarios assumed lower likelihoods of nausea to be considered the MBS and allowed for the other symptoms (either phonophobia or photophobia) to be considered the MBS at a higher rate. This resulted in power estimates of > 95% for MBS at a sample size of 570 for the lasmiditan 50 mg dose and >99% for MBS at sample sizes of 450 to 570 per arm for the 100 mg dose across all 4 scenarios. For the 200 mg dose, an average power of 71% was estimated across five seeds under the most conservative Scenario 1. In contrast, the 3 scenarios that did not declare nausea to be the default MBS if it was present estimated a greater average power of 82.6% to 91%.

Group	Scenario	Variable	Seed				
			55405	74951	82002	82377	90075
Placebo vs D50	1	Power (MBS)	96.90%	95.90%	96.10%	95.60%	96.80%
		Sample Size	570	570	570	570	570
	2	Power	93.70%	94.30%	94.80%	93.90%	93.90%
		Sample Size	450	450	450	450	450
	3	Power	90.40%	90.40%	90.10%	91.00%	91.40%
		Sample Size	575	575	575	575	575
	4	Power	93.70%	94.30%	94.80%	93.90%	93.90%
		Sample Size	450	450	450	450	450
Placebo vs D100	1	Power (MBS)	>99.99%	>99.99%	>99.99%	>99.99%	>99.99%
		Sample Size	570	570	570	570	570
	2	Power	99.90%	>99.99%	>99.99%	>99.99%	>99.99%
		Sample Size	450	450	450	450	450
	3	Power	>99.99%	>99.99%	>99.99%	>99.99%	>99.99%
		Sample Size	575	575	575	575	575
	4	Power	99.90%	>99.99%	>99.99%	>99.99%	>99.99%
		Sample Size	450	450	450	450	450
Placebo vs D200	1	Power	70.87%	70.87%	72.97%	71.17%	68.47%
		Sample Size	570	570	570	570	570
	2	Power	84.40%	85.00%	85.80%	85.90%	85.80%
		Sample Size	450	450	450	450	450
	3	Power	83.50%	83.20%	81.30%	83.40%	81.80%
		Sample Size	575	575	575	575	575
	4	Power	90.20%	90.50%	92.50%	91.40%	90.40%
		Sample Size	450	450	450	450	450

It is expected for a one-sided, two-sample comparison of proportions at the 2.5% level of significance, a sample size of 570 subjects per treatment group (as defined by the first dose) provides >90% power to detect a difference in headache pain-free response rates for assumed true rates of 7.4% and 18.8% (placebo and 200 mg), 7.4% and 13.6% (placebo and 100 mg), and 7.4% and 13.9% (placebo and 50 mg) >90 % power for MBS for both the 50 mg dose arm and the 100 mg dose arm and very near or higher than 80% power for MBS in the 200 mg dose arm.

2.3 Randomization

Subjects will be centrally randomized to one of 7 treatment sequences to receive lasmiditan 50 mg (L50 mg), lasmiditan 100 mg (L100 mg) or lasmiditan 200 mg (L200 mg) or placebo (P) for the first dose (in a 1:1:1:1 ratio) and a second dose for rescue or recurrence of migraine (if needed). Subjects will be stratified (yes or no) for current use of concomitant medication(s) that reduce the frequency of migraine episodes. Study drug will be randomized and dispensed at Visit 1 as follows:

First dose for treatment of migraine	Second dose for rescue or recurrence of migraine (if needed)
L50 mg	L50 mg
	L50 mg
	placebo
L100 mg	L100 mg
	L100 mg
	placebo
L200 mg	L200 mg

	L200 mg
	placebo
Placebo	placebo

3 EFFICACY AND SAFETY ENDPOINTS

3.1 Primary Efficacy Endpoint

The primary efficacy endpoint is the treatment comparison, between lasmiditan 200 mg and placebo, as measured by subjects who are headache pain-free at 2 hours post first dose.

3.2 Key Secondary Efficacy Endpoint

- Treatment comparison, between lasmiditan 200 mg and placebo, as measured by subjects who are MBS-free at 2 hours post first dose.
- Treatment comparison, between lasmiditan 100 mg and placebo, as measured by subjects who are headache pain-free at 2 hours post first dose.
- Treatment comparison, between lasmiditan 100 mg and placebo, as measured by subjects who are MBS-free at 2 hours post first dose.
- Treatment comparison, between lasmiditan 50 mg and placebo, as measured by subjects who are headache pain-free at 2 hours post first dose.
- Treatment comparison, between lasmiditan 50 mg and placebo, as measured by subjects who are MBS-free at 2 hours post first dose.

3.3 Exploratory Efficacy Endpoints

- Headache pain-free at 0.5, 1, 1.5, 3, 4, 24, and 48 hours post-dose based on first dose
- Sustained headache pain-free at 24 and 48 hours post-dose based on first dose
- MBS-free at 0.5, 1, 1.5, 3, 4, 24, and 48 hours post-dose based on first dose
- Presence of migraine symptoms (nausea, phonophobia, photophobia, vomiting) at all-time points based on first and second dose
- Headache relief at all time points based on first dose
- MBS-free at 0.5, 1, 1.5, 2, 3, 4, 24, and 48 hours post-dose by chosen MBS based on first dose
- Time to headache pain-free through 24 hours after first dose
- Time to headache relief through 24 hours after first dose
- Time to MBS-free through 24 hours after first dose, overall and separately for each symptom
- Disability at all time points based on elapsed times since first and second doses
- Incidence of rescue or recurrence medication use at 2 hours, between 2 and 24 hours, and between 24 and 48 hours post first dose
- Incidence of headache recurrence
- Patient global impression of change (PGIC) scale at two hours post-dose, based on elapsed times since first and second dose
- Headache pain-free after a second dose, separately for rescue and recurrence, at all time points
- Time to headache pain-free through 24 hours after a second dose, separately for rescue and recurrence

- Headache relief after a second dose, separately for rescue and recurrence, at all time points
- Time to headache relief through 24 hours after a second dose, separately for rescue and recurrence
- MBS-free after a second dose, separately for rescue and recurrence, at all time points, overall and separately for each symptom
- Time to MBS-free through 24 hours after a second dose, separately for rescue and recurrence, overall and separately for each symptom

3.4 Safety Endpoints

- Adverse events
- Physical examination
- Vital signs
- 12-lead electrocardiograms
- Clinical laboratory parameters
- Columbia Suicide Severity Rating Scale (C-SSRS)

3.5 Resource Utilization Endpoints

- Visits to a cardiologist, or any procedures, hospitalizations, new treatments, or adjustments to treatments for any cardiovascular conditions or disease
- Visits to an emergency room or urgent care for treatment of migraine

4 ANALYSIS POPULATIONS

The following analysis populations will be defined for this study. Subjects' inclusion in or exclusion from these analysis populations will be finalized prior to study unblinding

Randomized population	All randomized subjects. Subjects will be evaluated by the drug to which they are randomized.
Safety population	All randomized subjects who use at least one dose of study drug, regardless of whether or not they undergo any study assessments. Subjects will be evaluated by the drug they use, not by the drug to which they are randomized, when data indicate a difference.
ITT population	All randomized subjects who use at least one dose of study drug and have any post-dose headache severity or symptom assessments. Subjects are evaluated by the drug to which they are randomized.
mITT population	All ITT subjects who treat a migraine attack within four hours of onset. Subjects will be evaluated by the drug to which they are randomized. The mITT population is the primary analysis population.
PP population	All mITT subjects will be considered per protocol (PP) if they do not have major protocol deviations, enumerated below, which might impact the assessment of efficacy. Subjects will be evaluated by the drug to which they are randomized.

Safety-2nd Dose population	All randomized subjects who were considered in the safety population after the first dose and use a second dose of study drug, regardless of whether or not they undergo any study assessments. Subjects will be evaluated by the drug they use, not by the drug to which they are randomized.
ITT-2nd Dose population	All randomized subjects who were considered ITT after the first dose and use a second dose of study drug and have any post-dose headache severity or symptom assessments. Subjects will be evaluated by the drug to which they are randomized.

4.1 Subpopulations

The Safety-2nd Dose and ITT-2nd Dose populations will be further classified as rescue or recurrence populations. Subjects who took a second dose will be classified as either rescue or recurrence as follows:

- **Rescue:** subjects who did not achieve headache pain-free at 2 hours, completed the 2-hour assessments, and took a second dose of study drug between 2 hours and 24 hours post first dose.
- **Recurrence:** subjects who achieved headache pain-free at 2 hours, but then experienced recurrence of mild, moderate, or severe migraine pain and took a second dose of study drug up to 24 hours from the first dose.

4.2 Exclusions from Per-protocol population

The following protocol deviations are considered major and might impact the assessment of efficacy. These deviations would exclude subjects from the PP population.

- Any violation of the following inclusion/exclusion criteria:
Inclusion criteria:
 2. Subjects with migraine with or without aura fulfilling the International Headache Society (IHS) diagnostic criteria 1.1 and 1.2.1 (International Headache Classification (ICHD)-2004).
 4. MIDAS score ≥ 11 .
 6. History of 3-8 migraine attacks per month (< 15 headache days per month).

Exclusion criteria:

12. Previous participation in this clinical trial.
15. History, within past 12 months, of chronic migraine or other forms of primary or secondary chronic headache disorder (e.g. hemicranias continua, medication overuse headache) where headache frequency is greater than or equal to 15 headache days per month.
16. Use of more than 3 doses per month of either opiates or barbiturates.

The criteria violations above will be identified from entries on CRF page Inclusion/Exclusion Criteria or explicitly recorded in Protocol Deviations log.

- First Treatment with study drug beyond 4 hours after the onset of migraine
- Use of triptans and ergots as concomitant medications within 24 hours of study drug administration. As concomitant medications are entered in the CRF with start dates but not times, this 24-hour period will be identified as the date of dosing and the next day. Use of excluded rescue (concomitant) medications before 24 hours after dosing or use of any early

rescue medication (study drug or not) before 2-hour time point. Cases of early rescue medication use will be identified from e-diary entries. Cases of using excluded rescue medication will be identified from concomitant medications data with an entered indication entry that indicates use for migraine. (A listing of all rescue medications will be generated and reviewed prior to study unblinding, and will be used to evaluate this protocol deviation.) As concomitant medications are entered in the CRF with start dates but not times, the 24-hour period will be identified as the date of dosing and the next day.

- Subject begins, or has a change in ongoing medication to reduce the frequency of migraine episodes after randomization. These medications will be identified by drug indication that includes the string “MIGR,” and the string “PROPH” or “MIGR,” and the string “PREV,” and a dosing frequency that does not indicate as-needed use from the concomitant medication page of the CRF. If such a drug is on the migraine history page without a stop date, even if not on concomitant medications page, the subject will be interpreted to be stable on it and the drug will not be considered to represent a deviation for this category. (A listing of all rescue medications will be generated and reviewed prior to study unblinding, and will be used to evaluate this protocol deviation.)
- Subject did not receive study drug as assigned
- Subject did not treat a migraine of at least mild severity
- Subject takes only one of the two required tablets for first dose. These will be identified from entries on the Dosing form of CRF. Entries include counts of tablets dispensed and returned, and comments associated with dispensing and return.

