H8H-CD-LAHL (COL MIG-305)

An Open-label, LonG-term, Safety Study of LAsmiDItan (100 mg and 200 mg) in the Acute Treatment Of MigRaine (GLADIATOR)

NCT02565186

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STATISTICAL ANALYSIS PLAN

An Open-label, LonG-term, Safety Study of LAsmiDItan (100 mg and 200 mg) in the Acute Treatment Of MigRaine (GLADIATOR)

Protocol: H8H-CD-LAHL (COL MIG-305)
10 June 2019

Sponsor: Eli Lilly & Company

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Output Templates Signature Page

Output Templates V1.0 (Dated 10 June 2019) for Protocol H8H-CD-LAHL (COL MIG-305)

	Name	Signature	Date
Author:	PPD		12-June-2019
Position:			
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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		10-Jun-2019
Position:			
Company:	Eli Lilly & Company		

	Name	Signature	Date
Approved By:	PPD		10-JUN-2019
Position:			
Company:			

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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
AE(s)	Adverse event(s)
ALT	Alanine aminotransferase
AP	Alkaline phosphatase
AST	Aspartate aminotransferase
BMI	Body Mass Index
BP	Blood pressure
bpm	Beats per minute
BUN	Blood urea nitrogen
CAD	Coronary artery disease
CRF	Case Report Form
C-SSRS	Columbia Suicide Severity Rating Scale
CV	Cardiovascular
DBP	Diastolic blood pressure
ECG	Electrocardiogram
EoS	End of study
ET	Early termination
FDA	Food and Drug Administration
HEENT	Head, eyes, ears, nose, and throat
HIPAA	Health Insurance Portability and Accountability Act
HR	Heart rate
ITT	Intent-to-treat
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
PGIC	Subject global impression of change
PP	Per protocol

PT	Preferred term
RBC	Red blood cells
RR	R-R interval (msec)
SAE	Serious adverse event
SBP	Systolic blood pressure
SD	Standard deviation
SI	Standard international
SOC	System organ class
TEAE	Treatment emergent adverse events
WBC	White blood cells
WHO	World Health Organization
WOCBP	Women of child-bearing potential

1 PURPOSE

This Statistical Analysis Plan, defined by the Sponsor and the responsible statistician, is based on the Study Protocol and 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, open-label study in subjects with migraine who have completed COL MIG-301/H8H-CD-LAHJ or COL MIG-302/H8H-CD-LAHK. Subjects will be stratified (yes or no) for use of concomitant medications that reduce the frequency of migraine episodes.

Subjects will be asked to treat all migraine attacks with study drug on an outpatient basis for up to 12 months. Each subject's study participation will consist of a screening visit (Visit 1) and a treatment period of up to 12 months during which the subject will treat all migraine attacks with either lasmiditan 200 mg or lasmiditan 100 mg (with a second dose permitted between 2 and 24 hours (h) for rescue or recurrence of migraine). During the treatment period subjects will return to the clinic at 1, 3, 6, 9 and 12 months. There will be an early termination (ET) visit within two weeks (14 days) of treatment discontinuation for all subjects that discontinue between scheduled visits. The End-of-Study (EoS) visit will be at 12 months or at any scheduled visit when the subject's participation in the study is ended. Participation in the study for 6 months will be defined as completing **Month 6/Visit 4**. Participation in the study for 12 months will be defined as completing **Month 12/Visit 6** (not including early termination subjects).

At Screening/Visit 1 subjects will provide written informed consent and authorize Health Insurance Portability and Accountability Act (HIPAA). Study eligibility will be assessed on the basis of completing Study 301/LAHJ or Study 302/LAHK. The EoS/Visit 2 of Study 301/LAHJ or Study 302/LAHK can be the same day as Screening/Visit 1. Assessments required for this visit can be the same assessments obtained at the EoS/Visit 2 of Study 301/LAHJ or Study 302/LAHK as long as that visit occurred on the same day or no more than two weeks prior to signing informed consent and HIPAA for participation in COL MIG-305/H8H-CD-LAHL as outlined in the Schedule of Assessments (Table 1). Regardless of the timing of signing of informed consent for COL MIG-305, medical history, migraine history and concomitant medication use will be reviewed and any changes or updates since enrolling in Study 301/LAHJ or Study 302/LAHK will be noted. All subjects will complete the MIDAS questionnaire. If Screening/Visit 1 is not the same day as EoS/V2 of Study 301/LAHJ or Study 302/LAHK but within 2 weeks, a complete physical examination, vital signs and urine pregnancy test will also be done. Subjects that are consented more than two weeks after EoS/Visit 2 of Study 301/LAHJ or Study 302/LAHK will undergo the following assessments: a complete physical examination, vital signs, clinical laboratory tests (including urine pregnancy test on women of child-bearing potential (WOCBP)) and 12-lead electrocardiogram (ECG). A Columbia Suicide Severity Rating Scale (C-SSRS) will be completed.

All subjects will be randomized and dispensed study drug and instructed to use lasmiditan as the first treatment for each new migraine attack. Subjects will be randomly assigned in a 1:1 ratio, to receive lasmiditan 100 mg (L100 mg) or lasmiditan 200 mg (L200 mg). Subjects will be allowed to take a second dose of their assigned treatment if needed for rescue or recurrence of migraine.

Subjects will be asked to use lasmiditan as the first treatment for each new migraine attack within 4 hours of onset providing that the headache severity is at least moderate at that time and not improving. Subjects will record their response to the first dose over the next 48 hours using an electronic 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 (headache pain) 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 electronic diary. The total time for recording response to study drug is up to 72 hours depending on whether or not a second dose of study drug is used. Subjects using an alternate medication other than a second dose of study drug for the treatment of migraine rescue or recurrence will report the use of medication and continue to record their responses in the electronic diary up to the 48 hour timepoint.

Subjects will be asked to return to the clinic at months 1, 3, 6, 9 and 12 (Visits 2, 3, 4, 5 and 6). At each visit a brief physical examination based on adverse events (AEs), vital signs and a urine pregnancy test on all WOCBP will be obtained. Blood and urine samples for clinical laboratory parameters (hematology, serum chemistry and urinalysis) will be obtained at **Month 1/Visit 2**, **Month 6/Visit 4** and **Month 12/Visit 6** (**EoS/ET**). A 12-lead ECG will be obtained at **Month 6/Visit 4** and **Month 12/Visit 6** (**EoS/ET**). C-SSRS will be completed at each visit. The MIDAS questionnaire will be completed at **Month 1/Visit 2**, **Month 3/Visit 3**, **Month 6/Visit 4**, **Month 9/Visit 5** and **Month 12/Visit 6 (EoS/ET).** At each visit, resource utilization, AEs, use of concomitant medication, use of study drug and subject diary compliance will be assessed; subjects who are continuing will be dispensed study drug. Subjects who decide to withdraw at a scheduled visit should confirm the date of the visit is 7 days (± 2 days) from their last migraine treated with study drug. Subjects who decide to discontinue between scheduled visits are asked to contact the clinic to schedule an **ET /Visit 6** within two weeks (14 days) after discontinuation of dosing. Subjects may be discontinued if more than one month of no migraine(s) treated with study drug is reported. The total time on study is up to 54 weeks (a maximum of 378 days).
This study is designed to evaluate the safety and tolerability of long-term intermittent use of lasmiditan 100 mg and of lasmiditan 200 mg, as the first dose and as a second dose, for the acute treatment of migraine.

The study will be conducted at up to 180 centers in US and ex-US (all Study 301/LAHJ or Study 302/LAHK centers will be included).

Schedule of Assessments

	Visit 1 Screening and Baseline	**Visit 2, 3, 4 and 5** (Months 1, 3, 6 and 9)	**Visit 6/EoS/ ET**[1]
Obtain informed consent/HIPAA		**X**	
Review inclusion / exclusion criteria		**X**	
Review migraine history, medical history and concomitant medications		**X**	
MIDAS questionnaire	**X**	**X**	**X**
Review resource utilization (visits to specialists, ERs, etc.)	**X**	**X**	**X**
Complete physical examination		**X**	
Vital signs (heart rate, blood pressure)	**X**[2]	**X**	**X**
Brief physical examination based on AE(s)	**X**[2]	**X**	**X**
Weight		**X**	**X**
12-lead ECG	**X3**	**VISIT 4 ONLY**	**X**
Clinical laboratory[4]	**X**[3]	**VISIT 2 and 4**	**X**
Urine pregnancy for women of child-bearing potential	**X**[5,6]	**X**[6]	**X**[6]
Columbia Suicide Severity Rating Scale	**X**[3]	**X**	**X**
Randomization		**X**	
Dispense study drug, study diary, and provide detailed instructions		**X**	**X**
Collect empty dosing card(s) and unused study drug.		**X**	**X**
Review dosing compliance and diary completion			
Migraine attack (electronic diary) documentation by subject		**X**	
Documentation of rescue/recurrence medication		**X**	**X**
Documentation of adverse events and concomitant medication		**X**	**X**