4.3 Examination of subgroups

Subgroup analyses will be conducted as stated in the exploratory analyses section. It should be noted that the study was not designed to detect treatment differences with high statistical power within subgroups.

The following subgroups will be assessed and are classified as follows:

- Subjects with any triptan use within three months of screening.
- Subjects that dosed a migraine greater than 4 hours after migraine start.
- Subjects with either Topamax or Propranolol use while on study.
- Subjects with Topamax use while on study.
- Subjects with Propranolol use while on study.
- Subjects with one or more cardiovascular risk factors (CVRF)
- Subjects with treatment emergent adverse events (TEAE) of dizziness

5 GENERAL SPECIFICATIONS

This section details the specifications for summarizing all efficacy and safety endpoints.

Continuous variables will be summarized using descriptive statistics, i.e. n (number of subjects with available data), mean, median, standard deviation, minimum, and maximum. For those measures that are analyzed using change from baseline scores, descriptive statistics will also be presented on observed scores, unless otherwise noted.

Minimum and maximum values will be presented to the same precision as the raw data. Mean and median will be presented to one more decimal place than the raw data. Standard deviation will be

presented to two more decimal places than the raw data. P-values will be presented to three decimal places.

Categorical variables will be summarized using counts and percentages. Unless otherwise specified, percentages will be calculated using the numbers of subjects in the summarized population in each treatment group as denominators. Percentages will be presented with a precision of 1 digit after the decimal.

In this study, subject will enter the efficacy data on dosing and post-dose assessments in an e-diary. The e-diary records the date and time of the first dose and of the second dose and is programmed to assess specific time points and assessments as defined in the protocol based on the timing of the dose as recorded. This data is collected in the e-diary when e-diary is in migraine mode. Specifics of Migraine Mode are as below:

- Migraine Mode – First Dose
 - The e-diary enters Migraine Mode **ONLY** if the subject indicates taking his/her first dose of study medication
 - Post Dose Assessments will be completed using the Migraine Questions button at specific time intervals for up to 48 hours after the subject confirms taking study medication
 - The time intervals are 30 minutes, 1 hour, 1.5 hours, 2 hours, 3 hours, 4 hours, 24 hours, and 48 hours after the first dose of study medication. The e-diary sets the post dose assessments based on the recorded time of dosing. A subject that begins reporting their migraine at the exact time of dosing will have all of the post dose assessment time points available to them. If a subject starts recording their information in the e-diary after they dose including the time of dosing, the assessments that become available for them are based on the time of dosing, relative to when they accessed the e-diary. For example, if at 1-hour post actual dosing the subject initiates migraine mode and begins entering data into the e-diary, the subject will be allowed to respond to the initial questions about their migraine and time of dosing and then based on the time they record for dosing they automatically will miss subsequent time points, i.e.; the 30 minute and 1-hour time points. A missed time point is missed.
 - Alarms occur at the predefined time points to remind the subject it is time to complete the assessments. The Migraine Questions button is always available, but the subject is not be able to answer the questions until prompted by an alarm within a study migraine.
- Migraine Mode – Second Dose (Optional)
 - The subject should only take a second dose of study medication if the migraine pain is not gone by two hours after the first dose or the migraine pain was gone and came back two hours or more after the first dose (up to 24 hours after first dose).
 - The Dose 2 button will appear AFTER the e-diary recognizes 2 hours have passed since the first dose and remains until the 24-hour time point.
 - During the 2-hour post dose assessment the subject will be asked to indicate if he/she would like to take a second dose of study medication
 - If a second dose is reported alarm intervals are the same as for the reporting of the first dose and any remaining alarms from the first dose are cancelled. However, if

the subject inadvertently enters a dosing time of the second dose occurring prior to the first dose the first dose alarms do not stop and subject can therefore response to post-dose assessments based on time of dosing of first dose, therefore not really assessing their response to the second dose.

In the event that e-diary dates and times are not entered by subject as described in specifics of Migraine Mode but subject actually takes a dose, the dates and times for first and second dose based on subject report will be recorded in the CRF at the site when subject comes to site at Visit 2 /End of Study (EoS). Subject will be asked about their dosing and any unusual symptoms they experienced with their migraine that they had not experienced before. To make the use of CRF date entry consistent across all subjects, these CRF dates and times data will be completed for all subjects even if subject has entered the dates and times on e-diary. This may cause more validation for efficacy and safety analysis dates and times and will be further described in detail in below sections.

Observations collected prior to first dose will serve to determine a baseline measurement; the latest available measurement prior to first dose will be used as the baseline. For safety purposes, the first recorded date and time at which a dose was taken will be used for baseline, without regard for the source of that date (e-diary or CRF). For efficacy purposes, baseline values will be the Hour-0 assessment times identified in the e-diary. Analyses of efficacy data collected after the second dose may require a second "Hour-0" defined by the e-diary relative to the entered time of that second dose.

The start and end of treatment exposure for efficacy and safety analysis will always be identified from the first and last dates of dosing entered in the e-diary, when available and appear to be analysis useful data. As mentioned before if cases like those described in detailed Scenarios #4, #5 and #7 in Section 5.4 leave e-diary dates missing, alternatives from the CRF data will be used for first and second dose dates for safety analysis if there is a confirmation of dosing in the CRF. In some cases if e-diary dates appear to be out of order (CRF dates are clear legitimate corrections of e-diary for first dose and second dose), i.e.: second dose date and/or time recorded in e-diary is before first dose date and/or time; same first and second dose dates and time in e-diary, such dates and/or time will be corrected by CRF data as provided by the subject at Visit 2/EoS. These will be the exceptions where CRF dates will be considered for safety analysis. Otherwise, if the CRF dates and e-diary dates do not match, then for overall treatment exposure, earliest date available from CRF or e-diary will be considered for start of exposure and latest date available from CRF or e-diary will be considered for end of exposure. Additionally, for first dose exposure, earliest date available from CRF or e-diary will be considered for start of exposure of first dose and latest date will be considered for end of exposure of first dose. Similarly, for second dose exposure, earliest date available from CRF or e-diary will be considered for start of exposure of second dose and latest date will be considered for end of exposure of second dose. If the first dose date is missing from the e-diary data as well as CRF data but CRF has a confirmation of first dose, the eligibility-confirmation date will be used as the first alternative for safety analyses, and the randomization date will be the second alternative for safety analyses. If the confirmation of second dose is available on CRF but the second-dose date is missing in e-diary as well as CRF, the alternative will be the study-completion/discontinuation date from the Discontinuation form for safety analysis. Subjects lost to follow-up with no information on dosing on e-diary will be excluded from safety analysis.

The statistical evaluation will be performed using SAS version 9.4 or higher.

5.1 Changes and Clarifications from the Planned Analysis

The protocol detailed mITT-2nd Dose and PP-2nd Dose populations. However, the second dose

analyses are all exploratory, and the decision was made to run all exploratory analyses on the ITT and ITT-2nd Dose populations. The mITT-2nd Dose and PP-2nd Dose populations were, therefore, removed.

The protocol stated that statistical testing would be performed to compare demographic data between treatment groups. It was decided that this testing was unnecessary due to the randomization of the study, and these statistical tests were removed from the analysis.

The analyses of the primary efficacy measure and other related measures described in the protocol were limited to headaches that were of moderate or severe intensity at the time of dosing. In keeping with subsequent input to CoLucid from the Food & Drug Administration (FDA), the efficacy endpoints will take into account headaches that were of mild intensity at the time of treatment.

The protocol stated that logistic regression would be used to model efficacy endpoints, but did not detail what method was to be used for non-binary categorical endpoints. The addition of the Cochran-Mantel-Haenszel test is detailed in the relevant sections below to test these endpoints.

Although the protocol did not specify this, it was decided that the exploratory MBS analyses would be repeated separately for each chosen most bothersome symptom (nausea, phonophobia or photophobia). Additionally, a time to MBS-free analysis was added for all MBS endpoints.

The protocol does not mention an additional subgroup analysis but subgroup analysis described in Section 11.8 will be provided.

5.2 Analysis of First and Second Doses

Any analyses based on first dose will only include data observed up to the time of dosing with a second dose. These summaries will be presented based on the first dose taken. The exception to this is the primary and secondary endpoints at the 2-hour time point; if a second dose is taken before the 2-hour time point, the subject will still be included in the summary at 2 hours and will be analysed as having not achieved headache pain-free or MBS-free status at 2 hours.

Any analyses based on the second dose will only include data observed on or after the time of dosing with a second dose. These summaries will be presented by treatment sequence, listed in Section 2.3. Analyses based on the second dose will be done for both the rescue and recurrence subpopulations.

5.3 Handling of Missing Values

Subjects who fail to record information at a particular analysis time point will have that value considered missing in the respective table, unless otherwise specified.

The primary and key secondary endpoints of headache severity and MBS presence at 2 hours post-dosing are two exceptions to this: (1) Subjects who fail to record a headache severity at 2 hours will be assumed to have not achieved headache pain-free, and (2) subjects who fail to record the absence of a symptom at 2 hours that was considered their MBS at baseline will be assumed to have not achieved MBS-free. A sensitivity analysis for missing data under alternative assumptions will be performed, as described in Section 11.5.

5.4 Derivation of Electronic Diary Assessment Times for Efficacy and Exploratory Analysis

Primary and secondary efficacy endpoints along with second-dose exploratory analysis endpoints will be summarized at various elapsed times following dosing. The endpoints will depend on data collected by an e-diary that requires a subject's response entries in the correct order and at the expected, scheduled assessment times. These assessment times are calculated by the e-diary from elapsed time since dosing. (They will not be recalculated as a part of analysis programming.) The e-diary poses questions to be answered within a pre-specified window of elapsed time after dosing. There will be some scenarios when responses appear to have been limited by the e-diary programming, if questions are not answered in the expected order or during the programmed window, which may cause unscheduled data at some time points.

Unscheduled data can be defined as invalid data at time points which do not correspond to the actual dosing data at the intended time point entered by subject. Listed are some examples of unscheduled data:

1. When subject takes 2nd dose but due to subject's response to the timing of dosing question in e-diary, the e-diary does not understand that subject took 2nd dose, but continues to collect the first dose time points because they are still 'valid' based on subject's entry. Thereby second dose questions do not become available until the time points align. In this case, the data for first dose is unscheduled.
2. Due to subject's responses to e-diary questions, e-diary assumes that subject took 2nd dose at one-time point but subject indicates dosing at a different time point. This makes their second dose data unscheduled but often keeps first dose data from being unscheduled.
3. Due to subject's responses to e-diary questions, e-diary assumes that subject took 2nd dose but subject indicates not dosing as per study drug accountability and CRF confirmation so 2nd dose data will be unscheduled.