ET is for subjects that discontinue the study between scheduled visits. The subject should return to the clinic within 14 days of the decision to withdraw from the study. **EoS** is the designation for any scheduled visit that the subject discontinues at or Visit 6 (month 12).
2. Brief physical examination based on AE (s) and vital signs will be the values obtained from **EoS/Visit 2** of COL MIG-301 or COL MIG-302 only if subject signs consent and enrolls in COL MIG-305 on the same day.
3. Laboratory tests, ECG and C-SSRS will be the values obtained from **EoS/Visit 2** of COL MIG-301 or COL MIG-302, as long as the subject signs consent and enrolls in COL MIG-305 on the same day or within two weeks (14 days) of **EoS/Visit 2**.
4. Clinical laboratory tests include hematology, biochemistry, lipid profile and urinalysis.
5. A urine pregnancy test for women of childbearing potential is required unless **Visit 1** is same day as **EoS/Visit 2** of COL MIG-301 or COL MIG-302.
6. If urine pregnancy test is positive a confirmatory serum βHCG test must be performed. The confirmatory test may be run in the local clinical laboratory. The subject should be told not to dose with study drug until the confirmatory test results are obtained. If serum test is positive the subject is to be discontinued from the study.

2.2 Sample Size

This Phase 3 study is designed to demonstrate that lasmiditan is safe in the long-term intermittent acute treatment of migraine in adult subjects with and without aura. The sample size was chosen to provide an appropriate long-term safety database. It is not based on statistical hypotheses. In

accordance with ICH guidelines at least 300 subjects will treat, on average, at least 2 migraines per month for 6 months and at least 100 subjects will treat, on average, at least 2 migraines per month for 12 months.

2.3 Randomization

This is a multicenter, randomized, open-label, parallel group study. At study entry, subjects will be centrally randomized to receive lasmiditan 200 mg (L200 mg) or lasmiditan 100 mg (L100 mg) in a 1:1 ratio. Whether taken as a first dose or a second dose, the same dosage will always be taken by a subject. Subjects will be stratified (yes or no) for use of concomitant medications that reduce the frequency of migraine episodes. Study drug will be dispensed at each study visit.

3 EFFICACY AND SAFETY ENDPOINTS

3.1 Primary Safety Endpoint

The proportion of subjects and the proportion of attacks associated with all adverse events and TEAE and other adverse events.

3.2 Secondary Efficacy Endpoint

The proportion of migraine attacks treated with lasmiditan 100 mg and with lasmiditan 200 mg which respond at 2 hours, calculated for each 3 month period.

3.3 Additional Efficacy Endpoints (for each attack unless otherwise specified)

- Headache pain relief: 4 point scale: none (0), mild (1), moderate (2), severe (3))
- Most bothersome symptom (MBS) (selected from a list of the associated symptoms of migraine (nausea, phonophobia or photophobia) present at predose)
- Nausea (yes or no)
- Phonophobia (yes or no)
- Photophobia (yes or no)
- Vomiting (yes or no)
- Headache response within 24 hours - time to headache relief and time to pain free
- 24 and 48 hour sustained pain free response
- Disability ((0) Not at all', (1) 'Mild interference', (2) 'Marked interference', (3) 'Completely, needs bed rest')
- Patient global impression of change (7 point scale)
- Time to headache relief and time to pain free after a second dose of lasmiditan for rescue or recurrence of migraine
- Migraine attacks treated with study medication over each 3 month period

3.4 Additional Safety Endpoints

- Adverse events (spontaneously reported)

- Physical examination
- Vital signs
- 12-lead electrocardiograms
- Clinical laboratory parameters
- C-SSRS

3.5 Resource utilization:

- Any CV events and/or related resource utilization such as visits to cardiologists, procedures, hospitalizations, new treatments or treatment adjustments for CV disease on study **Visit 1** through **Visit 6/EoS/ET.**
- Any visits to an emergency room or physician's office for treatment of migraine on study **Visit 1** through **Visit 6/EoS/ET** excluding study specific visits.
- Concomitant medications for the treatment of migraine and/or pain **Visit 1** through **Visit 6/EoS/ET.**
- Missed days of work and/or school or daily activities based on responses to MIDAS questionnaire.
- MIDAS Total score.

4 ANALYSIS POPULATIONS

The following analysis populations will be defined for this study.

Definitions:

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.

Subjects Randomized and Discontinued Prior to 10NOV 2015 **(Pre-Administrative Hold Population)**	See section 5.2 for an explanation of this subject population and the extent of analyses that will be conducted for them.
Randomized population	All randomized subjects. Subjects will be evaluated by the dose 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 dose they use, not by the dose to which they are randomized, when data indicate a difference.

ITT population	Subject-level: All randomized subjects who use at least one dose of study drug and have any post-dose headache severity or symptom assessments for at least one migraine attack during the study. Subjects are evaluated by the dose to which they are randomized. Treated migraine-level: a migraine treated with at least one dose of study drug and having any post-dose headache severity or symptom assessments. Treated migraines are evaluated by the dose to which the subject was randomized.
mITT population	Subject-level: All ITT subjects who treat a migraine attack within four hours of onset for at least one migraine attack during the study. Subjects will be evaluated by the dose to which they are randomized. The mITT population is the primary analysis population only for headache pain-free and MBS-free analyses. Treated migraine-level: All ITT migraines treated within four hours of onset. Migraines will be evaluated by the dose to which the subject was randomized. The mITT population is the primary analysis population only for headache pain-free and MBS-free analyses.
ITT 2nd Dose Rescue population	Subject-level: All randomized subjects who use at least one 2nd dose of study drug for rescue purposes and have any post-dose headache severity or symptom assessments associated with that second dose. Subjects are evaluated by the dose to which they are randomized. Treated migraine-level: a migraine treated with at least one 2nd dose of study drug for rescue purposes and having any post-dose headache severity or symptom assessments. Treated migraines are evaluated by the dose to which the subject was randomized.
ITT 2nd Dose Recurrence population	All randomized subjects who use at least one 2nd dose of study drug for recurrence purposes and have any post-dose headache severity or symptom assessments associated with that second dose. Subjects are evaluated by the dose to which they are randomized.

	Treated migraine-level: a migraine treated with at least one 2nd dose of study drug for recurrence purposes and having any post-dose headache severity or symptom assessments. Treated migraines are evaluated by the dose to which the subject was randomized.
12-month safety population	Subjects who **were known to have participated at least 12 months (348 days)** and dosed, on average, at least 2 migraine attacks per month (i.e.24 or more treated migraine attacks over their participation in the study.)
6-month safety population	Subjects who **were known to have participated at least 6 months (174 days)** and dosed, on average, at least 2 migraine attacks per month over a six-month window during the study
3- Month safety population	Subjects who **were known to have participated at least 3 months (87 days)** and dosed, on average, at least 2 migraine attacks per month over a three-month window during the study
Addendum 1 and Addendum 2 population	Subjects randomized per Addendum 1 or Addendum 2. See Section 5.3 for an explanation and analyses conducted for this subject population.

4.1 Examination of Subgroups

Subgroup analyses will be performed for subjects with one or more cardiovascular risk factors. Similar criteria as parent study will be used to identify the subjects with one or more cardiovascular risk factors. It should be noted that the parent or current study was not designed to detect treatment differences with high statistical power within subgroups.

- Cardiovascular Disease Risk Factors
  - Hypertension
  - Hypercholesterolemia
  - Smoking
  - Obesity
  - Diabetes Mellitus
  - Strong family history of coronary artery disease
  - Males over 40 years
  - Post-menopausal females

5 GENERAL SPECIFICATIONS

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

All safety analyses will be based on the safety population. Efficacy analyses will be performed on ITT population, with the exception of the MBS-free and headache pain-free analyses secondary endpoint which will be performed on the mITT population.