Some specific scenarios are listed below for derivation of analysis time points for efficacy and exploratory endpoints.

1. Retroactive dose entry. If a subject enters the time of a dose retroactively, rather than at the time of taking the dose, the recorded time, and potentially date, of the second dose may be before some or all of the scheduled times of assessments that would otherwise have appeared to be associated with the first dose. In those cases, the apparent first-dose assessments after the recorded time of the second dose, and the second-dose assessments at times calculated from the retroactively entered dosing time will not be included in efficacy analyses.
2. Reports intention to take second dose, without confirmation. Subjects report their intention to take a second dose but may not *confirm* having done so in e-diary. Even if indications of taking second dose are observed in e-diary data, until the entry shows confirmation of second dose times, the e-diary will not have a confirmed second-dose time from which to calculate post-dose assessment times after that second dose, and it will not switch to second-dose mode. In this state, second-dose assessments will be missing. Additionally e-diary continues to collect first dose data although the subject may have taken second dose. Even if use of a second dose is recorded on the on CRF, the related second-dose assessments may not be available in the e-diary because the e-diary is not working in second-dose mode; hence, the exploratory endpoints for second dose will not

be available at those analysis times. Additionally, first dose assessments collected after this time will be considered unscheduled.

3. Multiple reports of a migraine - complicated by aura. If a subject reports a migraine, but does not indicate taking first dose at a specific time due to presence of aura, the efficacy and exploratory analysis endpoints for first and second dose will be summarized for the migraine, which has the reference for most recent available treated migraine data at analysis time points.
4. Missing first dose dates and associated assessments in e-diary. If the first dose is reported taken in the CRF with the appropriate date entered in CRF but the subject did not complete the e-diary for assessments, then the date of first dose and associated assessments will be missing in e-diary data. These subjects (e.g. lost to follow-up) will not be included in appropriate populations of efficacy analysis.
5. Missing second dose date and associated assessments in e-diary. If a second dose is reported taken in CRF with appropriate date entered in CRF but the subject is not able to complete e-diary for assessments, then the date and associated assessments of second dose will be missing in e-diary data. These subjects might not be included in appropriate populations of efficacy analysis based on the timing of second dose with respect to first dose. For purposes other than timed efficacy assessments, first and last dates of exposure to treatment will be identified from CRF sources as described in Section 5.
6. First and second dose dates and times in e-diary do not match CRF dates and times. Subjects may have entered dates and times in the e-diary that do not match dates and times ultimately entered in the CRF (data entered in Inform by sites based on subject's recall of dosing). The screens for post dose assessments entered by subjects are auto-generated by the e-diary at times with respect to dosing dates and times entered in the e-diary. As a result of this e-diary function, these subjects will be included in appropriate populations of efficacy analysis with respect to e-diary dates and times and their relative post-dose assessments times. Data handling rules in these cases are listed in Appendix 16.3.

Some additional scenarios under this category are listed as points a. and b. below.

- a. Subjects which indicates that the CRF dates are most appropriate but different than e-diary and can be confirmed with e-diary assessment times, CRF dates will be considered over e-diary dates. For example, subject initially reports in the e-diary that they took second dose at the same time as first dose. However, when they return to site at visit 2 and report their mistake and provide the correct dosing information to be recorded in the CRF the corrected time allows us to preserve first dose assessment data. In those cases, subjects second dose data will be considered as unscheduled and first dose efficacy assessment will be used for appropriate populations of efficacy analysis based on CRF date and times.
- b. For subjects with different e-diary and CRF times, if the e-diary assessments are done retroactively as in Scenario #1, CRF time will be compared with e-diary time. Subjects with the time difference of less than 1 hour will be included in appropriate populations of efficacy analysis for first dose. Subjects with the time difference of greater than 1 hour will be included in appropriate populations of efficacy analysis with the assumption e-diary assessments are correct on CRF. These subjects will be removed from additional sensitivity analysis as described in Section 11.6 for primary and key secondary analysis.

7. Treating more than one migraine, or taking second dose too late. If a subject treats two distinct migraines with the first and second doses or takes the second dose later than 24 hours after first dose, the date and times for second dose assessments will not be available for recording assessment results in the e-diary. As in Scenario #4 and #5 above, for these subjects, the date of the last dose date for purposes other than timed efficacy assessments will be identified from CRF data as described in Section 5.
8. Subjects reporting migraine start time or dosing time in future in e-diary. If a subject reports a migraine start time in the future and if the time reported is less than one hour in the future, this will be considered as minor minute or hour entry issues and the migraine start time will be set as time of collection. The remaining time issues will be assumed on visual confirmation as AM/PM (midnight/noon) and PM/AM (yesterday/today) entry issues then these will be rolled back by increments of 12 hours until the time is before time of data collection. After these corrections if migraine start is still after dosing time then the migraine start time is set to dosing time. These subjects will be included in the appropriate populations of efficacy analysis with these assumptions but will be removed from additional sensitivity analysis as described in Section 11.6 for primary and key secondary analysis.
 - a. Similarly for subjects who report a first dose time with start in the future (by several hours) than indicated dosing with question “Treating Migraine with Study Med now” as “Y” at the migraine pain begin time, their efficacy assessments for first dose will be those many hours ahead of the actual assessment time for severity reporting. For example, e-diary’s 0.5 hour time point is actually 7.5 hours if the first dose time is after 7 hours of the reported migraine start time. If the reported dose time is less than 10 minutes than the time of reporting migraine as in the stated question, then these will be ignored and subject’s efficacy assessments will be used for appropriate populations of efficacy analysis. All other subjects with time difference of greater than 10 minutes will be excluded from the appropriate populations of efficacy analysis.
9. Subjects with partial second dose time on CRF and no e-diary date and time for second dose Subjects who are able to enter the first dose assessment data in e-diary but they are not able to complete the e-diary for second dose. These subjects will be able to give second dose confirmation date on the CRF at site for visit 2 but may not remember the time of the dosing for second dose after first dose. These subjects will be considered in the appropriate populations of efficacy analysis for first dose available assessments based on the assumption that they took the second dose after the minimum of 2 hours post first dose. For these subjects any assessments for first dose data after 2 hours will be unscheduled and not be summarized. To rule out this assumption, these subjects will be removed from additional sensitivity analysis as described in Section 11.6 for primary and key secondary analysis.

6 DISPOSITION OF SUBJECTS AND DISCONTINUATIONS

The following will be summarized overall and by treatment sequence, for all subjects, as counts and percentages of all subjects:

- Subjects randomized
- Subjects with confirmed eligibility
- Subjects treated

- Subjects treated with second dose
 - Treated with second dose for rescue
 - Treated with second dose for recurrence
- Subjects in each of the analysis populations:
 - Randomized population
 - ITT population
 - mITT population
 - PP population
 - ITT-2nd Dose population; overall, for rescue, and for recurrence
 - Safety population
 - Safety-2nd Dose population
- Subjects who completed the study
 - Treated
 - Not treated
 - Reason for not having been treated
 - No Migraine
 - No access to study medication during migraine
 - No eligible migraine within 8 weeks
- Treated but did not return for Visit 2 (EOS)
- Discontinued subjects
 - Treated
 - Not treated
- Reasons for subject discontinuation
 - Adverse event
 - Death
 - Lost to follow-up
 - Non-compliance with protocol requirements
 - Pregnancy
 - Subject request
 - Investigator request
 - Sponsor request
 - Randomization failure
- Randomized subjects at each investigative site
- Subjects with treatment unblinded by site
- Subjects with headache severity data at 2 hours post first dose
- Subjects with MBS data at 2 hours post first dose

The number and percentage of subjects in each disposition category will be presented; percentages will be based on the number of randomized subjects. Percentages for the number of subjects randomized will be based on the total number of subjects who enrolled in the study. Percentages for the number of subjects treated with a second dose for rescue or recurrence will be based on the total number of subjects who took a second dose. Percentages for the treated status of discontinued subjects will be based on the number of subjects who discontinued. For discontinuation reasons, percentages will be based on the number of subjects who discontinued. Subjects' inclusion in the analysis populations will be listed. Disposition data, and all subjects who discontinue from the study, will be presented in listings.

7 PROTOCOL DEVIATIONS

The number and percentage of subjects with protocol deviations leading to exclusion from the PP population will be presented by reason for exclusion and treatment sequence. Summaries will be run on all confirmed eligible subjects in the Randomized population and on the mITT population, with percentages based on the number of subjects in those populations. All deviations will be listed.

8 DEMOGRAPHICS AND BASELINE CHARACTERISTICS

8.1 Demographics

The following will be summarized by treatment group and overall for the ITT, mITT, PP, and Safety populations, and by treatment sequence and overall for the Randomized, ITT-2nd Dose, and Safety-2nd Dose populations.

- Age
- Gender
 - Female
 - Male
- Race
 - American Indian or Alaska Native
 - Asian
 - Black or African American
 - Native Hawaiian or other Pacific Islander
 - White
 - Other
 - Multiple
- Ethnicity
 - Hispanic or Latino
 - Not Hispanic or Latino
 - Not Reported
 - Unknown
- Height (in)
- Weight (lb)
- BMI (kg/m²)
- Smoking history
 - Never
 - Former
 - Currently
- Family history of coronary artery disease
 - Yes
 - No
- Cardiovascular Risk factors by Gender and Male greater than or equal to 40
- Duration of migraine history (years)
- Average migraines per month during the past 3 months from the date of Visit 1
- Experiencing migraine attacks both with and without aura (yes or no)
- Use of medication that reduces the frequency of migraine episodes as recorded in IVRS.

Age will be calculated using the difference in days between the date of birth and the date of informed consent.

BMI will be calculated as:

$$\text{Weight (lb)} / \text{height (in)}^2 * 703$$

Duration of migraine history, presented in years, will be calculated using the difference in days between the date of migraine diagnosis and the date of informed consent.

All demographic data will be presented in a listing.

8.2 MIDAS

Migraine Disability Assessment (MIDAS) total scores will be summarized by treatment sequence for the Randomized, ITT, and mITT populations. The MIDAS is a five-item questionnaire; the MIDAS total score is calculated as the sum of the answers to all five questions. The specifics of the questionnaire are detailed in Appendix 3 of the Protocol. The total MIDAS score will be calculated at each site on the questionnaire and any analytical missing data imputation will not be performed for missing value. The total score will be calculated based on the available score for each subject.

Additionally, descriptive statistics on the number of days subjects experienced headaches in the past three months and the average pain of those headaches will be presented. Average pain is measured on a scale from 0 to 10, where 0 is no pain at all and 10 is pain as bad as it can be.

Answers to individual MIDAS questions will be presented in a listing.

8.3 Medical History

Medical history will be summarized by treatment group for the Safety population, and treatment sequence for the Safety-2nd Dose population. Medical history will be coded using the Medical Dictionary for Regulatory Activities (MedDRA), version 18.0, and sorted alphabetically by system organ class and then preferred term by frequency. Subjects with multiple occurrences of the same medical history term will be counted once within the corresponding system organ class and preferred term.

All medical history will be presented in a listing.

8.4 Migraine Treatment History

Migraine treatment history will be summarized by treatment sequence. The summaries will be presented for the ITT and mITT populations. Migraine treatment history will be coded using the WHO Drug Dictionary, version WHODDE 01MAR2015E, and sorted by frequency of preferred name. Subjects with multiple occurrences of the same medication will be counted once within the corresponding preferred name.

All migraine history and migraine characteristics data will be presented in listings.

8.5 Characteristics of Treated Migraine Attacks

The following will be summarized by treatment group for the mITT and ITT populations, and by treatment sequence for the ITT-2nd Dose population.

- Time to dosing (or second dosing) from the start of migraine attack (hours)
- Time to dosing (or second dosing) from the start of moderate or severe pain (hours)
- Baseline migraine severity
 - Severe (3)

- Moderate (2)
 - Mild (1)
 - None (0)
- Baseline associated symptoms (yes or no)
 - Nausea
 - Phonophobia
 - Photophobia
 - Vomiting
 - None
- Baseline most bothersome symptom
 - Nausea
 - Phonophobia
 - Photophobia
- Accompanying aura at time of first dose (yes or no)
- Second dose of study drug taken before the 2-hour assessment (yes or no)
- Other medications taken to treat migraine (yes or no)
 - No
 - Yes, before 2-hour assessment
 - Yes, after 2-hour assessment
- Number of days of school or work missed due to migraine

Time to dosing from start of the migraine attack (hours) will be calculated as:

date/time of dosing –
date/time of start of the acute migraine attack

Time to dosing from start of moderate or severe pain (hours) will be calculated as:

date/time of dosing –
date/time of start of moderate to severe pain

Date and time of dosing will be taken from the subject e-diary.

9 PRIOR, CONCOMITANT, AND POST-DOSE MEDICATIONS

The frequency and percentage of prior, concomitant, and post-dose medication use will be presented by treatment group based on first dose and summarized for the Safety population. Medications will be coded using the WHO Drug Dictionary, version WHODDE 01MAR2015E, and sorted by frequency of preferred name.

Prior medications are those taken on or after the date of Visit 1 and before the day of any dosing of study drug. Concomitant medications are those taken on the day of, or within two days after, any dose of study drug. Post-dose medications are those taken after two days after any dose of study drug and on or before the end of the study. (Sources of these dates are elaborated in Section 5.)

Medications missing a start and end date will be considered prior, concomitant, and post-dose. Medications missing a start or end date will be considered as having been taken in all applicable time points based on the non-missing date. See Appendix 1 for derivations related to partial dates and times.

All medication data will be presented in a listing.

10 TREATMENT COMPLIANCE

Both the first and second dose of study drug requires taking two tablets for each dose. Compliance with a prescribed dose can be either 50% (the subject only took one of the tablets), or 100% (the subject took both tablets for the first dose). Compliance is not calculated for subjects who did not take a dose. If the CRF entries leave the number of tablets taken per dose unclear, 50% compliance will be assumed for one or both doses.

Descriptive statistics will be used to summarize compliance separately for subjects who took a first dose, and for subjects who took a second dose.

Subjects are asked not to use a second dose until at least two hours after the first dose. The time from first to second dose will be summarized with descriptive statistics for subjects who took a second dose.

Compliance data will also be presented in a listing.

11 EFFICACY ANALYSES

This section details the specifications for summarizing efficacy endpoints.

The primary and key secondary efficacy analyses will be performed on the ITT, mITT, and PP populations. The primary analysis population is the mITT population. Exploratory efficacy analyses will be performed on the ITT and ITT-2nd Dose populations, depending on the endpoint. Efficacy responses will also be presented in a listing.

Unless otherwise stated, all primary, secondary, and exploratory efficacy hypotheses will be tested using a logistic regression model with treatment group and background use of medication to reduce the frequency of migraine episodes as covariates. For treatment comparisons, an estimate of the odds ratio of achieving a response, as well as the corresponding confidence interval and p-value using Wald's test, will be computed. Tests of the primary and key secondary endpoints will be conducted at a one-sided significance level of 0.025; tests of all other endpoints will be conducted at a two-sided significance level of 0.05.

Analyses of second-dose endpoints with too few subjects in the treatment-sequence-subpopulation groups may have too little data separation for a logistic regression model to reach a stable solution. For these models, the "Firth" modification of the maximum likelihood estimation will be used to achieve a solution.

The efficacy endpoints will depend on data collected by e-diary that depends on subject's response entry in the correct order and at the expected scheduled e-diary assessment times. Assessment times are analyzed as calculated by the e-diary and not as part of analysis programming.

11.1 Multiplicity Adjustment

The gatekeeping procedure will be implemented to prevent Type I error inflation for multiple comparisons among the primary and secondary analyses. The primary efficacy endpoint will be tested first. If the primary analysis is statistically significant (one-sided $p < 0.025$), additional confirmatory hypotheses will be tested sequentially, in the following order:

1. Treatment comparison, between lasmiditan 200 mg and placebo, as measured by subjects who

- are MBS-free at 2 hours post-dose.
2. Treatment comparison, between lasmiditan 100 mg and placebo, as measured by subjects who are headache pain-free at 2 hours post-dose.
 3. Treatment comparison, between lasmiditan 100 mg and placebo, as measured by subjects who are MBS-free at 2 hours post-dose.
 4. Treatment comparison, between lasmiditan 50 mg and placebo, as measured by subjects who are headache pain-free at 2 hours post-dose.
 5. Treatment comparison, between lasmiditan 50 mg and placebo, as measured by subjects who are MBS-free at 2 hours post-dose.

If one of the analyses is not statistically significant, then all subsequent analyses will be exploratory rather than confirmatory.

11.2 Primary Efficacy Analysis

The primary efficacy analysis will test the treatment effect, between lasmiditan 200 mg and placebo, of the primary efficacy endpoint of the proportion of subject's headache pain-free at 2 hours post-dose. This analysis will be presented by treatment group, based on the first dose.

Headache pain-free is defined as a reduction in headache severity from mild (1), moderate (2), or severe (3) at baseline to none (0).

Subjects who do not provide a headache pain severity rating at baseline, or who do not provide a headache pain severity rating at the two-hour time point will be assumed to have not achieved headache pain-free.

Subjects taking any rescue medication within the first two hours will be assumed to have not achieved headache pain-free. Subjects who use other medication prior to the study drug to treat the migraine attack will also be assumed to have not achieved headache pain-free.

Subjects who treat a no (0) severity migraine will not be included in the primary analysis. Sensitivity analyses, as described in Sections 11.4, 11.5 and 11.6 will also be performed for the primary endpoint on the mITT population.

11.3 Key Secondary Efficacy Analysis

The key secondary efficacy analyses will test the following:

- The treatment effect, between lasmiditan 200 mg and placebo, of the key secondary efficacy endpoint of MBS-free at 2 hours post-dose.
- The treatment effect, between lasmiditan 100 mg and placebo, of the key secondary efficacy endpoint of headache pain-free at 2 hours post-dose.
- The treatment effect, between lasmiditan 100 mg and placebo, of the key secondary efficacy endpoint of MBS-free at 2 hours post-dose.
- The treatment effect, between lasmiditan 50 mg and placebo, of the key secondary efficacy endpoint of headache pain-free at 2 hours post-dose.
- The treatment effect, between lasmiditan 50 mg and placebo, of the key secondary efficacy endpoint of MBS-free at 2 hours post-dose.

MBS-free is defined as the absence of the associated symptom of migraine (either nausea, phonophobia, or photophobia) at 2-hour post-dose that was identified pre-dose as the most bothersome symptom. Subjects who record that no symptoms were present at baseline will be

excluded from the key MBS analyses. Likewise, subjects who treat a migraine of no (0) severity will not be included in the key analysis of headache pain. Such subjects will also be excluded from the table produced for the sensitivity analysis described in Section 11.5, but not from the programming steps that impute missing MBS data.

Subjects who do not provide a symptom rating at baseline will be considered as follows:

- Subjects who record at least one symptom present at baseline, but who do not designate one as most bothersome, will be treated as if all symptoms present are most bothersome and will be considered MBS-free at any time point post-dose only if all symptoms present at baseline are no longer present at that time point.

Subjects taking rescue medication within the first two hours, or who fail to record a symptom rating at 2 hours, will be assumed to have not achieved MBS-free. Subjects who use other medication prior to the study drug to treat the migraine attack will also be assumed to have not achieved MBS-free.

The counts and percentages of which symptom was chosen as the most bothersome symptom will also be presented.

These analyses will be presented by treatment group, based on the first dose.

Sensitivity analyses, as described in Sections 11.4, 11.5 and 11.6 will also be performed for the key secondary endpoints on the mITT population.

11.4 Sensitivity Analysis of Primary and Key Secondary Endpoint for Corrected Stratum

While randomizing subjects in the study, subjects were to be stratified (yes or no) for use of prophylactic medications that prevent or reduce the frequency of migraine episodes. In the event of mis-stratification occurring while randomizing these subjects, the primary and key secondary analyses will be redone using stratification as corrected in the course of data review. The data for headache pain free and MBS free at 2-hour post dose will be analyzed as described in Sections 11.2 and 11.3, but using the corrected stratifications.

11.5 Sensitivity Analysis of Primary and Key Secondary Endpoints for Missing Data

The proposed primary method of handling missing data that considers subjects with missing data at 2 hours as non-responders may be regarded as not conservative if the proportion of subjects with missing data at 2 hours is greater in the placebo arm than in the lasmiditan arms. To address the possibility of this scenario, headache severity score/MBS presence at 2 hours will be imputed under the following assumptions.

Missing data for subjects from the placebo arm will be imputed under the assumption of the missing at random (MAR) mechanism, where these subjects are assumed to have unobserved values in line with similar placebo subjects with available data, taking into account their values observed prior to time points with missing data. For subjects from the lasmiditan arms, monotone missing data (missing from a given time point through 2 hours) will be imputed from the MAR-based imputation model that was estimated from the placebo subjects, assuming that the lasmiditan subjects with missing data will drift towards the mean response of the placebo arm. This approach is likely to result in more favorable imputations for the placebo arm compared with the non-responder assumption, while for the lasmiditan arms it will not assume a treatment effect beyond the study effect. This approach will be more conservative than the primary analysis if the proportion of subjects dropping out is greater in the placebo arm than in the lasmiditan arms.

This approach will be implemented with multiple imputation (using PROC MI in SAS v9.4) as described in the following 3 steps.

- Early rescue. Subjects taking any rescue medication within the first two hours will be assumed to have the worst possible value (i.e., headache severity = 3/MBS still present) for all time points up to 2 hours (missing or not) after the intake of rescue medication.
- Establish monotone missing pattern. Intermediate missing data will be imputed under the MAR assumption within each treatment arm using a Fully Conditional Specification (FCS) method using a logistic regression imputation model with variables for treatment group, background use of medication to reduce the frequency of migraine episodes, baseline headache severity score, baseline MBS, pain severity score, and MBS presence at all time points. Five hundred imputations will be generated. The seed to start the random number generator will be 416713. Only imputations for intermediate missing values will be retained from this step. The remaining (monotone) missing data will be imputed as described below.

To accomplish this, original data with missing values will be reconfigured to a “horizontal” data set wherein missing data are to be imputed. Consistent with the table to be generated, treatment sequences will be combined by the first dose in each sequence. It will include assessments of headache severity and MBS free. Each subject will have one observation and 1 response variable for headache severity at each time point and 1 response variable for MBS at each time point. (e.g., HAsev_0, HAsev_1,..., HAsev_8, MBS_0, MBS_1, ..., MBS_8). Original headache severity ratings will be kept in the reconfigured data and reduced to pain-free, or not, at the step where analysis models are run. An entered assessment of no MBS at the time of dosing will be kept in the reconfigured data and that result of no MBS will be propagated to the last assessment time for which a subject also has headache-pain assessments.

The PROC MI procedure will be used to fill in the missing data to get “monotone missing pattern,” using code of this general form:

```
proc mi data = horizontal
    out = monotone
    nimpute=500
    seed = 416713
    ;
var trtp cmuse2fl HAsev_0 MBS_0 HAsev_1 MBS_1 HAsev_2 MBS_2 HAsev_3 MBS_3
    ... HAsev_8 MBS_8;

class trtp cmuse2fl HAsev_0 MBS_0 HAsev_1 MBS_1 HAsev_2 MBS_2 HAsev_3 MBS_3
    ... HAsev_8 MBS_8;

FCS LOGISTIC;

run;
```

- MAR-based placebo model. Data partially imputed on previous steps will then be used together with observed data for the estimation of the MAR-based model from the placebo arm, which will be done using a sequential logistic regression imputation model (Ratitch et al, 2013). The seed to start the random number generator will be 482112.

The MAR-based placebo imputation model for headache severity score as well as for MBS presence will be estimated based on data from placebo subjects and will include background use of medication to reduce the frequency of migraine episodes, baseline headache severity score, baseline MBS, pain severity score, and MBS presence at the previous time point before the one being imputed as explanatory variables. The placebo treatment group value will be set to make it the reference value. Missing values of headache severity score and MBS presence in all treatment arms will then be imputed from this single placebo imputation model.

For this step, PROC MI will be run second time with a BY variable that identifies the individual imputations from the previous steps. Code will have this form.

```
proc mi data = monotone_post
/* "monotone_post" contains data after a post-processing step above, in which imputed
values were retained for only the original intermediate missing values (those not originally
fitting the monotone missing pattern). */

    out = imputed_all
    nimpute = 1
    seed = 482112
    ;
    by _imputation ;

/*Note: treatment variable in the CLASS statement for compatibility with the MNAR
statement*/

CLASS trtp cmuse2fl HAsev_0 MBS_0 HAsev_1 MBS_1 HAsev_2 MBS_2 HAsev_3
MBS_3 HAsev_4 MBS_4;

var cmuse2fl HAsev_0 MBS_0 HAsev_1 MBS_1 HAsev_2 MBS_2 HAsev_3 MBS_3
HAsev_4 MBS_4;

/*MONOTONE LOGISTIC statement and MNAR statement will be added for each imputed
variable as below */

monotone logistic (HAsev_1 = cmuse2fl HAsev_0 MBS_0);
monotone logistic (MBS_1 = cmuse2fl HAsev_0 MBS_0 );
monotone logistic (HAsev_2 = cmuse2fl HAsev_0 MBS_0 HAsev_1 MBS_1);
monotone logistic (MBS_2 = cmuse2fl HAsev_0 MBS_0 HAsev_1 MBS_1);

...

monotone logistic (HAsev_4 = cmuse2fl HAsev_0 MBS_0 HAsev_3 MBS_3);
monotone logistic (MBS_4 = cmuse2fl HAsev_0 MBS_0 HAsev_3 MBS_3);

mnar model(HAsev_1 / modelobs=(trtp='0'));
mnar model(MBS_1 / modelobs=(trtp='0'));

...
```

```
mnnar model(HAsev_4 / modelobs=(trtp='0'));
mnnar model(MBS_4 / modelobs=(trtp='0'));

run;
```

Headache pain-free status and MBS-free status will then be computed from the multiple imputed data. The multiple imputed datasets will be analysed using the same methods as in the primary or secondary analysis for each imputation created above, followed by combining the results using Rubin's rule (Rubin, 1987). Odds ratios and the corresponding standard error estimates obtained from analysis of each imputed dataset will be log-transformed before applying Rubin's combination rule. The combined estimate and confidence limits will then be exponentiated to obtain the combined odds ratio and confidence interval.

For this purpose, proportions of responders and confidence intervals about those proportions will be estimated for each imputation and treatment group using the FREQ procedure. Those estimates will then be combined using the MIANALYZE procedure, using code of this form:

```
*** Combine proportion estimates of responders in each treatment arm;
PROC SORT DATA=prop_trtp
  BY trtp _Imputation_
RUN;

PROC MIANALYZE DATA=prop_trtp ;
  MODELEFFECTS prop ;
  STDERR prop_se ;
  BY trtp ;
  ODS OUTPUT PARAMETERESTIMATES=mian_prop_trtp ;
RUN ;
```

Such data for proportion of headache pain free and MBS free will be presented only up to 2-hour time points.

For the hypothesis test and odds ratio at 2 hours, parameter estimates and confidence intervals about the parameters will be produced using the LOGISTIC procedure for each imputation created in PROC MI. The predictor variables in the LOGISTIC model will include treatment group and stratification value. The estimates will then be combined using the MIANALYZE procedure in a step of this form:

```
PROC MIANALYZE PARMS(CLASSVAR=CLASSVAL)=lgsparms ;
  CLASS trtp cmuse2fl ;
  MODELEFFECTS trtpn ;
  ODS OUTPUT PARAMETERESTIMATES=mian_ ;
RUN ;
```

Odds ratios and corresponding confidence intervals will be calculated by exponentiating the combined parameter estimates.

Additionally percent of subjects with missing data to be imputed, and percent of data points imputed at each times before 2 hours will be summarized for headache pain free and MBS free.

11.6 Sensitivity analysis of Primary and Key Secondary Endpoint by removal of subjects due to complex e-diary data

As described in the Section 5.4, #6b, #8 and #9, some complex e-diary data issues may lead some subjects to be included in the original efficacy analysis of primary and key secondary endpoint under some listed assumptions. To these assumptions, the primary and key secondary efficacy analyses will be redone by removing these subjects. The data for headache pain free and MBS free at 2-hour post dose will be analysed as described in Sections 11.2 and 11.3, but by removing these subjects in the described section.

11.7 Exploratory Efficacy Analyses

The exploratory endpoints depend on data collected in an e-diary under the same constraints as the primary and secondary endpoints with response entry in the correct order and at the expected scheduled assessment times.

11.7.1 Headache Pain-Free

The endpoint of headache pain-free will be summarized at the 0.5, 1, 1.5, 3, 4, 24, and 48-hour post-dose time points. This summary will be presented by treatment group for the ITT, mITT, and PP populations, based on first dose.

Subjects who had a mild, moderate, or severe headache at the time of dosing will be the reference subjects for this summary. Subjects missing a headache severity at baseline will not be summarized. Subjects missing a severity assessment at a post-dose time point will not be counted as pain-free.

11.7.2 Sustained Headache Pain-Free

Sustained pain-free response will also be summarized at the 24 and 48-hour post-dose time points. This summary will be presented by treatment group for the ITT population, based on first dose.

Sustained Pain-Free is defined as experiencing headache pain-free at two hours after first dose and at the subsequent indicated assessment time, having not used any medications after the first dose.

11.7.3 MBS-Free

The endpoint of MBS-free will be summarized at the 0.5, 1, 1.5, 3, 4, 24, and 48-hour post-dose time points. This summary will be presented by treatment group for the ITT, mITT, and PP populations, based on first dose. This summary will be repeated separately for each symptom (nausea, phonophobia, and photophobia) on the ITT population.

Subjects missing symptoms at baseline or at the summarized time point will not be summarized at that time point.

11.7.4 Presence of Migraine Symptoms

Counts and percentages of the presence of migraine symptoms will be presented at the 0.5, 1, 1.5, 2, 3, 4, 24, and 48-hour post-dose time points. This will be summarized based on the first dose using the ITT population, and based on the second dose for recurrence and rescue using the ITT-2nd Dose population.

The presence of the following symptoms will be presented based on the response to the presence of that symptom at that time point.

- Nausea
- Phonophobia
- Photophobia
- Vomiting

11.7.5 Headache Relief

Counts and percentages of the number of subjects with headache relief will be presented at the 0.5, 1, 1.5, 2, 3, 4, 24, and 48-hour post-dose time points. This summary will be presented by treatment group for the ITT population, based on first dose.

Headache relief is defined as experiencing a moderate (2) or severe (3) headache at baseline which becomes mild (1) or none (0) at the summarized time point, or a mild headache at baseline which becomes none at the summarized time point.

Subjects missing a headache severity at baseline or at the summarized time point will not be summarized at that time point.

11.7.6 Time to Headache Pain-Free

The time to headache pain-free will be presented by treatment group using a Kaplan-Meier analysis. This summary will be presented for the ITT population, based on the first dose.

The number of subjects experiencing headache pain-free, and the number of subjects censored, will be summarized. The Kaplan-Meier estimates, and 95% confidence intervals calculated using the log-log transformation, of the number of hours for 25%, 50%, and 75% of subjects to experience headache pain-free will be presented. The Kaplan-Meier estimate, and 95% confidence interval, of the probability of experiencing headache pain-free will be presented at the 0.5, 1, 1.5, 2, 3, 4, and 24-hour post-dose time points.

Time to headache pain-free will be calculated as:

date/time headache severity is reported as none (0) –
date/time of dosing of mild (1), moderate (2), or severe (3) headache

Subjects who do not report a headache with severity of none, or who report a headache with a severity of none after 24 hours post-dose, will be censored at the time of their last non-missing post-dose headache severity assessment at or before 24 hours. Subjects with missing baseline headache severity, or who report a headache severity of none (0) at baseline, will be censored at the time of first dose.

A figure of the Kaplan-Meier analysis will also be presented.

11.7.7 Time to Headache Relief

The time to headache relief will be presented by treatment group using a Kaplan-Meier analysis. This summary will be presented for the ITT population, based on the first dose.

The number of subjects experiencing headache relief, and the number of subjects censored, will be summarized. The Kaplan-Meier estimates, and 95% confidence intervals calculated using the log-log transformation, of the number of hours for 25%, 50%, and 75% of subjects to experience headache relief will be presented. The Kaplan-Meier estimate, and 95% confidence interval, of the probability of experiencing headache relief will be presented at the 0.5, 1, 1.5, 2, 3, 4, and 24-hour post-dose time points.

Time to headache relief is calculated as:

{1} For subjects randomized with moderate or severe headache pain: time [pain is none or mild] minus time [dosing for moderate or severe pain] and {2} For subjects randomized with mild headache pain: time [pain is none] minus time [dosing for mild pain]

Subjects who do not report a headache with severity of mild or none, or who report a headache with a severity of mild or none after 24 hours post-dose will be censored at the time of their last non-missing post-dose headache severity assessment at or before 24 hours. Subjects with missing baseline headache severity, or who report a headache severity of none (0) at baseline, will be censored at the time of first dose.

A figure of the Kaplan-Meier analysis will also be presented.

11.7.8 Time to MBS-Free

The time to MBS-free will be presented by treatment group using a Kaplan-Meier analysis. This summary will be presented for the ITT population, based on the first dose.

The number of subjects experiencing MBS-free, and the number of subjects censored, will be summarized. The Kaplan-Meier estimates, and 95% confidence intervals calculated using the log-log transformation, of the number of hours for 25%, 50%, and 75% of subjects to experience MBS-free will be presented. The Kaplan-Meier estimate, and 95% confidence interval, of the probability of experiencing MBS-free will be presented at the 0.5, 1, 1.5, 2, 3, 4, and 24-hour post-dose time points.

Time to MBS-free will be calculated as:

date/time a lack of presence of the baseline MBS is reported –
date/time of first dosing

Subjects who do not record the absence of their baseline MBS, or who record such a response after 24 hours post-dose will be censored at the time of their last non-missing post-dose symptom assessment at or before 24 hours. Subjects with missing baseline MBS will be censored at the time of first dose. Subjects who report that no symptoms were present at baseline will be excluded from the analysis.

A figure of the Kaplan-Meier analysis will also be presented.

11.7.9 Disability

Counts and percentages of the level of disability will be presented at the 0.5, 1, 1.5, 2, 3, 4, 24, and 48-hour post-dose time points. This will be summarized based on the first dose using the ITT population, and based on the second dose for recurrence and rescue using the ITT-2nd Dose population.

Disability is measured on a four-point scale.

- Not at all (0)
- Mild interference (1)
- Marked interference (2)
- Completely, needs best rest (3)

Treatment comparisons between the lasmiditan groups and placebo will be tested using the

Cochran-Mantel-Haenszel test statistic using modified ridit scores, controlling for background use of medication to reduce the frequency of migraine episodes.

11.7.10 Incidence of Rescue or Recurrence Medication Use

The count and percentages of subjects who take rescue or recurrence medication will be presented by treatment group and time point. The summary will be based on first dose using the ITT population.

The summary of study rescue or recurrence medication use will use the following three time points as applicable:

- At 2-hours post first dose
- Greater than 2, but less than or equal to 24 hours post first dose
- Greater than 24, but less than or equal to 48 hours post first dose

The combined summary of all rescue or recurrence medication use will use the following three time points as applicable:

- Less than or equal to 2 hours post first dose
- Less than or equal to 24 hours post first dose
- Less than or equal to 48 hours post first dose

A subject is defined to have used rescue medication within the specified time point if the subject takes a second dose of study drug within the time point or answers “Yes” to the e-diary question asking if any other medications have been used since the start of the migraine, and the medication is not considered a recurrence medication.

A subject is defined to have used recurrence medication if he or she records a mild (1), moderate (2), or severe (3) headache at baseline which becomes pain-free at 2 hours after the first dose, becomes more severe up to 48 hours after the first dose, and the subject takes a second dose of study drug within the time point or answers “Yes” to the e-diary question asking if any other medications have been used since the start of the migraine.

If the subject becomes pain-free at 2 hours after the first dose and records the use of rescue medication, but no headache severity is recorded between 2 hours after the first dose and the time of administration of a second dose, it will be assumed that the medication is taken for recurrence.

11.7.11 Incidence of Headache Recurrence

The counts and percentages of subjects who experience headache recurrence will be presented by treatment group. The summary will be based on first dose using the ITT population.

A subject is defined to have experienced headache recurrence if they record a mild (1), moderate (2), or severe (3) headache at baseline which becomes pain-free at 2 hours post first dose and then becomes more severe up to 48 hours post first dose.

If the subject becomes pain-free at 2 hours post first dose and records the use of rescue medication, but no headache severity is recorded, it will be assumed that the medication is taken for recurrence, and the subject will be counted as having experienced headache recurrence.

11.7.12 Patient Global Impression of Change

Counts and percentages of the level of patient global impression of change (PGIC) will be presented by treatment group at the 2-hour post-dose time point. This will be summarized based on the first

dose using the ITT population, and based on the second dose for recurrence and rescue using the ITT-2nd Dose population.

Patient global impression is measured on a seven-point scale.

- Very much better
- Much better
- A little better
- No change
- A little worse
- Much worse
- Very much worse

Treatment comparisons between the lasmiditan groups and placebo will be tested using the Cochran-Mantel-Haenszel test statistic using modified ridit scores, controlling for background use of medication to reduce the frequency of migraine episodes.

A bar graph of the proportion of subjects with responses of “Much better” or “Very much better” to subjects with any other, or a missing, response at the 2-hour post-dose time point will be presented based on first dose using the ITT population, and based on the second dose for recurrence and rescue using the ITT-2nd Dose population.

11.7.13 Headache Pain-Free After Second Dose

Counts and percentages of the number of subjects who are headache pain-free after second dose will be presented at the 0.5, 1, 2, 4, 24, and 48-hour post second dose time points. This summary will be presented by treatment sequence for the ITT-2nd Dose population, and separately for subjects taking a second dose for rescue or recurrence.

Headache pain-free after second dose is defined as experiencing a mild (1), moderate (2) or severe (3) headache at second-dose baseline which becomes none (0) at the summarized time point after a second dose is taken.

Subjects missing a headache severity at baseline or at the summarized time point will not be summarized at that time point.

11.7.14 Time to Headache Pain-Free After Second Dose

The time to headache pain-free after second dose will be presented by treatment sequence using a Kaplan-Meier analysis. This summary will be presented for the ITT-2nd Dose population, and separately for subjects taking a second dose for rescue or recurrence.

The number of subjects experiencing headache pain-free, and the number of subjects censored, will be summarized. The Kaplan-Meier estimates, and 95% confidence intervals calculated using the log-log transformation, of the number of hours for 25%, 50%, and 75% of subjects to experience headache pain-free will be presented. The Kaplan-Meier estimate, and 95% confidence interval, of the probability of experiencing headache pain-free will be presented at the 0.5, 1, 2, 4, and 24-hour post second dose time points.

Time to headache pain-free after second dose is calculated as:

- date/time headache severity is reported as none (0) after second dose –
- date/time of second dosing of a headache that was mild (1) or moderate (2) or severe (3) at

baseline

Subjects who do not report a headache severity of none after dosing, or who report a headache with a severity of none after 24 hours post second dose, will be censored at the time of their last non-missing post second dose headache severity assessment at or before 24 hours. Subjects with missing second dose baseline headache severity will not be considered in time to event analysis for second dose. Subjects who report a headache severity of none (0) at second dose baseline, will be presented in a separate listing as a report at the time of second dose. Subjects who report headache severity of mild (1) or moderate (2) or severe (3) at second dose baseline, will be considered in time to event analysis for second dose.

A figure of the Kaplan-Meier analysis will also be presented.

11.7.15 Headache Relief After Second Dose

Counts and percentages of the number of subjects with headache relief after second dose will be presented at the 0.5, 1, 2, 4, 24, and 48-hour post second dose time points. This summary will be presented by treatment sequence for the ITT-2nd Dose population, and separately for subjects taking a second dose for rescue or recurrence.

Headache relief after second dose is defined as experiencing a moderate (2) or severe (3) headache at second dose baseline which becomes mild (1) or none (0) at the summarized time point after a second dose is taken, or experiencing a mild (1) headache at second dose baseline which becomes none (0) at the summarized time point after a second dose is taken.

Subjects missing a headache severity at baseline or at the summarized time point will not be summarized at that time point.

11.7.16 Time to Headache Relief After Second Dose

The time to headache pain-free after second dose will be presented by treatment sequence using a Kaplan-Meier analysis. This summary will be presented for the ITT-2nd Dose population, and separately for subjects taking a second dose for rescue or recurrence who report headache severity of mild (1) or moderate (2) or severe (3) at second dose baseline,.

The number of subjects experiencing headache relief, and the number of subjects censored, will be summarized. The Kaplan-Meier estimates, and 95% confidence intervals calculated using the log-log transformation, of the number of hours for 25%, 50%, and 75% of subjects to experience headache relief will be presented. The Kaplan-Meier estimate, and 95% confidence interval, of the probability of experiencing headache relief will be presented at the 0.5, 1, 2, 4, and 24-hour post second dose time points.

Time to headache relief after second dose will be calculated as:

date/time headache severity is reported as mild (1) or none (0) after second dose –
date/time of second dosing of a headache that was moderate (2) or severe (3) at second-dose baseline

or as

date/time headache severity is reported as none (0) after second dose –
date/time of second dosing of a headache that was mild (1) at second-dose baseline

Subjects who do not report a headache with severity of mild or none, or who report a headache with a severity of mild or none after 24 hours post second dose, will be censored at the time of their last non-missing post second dose headache severity assessment at or before 24 hours. Subjects with missing second dose baseline headache severity will not be considered in time to event analysis for second dose. Subjects who report a headache severity of none (0) at second dose baseline, will be presented in a separate listing as a report at the time of second dose but not included in this time-to-relief analysis.

A figure of the Kaplan-Meier analysis will also be presented.

11.7.17 MBS-Free After Second Dose

Counts and percentages of the number of subjects who are MBS-free after second dose will be presented at the 0.5, 1, 2, 4, 24, and 48-hour post second dose time points. This summary will be presented by treatment sequence for the ITT-2nd Dose population, and separately for subjects taking a second dose for rescue or recurrence. This summary will be repeated separately for each symptom (nausea, phonophobia, and photophobia) on the ITT-2nd Dose population.

MBS-free after second dose is defined as a lack, post second dose, of the presence of the associated symptom (either nausea, phonophobia, or photophobia) that was identified as the most bothersome symptom at the time of the second dose. The counts and percentages of which symptom was chosen as the most bothersome symptom will also be presented. Subjects who record that none of these symptoms was present at the time of the second dose will be excluded from the MBS analysis.

Subjects who do not provide a symptom rating at the time of second dose will be considered as follows:

- Subjects who record at least one symptom present at the time of second dose, but who do not designate one as most bothersome, will be treated as if all symptoms present are most bothersome and will be considered MBS-free at a given time point post second dose only if all symptoms present at the time of second dose are no longer present at the time point post second dose.

Subjects free of symptoms at second-dose baseline or at the summarized time point will not be summarized at that time point.

11.7.18 Time to MBS-Free After Second Dose

The time to MBS-free after second dose will be presented by treatment group using a Kaplan-Meier analysis. This summary will be presented for the ITT-2nd Dose population, and separately for subjects taking a second dose for rescue or recurrence.

The number of subjects experiencing MBS-free, and the number of subjects censored, will be summarized. The Kaplan-Meier estimates, and 95% confidence intervals calculated using the log-log transformation, of the number of hours for 25%, 50%, and 75% of subjects to experience MBS-free will be presented. The Kaplan-Meier estimate, and 95% confidence interval, of the probability of experiencing MBS-free will be presented at the 0.5, 1, 2, 4, and 24-hour post-dose time points.

Time to MBS-free will be calculated as:

date/time a lack of presence of the MBS chosen at the time of second dosing is reported –
date/time of second dosing

Subjects who do not record the disappearance of their second-dose MBS, or who record such a response after 24 hours post second dose will be censored at the time of their last non-missing post second dose symptom assessment at or before 24 hours. Subjects with missing MBS at the time of second dose will be censored at the time of second dose. Subjects who report that no symptoms were present at the time of second dose will be excluded from the analysis.

A figure of the Kaplan-Meier analysis will also be presented.

11.7.19 Meaningful headache relief

This summary will be presented based on the e-diary question “Do you have meaningful relief” and subjects responses as “YES” to this question. Number and percentage of subjects with any meaningful headache relief after first dose (mITT population) and second dose (mITT and ITT 2nd dose population) will be summarized for each treatment group in total and for different categories of times after dosing. Median time to meaningful headache relief in hours will also be presented for each treatment group for subjects who took first dose and second dose.

11.8 Subgroup analysis

Analysis will be performed on subgroups of the population. Subjects will be classified into subgroups as follows:

11.8.1 Subjects with Anytriptan use within three months of screening:

Summary of Demographics and baseline characteristics for mITT Population, summary of Headache Pain for mITT population and summary of Most Bothersome symptom for mITT population tables will be provided. Additional tables that will be provided include summary of headache relief for ITT population and Incidence of Treatment-Emergent Adverse Events for safety population.

11.8.2 Subjects that dosed greater than 4 hours after migraine start:

The tables that will be provided include Summary of Demographics and Baseline Characteristics for ITT population, Summary of Headache Pain for ITT population, Summary of Most Bothersome Symptom for ITT population, and Summary of headache relief for ITT population.

11.8.3 Subjects with either Topamax or Propranolol use while on study:

The mITT population tables that will be included are Summary of Demographics and baseline characteristics for mITT population, Summary of headache pain for mITT population, and Summary of Most Bothersome symptom for mITT population. Additional tables will include Summary of Headache Relief for ITT population.

11.8.4 Subjects with Topamax use while on study:

The mITT population tables that will be included are Summary of demographics and baseline characteristics for mITT population, Summary of headache pain for mITT population, Summary of Most Bothersome symptom for mITT population. Additional tables will include Summary of headache relief for ITT population, Incidence of Treatment-Emergent Adverse Events for Safety population, and Incidence of Treatment-Emergent Adverse Events for Safety-2nd Dose population.

11.8.5 Subjects with propranolol use while on study:

The mITT population tables that will be included are Summary of Demographics and Baseline characteristics for mITT population, Summary of Headache Pain for mITT population, Summary of Most Bothersome Symptom for mITT population. Additional tables will include Summary of

Headache Relief for ITT population, Incidence of Treatment-Emergent Adverse Events for Safety Population, and Incidence of Treatment-Emergent Adverse Events for Safety-2nd Dose population.

11.8.6 Subjects with one or more CVRFs

The mITT population tables that will be included are Summary of Demographics and Baseline Characteristics for mITT population, Summary of Headache Pain for mITT population, Summary of Most Bothersome Symptom for mITT population. Additional tables include Summary of Headache Relief for ITT population, and Incidence of Treatment-Emergent Adverse Events for Safety Population. Cardiovascular risk factors considered are hypertension, hypercholesterolemia, smoker, obesity, diabetes, strong family history of coronary artery disease (CAD), female with surgical or physiological menopause and male over 40 years of age.

11.8.7 Subjects with TEAEs of dizziness:

The mITT population tables that will be included are Summary of Demographics and baseline characteristics for mITT population, Summary of headache pain for mITT population, and Summary of Most Bothersome symptom for mITT population. Additional tables will include Summary of Headache Relief, Summary of Patient Global Impression, and Summary of Disability for ITT population. Summary of Time-to-Onset and duration for First-Dose Treatment-Emergent Dizziness Relative to Dosing for Safety Population and safety-2nd dose population will be provided.

12 SAFETY ANALYSIS

This section details the specifications for summarizing safety endpoints.

Adverse event analyses will be presented on both the Safety and Safety-2nd Dose populations. Summaries on the Safety population will only include data up to the time of dosing with a second dose, and will be presented based on the first dose taken. Summaries on the Safety-2nd Dose population will only include data on or after the time of dosing with a second dose, and will be presented based on treatment sequence.

Laboratory, vitals, ECG, and C-SSRS analyses will be presented on the Safety population. These analyses will be presented by treatment sequence.

Safety endpoints will be summarized using descriptive or counts and percentages, as appropriate.

Values for all safety endpoints will also be presented in listings sorted by treatment group, site, and subject.

12.1 Adverse Events

An adverse event (AE) with the date/time of onset, or that worsens in intensity, at or within 48 hours after the time of dosing with study drug will be considered a TEAE. AEs with a missing start date will be assumed to be treatment-emergent, except as described in Appendix 1. If a subject takes at least one dose of study drug, but the date and time of dosing is missing in the e-diary, all AEs for that subject will be considered treatment-emergent, if the AEs occur between available date of dosing as recorded only in CRF for up to 48 hours (2 days) post recorded date of dosing. If the date and time of the second dose is missing in e-diary then all AEs for that subject will be considered as treatment emergent due to second dose, if AEs occur between available date of dosing in CRF for second dose, and an ending boundary of 2 days after recorded date of dosing with second dose, inclusive. See Appendix 1 for derivations related to partial dates and times.

Nausea and/or vomiting reported as adverse events during a migraine by any subject that also noted these as characteristics of their migraine will be compared against placebo and may not be considered related to treatment but rather an underlying condition of the migraine.

AEs will be coded by the Medical Dictionary for Regulatory Activities (MedDRA) version 18.0.

Unless otherwise stated, frequencies of adverse events will be displayed by applicable treatment group and overall. AEs will be sorted alphabetically by system organ class (SOC) and then preferred term (PT) by frequency. For the overall summary of AEs, both subjects ever experiencing an event, as well as total events, will be presented. For all other summaries, subjects with multiple occurrences of the same AE preferred term will be counted once within the corresponding system organ class and preferred term.

Adverse events will be summarized in the following tables:

- Overall summary of AEs, including:
 - AEs
 - TEAEs
 - Related TEAEs
 - TEAEs leading to study discontinuation
 - Serious TEAEs
 - Related serious TEAEs
 - TEAEs leading to death
- Incidence of TEAEs
- Incidence of TEAEs by relationship to study drug
- Incidence of TEAEs by maximum severity
- Incidence of AEs leading to study discontinuation
- Incidence of related AEs leading to study discontinuation
- Incidence of TEAEs leading to death
- Incidence of serious TEAEs
- Incidence of serious TEAEs by relationship to study drug
- Incidence of serious TEAEs by maximum severity

12.1.1 Relationship to Study Drug

Summaries of AEs by relationship to study drug will classify AEs as either:

- Reasonably or Possibly Related
- Not Reasonably or Possibly Related

Related AEs are those that are recorded on the AE CRF page as “Reasonably or Possibly Related” or those with a missing relationship.

12.1.2 Adverse Event Severity

Severity of AEs will be classified as one of the following:

- Mild
- Moderate
- Severe
- Life-threatening

If multiple severities are reported for a given adverse event for a subject, the highest severity reported will be used. Any adverse event with missing severity in the locked data base will not be summarized by severity.

12.1.3 Adverse Events Leading to Discontinuation

Adverse events leading to discontinuation of the study are those for which the answer to the AE CRF page's question of "Did the AE cause the subject to discontinue from the study?" is answered as "Yes."

12.1.4 Serious Adverse Events

Serious adverse events are those for which one or more of the following are indicated on the AE CRF page:

- Death
- Life-threatening
- Required or prolonged inpatient hospitalization
- Persistent or significant disability/incapacity
- Congenital anomaly
- Other medically important event

Subjects with "any serious adverse event" marked as "Yes" on CRF will be considered as serious AE even if one or more of the above specific events are not marked "Yes".

12.2 Clinical Laboratory Evaluation

Laboratory results will be classified based on the reference ranges provided by the central laboratory.

For quantitative laboratory parameters, observed and change from baseline measurements will be presented by time point using descriptive statistics. Categorical urinalysis parameters will only be presented in a listing. Laboratory parameters will be presented in SI units.

In the case of repeated laboratory values at the same visit, the last value collected will be used for the analysis.

The following laboratory parameters will be summarized:

- Hematology
 - White blood cell (WBC) count
 - Neutrophils
 - Lymphocytes
 - Eosinophils
 - Monocytes
 - Basophils
 - Hemoglobin
 - Hematocrit
 - Platelet count
 - Red blood cell (RBC) count
- Chemistry
 - Albumin
 - Alkaline phosphatase (AP)
 - Alanine aminotransferase (ALT)
 - Aspartate aminotransferase (AST)

- Blood urea nitrogen (BUN)
- Calcium
- Chloride
- Bicarbonate
- Creatinine
- Glucose
- Phosphorus
- Potassium
- Sodium
- Total bilirubin
- Total protein
- Total cholesterol
- High-density lipoprotein (HDL)
- Triglycerides
- Urinalysis
 - Protein
 - Glucose
 - Nitrite
 - Ketones
 - Blood
 - pH
 - Specific gravity
 - Leukocyte esterase
 - Microscopic bacteria
 - Red blood cells (RBC)
 - White blood cells (WBC)
 - Casts
 - Crystals
 - Cells

Microscopic examination of sediment will be performed only if the results of the urinalysis dipstick evaluation are positive, and will only be presented in a listing.

12.3 Vital Signs

Observed and change from baseline values for vital sign measurements will be summarized for the following parameters:

- Systolic blood pressure (mmHg)
- Diastolic blood pressure (mmHg)
- Heart rate (bpm)

Baseline observations will also be presented for:

- Height (in)
- Weight (lb)
- BMI (kg/m²)

12.4 12-lead Electrocardiograms (ECGs)

The 12-lead Electrocardiogram (ECG) assessments will be performed at Visits 1 and 2. Observed and change from baseline summaries will be presented for quantitative measurements using descriptive statistics. Shifts in categorical ECG parameters will be summarized from baseline to Visit 2, and will

be classified as either:

- Normal
- Abnormal, Insignificant
- Abnormal, Significant

The following ECG parameters will be summarized.

- Heart rate
- PR interval
- QRS
- QT, uncorrected
- QTcB
- QTcF

Rhythm assessments will be presented in a listing.

QTcB is the QT interval corrected using Bazett's formula. It will be calculated as:

$$QT \text{ (msec)} / (RR \text{ (sec)})^{1/2}$$

QTcF is the QT interval corrected using Fridericia's formula. It will be calculated as:

$$QT \text{ (msec)} / (RR \text{ (sec)})^{1/3}$$

Changes from baseline to Visit 2 in QTcB and QTcF will also be summarized categorically, classified as follows:

- Less than 30 msec
- Greater than or equal to 30 msec and less than 60 msec
- Greater than or equal to 60 msec

12.5 Physical Examination

The shift in physical examination evaluations from baseline to Visit 2 will be summarized for each system for subjects who had a physical examination at Visit 2 as indicated by an adverse event.

- General appearance
- Skin
- Head, eyes, ears, nose, and throat (HEENT)
- Heart
- Lymph nodes
- Lungs
- Abdomen
- Extremities/joints
- Neurologic systems
- Mental status

For each system, the evaluation will be classified as:

- Normal
- Abnormal
- Not done

12.6 Columbia-Suicide Severity Rating Scale (C-SSRS)

At Visit 1, the C-SSRS will be used to assess suicidal ideation and behavior in the past six months. At Visit 2, the Since Last Visit version will be used to assess suicidal ideation and behavior since the last visit. Listings will present all C-SSRS data for subjects with at least one positive response to

either C-SSRS assessment.

13 RESOURCE UTILIZATION

A summary table will present counts and percentages of subjects who visited a cardiologist, or having procedures, hospitalizations, new treatments, or adjustments to treatments for any cardiovascular conditions or disease. Presented time points will be in the last six months prior to Visit 1 and since Visit 1 at the end of the study. Counts and percentages of subjects with emergency room or urgent care visits for migraines in the last three months prior to Visit 1 will be presented. This summary will be presented on the Safety population by treatment sequence.

Additional information regarding these visits or changes will be presented in a listing.

14 INTERIM ANALYSIS AND DMC

No interim analysis is planned. No DMC is required for this study.

15 REFERENCES

1. Ratitch B, O'Kelly M, Tosiello R. Missing Data in Clinical Trials: From Clinical Assumptions to Statistical Analysis Using Pattern Mixture Models. *Pharmaceutical Statistics*. 2013; Volume 1, Issue 6: 337-347.
2. Rubin, D.B. *Multiple Imputation for Nonresponse in Surveys*. New York, New York: J. Wiley & Sons; 1987.

16 APPENDIX

16.1 PARTIAL DATE IMPUTATION: Algorithm for Prior/Concomitant Medications

Imputed dates will not be presented in the listings

• START DATE	• STOP DATE	• ACTION
Known	Known	<p>If start date < earliest dose date and stop date >= Visit 1, assign as prior.</p> <p>If start date <= (latest dose date + 2 days) and stop date >= earliest dose date, assign as concomitant.</p> <p>If start date <= end of study and stop date > (latest dose date + 2 days), assign as post-dose.</p>

• START DATE	• STOP DATE	• ACTION
	Partial	<ul style="list-style-type: none"> Impute stop date as latest possible date (e.g. last day of month if day unknown or 31st December if day and month are unknown), then: <ul style="list-style-type: none"> If start date < earliest dose date and stop date >= Visit 1, assign as prior. If start date <= (latest dose date + 2 days) and stop date >= earliest dose date, assign as concomitant. If start date <= end of study and stop date > (latest dose date + 2 days), assign as post-dose.
	Missing	<p>If start date < earliest dose date, assign as prior.</p> <p>If start date <= (latest dose date + 2 days), assign as concomitant.</p> <p>If start date <= end of study, assign as post-dose.</p>
Partial	Known	<ul style="list-style-type: none"> Impute start date as earliest possible date (e.g. first day of month if day unknown or 1st January if day and month are unknown), then: <ul style="list-style-type: none"> If start date < earliest dose date and stop date >= Visit 1, assign as prior. If start date <= (latest dose date + 2 days) and stop date >= earliest dose date, assign as concomitant. If start date <= end of study and stop date > (latest dose date + 2 days), assign as post-dose.
	Partial	<ul style="list-style-type: none"> Impute start date as earliest possible date (e.g. first day of month if day unknown or 1st January if day and month are unknown) and stop date as latest possible date (e.g. last day of month if day unknown or 31st December if day and month are unknown), then: <ul style="list-style-type: none"> If start date < earliest dose date and stop date >= Visit 1, assign as prior. If start date <= (latest dose date + 2 days) and stop date >= earliest dose date, assign as concomitant. If start date <= end of study and stop date > (latest dose date + 2 days), assign as post-dose.

• START DATE	• STOP DATE	• ACTION
	Missing	<ul style="list-style-type: none"> Impute start date as earliest possible date (e.g. first day of month if day unknown or 1st January if day and month are unknown), then: <ul style="list-style-type: none"> If start date < earliest dose date, assign as prior. If start date ≤ (latest dose date + 2 days), assign as concomitant. If start date ≤ end of study, assign as post-dose.
Missing	Known	<ul style="list-style-type: none"> If stop date ≥ Visit 1, assign as prior. If stop date ≥ earliest dose date, assign as concomitant. If stop date > (latest dose date + 2 days), assign as post-dose.
	Partial	<ul style="list-style-type: none"> Impute stop date as latest possible date (e.g. last day of month if day unknown or 31st December if day and month are unknown), then: <ul style="list-style-type: none"> If stop date ≥ Visit 1, assign as prior. If stop date ≥ earliest dose date, assign as concomitant. If stop date > (latest dose date + 2 days), assign as post-dose.
	Missing	Assign as prior, concomitant, and post-dose.

16.2 PARTIAL DATE IMPUTATION: Algorithm for Treatment Emergence of Adverse Events

Imputed dates will not be presented in the listings

• START DATE/TIME	• STOP DATE/TIME	• ACTION
• Known	• Known	<ul style="list-style-type: none"> If start date/time < dose date/time, then not TEAE. <ul style="list-style-type: none"> If start date/time ≥ dose date/time and < (dose date/time + 48 hours (or 2 days)), then TEAE
•	• Partial	<ul style="list-style-type: none"> If start date/time < dose date/time, then not TEAE.

• START DATE/TIME	• STOP DATE/TIME	• ACTION
		<ul style="list-style-type: none"> • If start date/time \geq dose date/time and $<$ (dose date/time + 48 hours (or 2 days)), then TEAE.
•	• Missing	<ul style="list-style-type: none"> • If start date/time $<$ dose date/time, then not TEAE. • If start date/time \geq dose date/time and $<$ (dose date/time + 48 hours (or 2 days)), then TEAE.
• Partial, but known components show that it cannot be on or within 48 hours after dose date/time	• Known	• Not TEAE.
•	• Partial	• Not TEAE.
•	• Missing	• Not TEAE.
• Partial, could be on or within 48 hours after dose date/time	• Known	<ul style="list-style-type: none"> • If stop date/time $<$ dose date/time, then not TEAE. • If stop date/time \geq dose date/time, then TEAE.
•	• Partial	<ul style="list-style-type: none"> • Impute stop date/time as latest possible date/time (e.g. last day of month if day unknown or 31st December if day and month are unknown), then: <ul style="list-style-type: none"> • If stop date/time $<$ dose date/time, then not TEAE. • If stop date/time \geq dose date/time, then TEAE.
•	• Missing	• Assumed TEAE.
• Missing	• Known	<ul style="list-style-type: none"> • If stop date/time $<$ dose date/time, then not TEAE.

• START DATE/TIME	• STOP DATE/TIME	• ACTION
		<ul style="list-style-type: none"> If stop date/time \geq dose date/time, then TEAE.
•	• Partial	<ul style="list-style-type: none"> Impute stop date/time as latest possible date/time (e.g. last day of month if day unknown or 31st December if day and month are unknown), then: <ul style="list-style-type: none"> • If stop date/time $<$ dose date/time, then not TEAE. • If stop date/time \geq dose date/time, then TEAE.
	Missing	<ul style="list-style-type: none"> Assumed TEAE.

16.3 DATA HANDLING RULES OF EFFICACY AND EXPLORATORY ANALYSIS FOR E-E-DIARY AND CRF DATES AND TIMES

As described in Section 5.4, Scenario #6 subjects will be included in efficacy analysis with respect to e-diary dates and times and their relative post-dose assessments times under below rules if their respective CRF date does not match.

Subjects with partial dates entered on CRF with missing time of dosing for first dose on CRF that do not contradict the e-diary date. These subjects will be considered for efficacy analysis with respect to e-diary date and time.

Subjects with CRF first dose date is after subject answered the question for 0.5 time point due to which the questions in the e-diary look appropriate with respect to e-diary first dose date. These subjects will be considered for efficacy analysis with respect to e-diary date and time.

Subjects with indication in CRF that they had taken first dose prior to all migraine start times recorded in e-diary due to which first dose e-diary date becomes closer to or after last migraine start in the e-diary. These subjects will be considered for efficacy analysis with respect to e-diary date and time.

Subjects with different first dose times in e-diary vs on CRF. If the e-diary data is not entered retroactively by subject, then e-diary first dose dates will be in accordance with assessments completed by subject. These subjects will be considered for efficacy analysis with respect to e-diary date and time.

Subjects with CRF dates for 2nd dose are entered more than 24 hours after first dose. These subjects will be considered for efficacy analysis with respect to e-diary date and time.

Subjects with indication in CRF that they had taken second dose prior to all migraine start times recorded in e-diary due to which second dose e-diary date becomes closer to or after last migraine start in the e-diary. These subjects will be considered for efficacy analysis with respect to e-diary date and time.

Subjects with indication of taking second dose on CRF with CRF date and time but second dose date is not in e-diary. Due to this, some first dose data from e-diary assessments before time of second dose on CRF will be used for analysis. These subjects' first dose data will be considered for efficacy analysis with respect to e-diary date and time.