Continuous variables will be summarized using descriptive statistics, i.e. n (number of subjects with available data), mean, median, standard deviation (SD), 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.

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. Subjects will record the dosing information for every migraine attack in this study. 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, 2 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.

- 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 able to answer the questions until the assessment time (+/- 5 minutes or +/- 10 minutes depending on the time point.

- 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 respond to post-dose assessments based on time of dosing of first 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 of dosing based on subject report will be recorded in the case report form (CRF) at the site. 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 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 each treated migraine attack. For efficacy purposes,

baseline values will be the Hour-0 assessment times identified in the e-diary for each treated migraine attack. 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 for each treated migraine attack.

Safety Analysis: Below assumptions will be considered for determining the start and end dates for treatment exposure.

1. If CRF dates data is matched with e-diary dates and times: The start and end of treatment exposure for analysis will always be identified from the first and last dates of dosing entered in the CRF, when available and appear to match the e-diary dosing data.

2. If CRF dates data is NOT matched with e-diary dates: CRF dates will be compared with e-diary dates and times for possible and reasonable match. If CRF dates appear to be out of order 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 not be corrected by CRF data as provided by the subject due to unavailability of times of dosing in CRF. In such cases, 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.

3. If CRF dosing dates are available but e-diary dosing information is missing: CRF dosing date will be determined as confirmation of dosing at sites even if subject could not enter dosing information in e-diary due to any reason. These subjects data will be used for analysis. If the first dose date is available in CRF but missing from e-diary then eligibility date will be used as the first alternative and the randomization date will be used as second alternative. If the second dose date is available in CRF but missing from e-diary then study completion/discontinuation date will be used as the alternative. Additionally, for CRF dosing dates which are partial dates, missing dates and dates which fall outside the visit window, reported visits windows with respect to reported CRF dosing dates windows will be used for treatment start and end dates.

4. If CRF dosing dates are NOT available but e-diary dosing information is available: It will be determined that these subjects have not confirmed this dosing at the site (or are lost to follow-up) and there is no confirmation on exact dosing on CRF. These unconfirmed migraines will be excluded from safety analyses.

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 decision was made to run efficacy analyses on the ITT and mITT populations. The populations such as safety-2nd, mITT-2nd Dose and PP-2nd Dose populations were therefore removed. Additionally PP population was removed, as primary endpoint of this study is safety.

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 mentioned sensitivity analysis for efficacy endpoints for missing diary data. It was decided not to conduct this analysis, as primary endpoint of this study is safety. The complications of missing efficacy diary data were tested in parent study.

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

Though the protocol did not specify this, it was decided that exploratory analyses would be repeated separately for relief of each associated symptom of headache, including vomiting.

5.2 Subjects Randomized and Discontinued Prior to 10 NOV 2015- (Pre-Administrative Hold Population)

On November 10, 2015, COL MIG-305/H8H-CD-LAHL was stopped per the FDA due to not filing the protocol prior to initiating enrollment. Subjects were advised to not dose a migraine and were asked to return to the clinic to be discontinued. The study was initiated with FDA approval on November 13, 2015. The study was amended to outline the process for the subjects to be discontinued from the study and then be allowed to restart the study if they wished. In summary subjects undergo an End-of-Study visit as outlined and if they are interested in participating in the study they are re-consented and then re-randomized. The data from all subjects enrolled in the period October 7, 2015 to November 10, 2015 will be maintained in the database and reported in

the clinical study report as a subset of the overall study.

Data generated during this period is not included in the randomized population, the safety population, or the ITT populations. Data from this period will be analysed separately and be limited to subject demographics, disposition, exposure, adverse events, and serious adverse events.

5.3 Addendum 1 and Addendum 2 Subjects

With the addition of these two addenda to Study 305/LAHL, additional subjects could be randomized after August 2016. The visit structure and procedures for this set of subjects are different from those for subjects that came from the parent studies. Therefore, observations that serve as baseline are different from those specified throughout this document. For this group of subjects, baseline will be defined as either Visit 0 or Visit 1, depending on when information is collected, and still represents observations prior to any study medication dosing. Other differences for this group of subjects includes the ability to dose migraines with baseline severity of 'Mild', the ability to dose a migraine up to 8 hours of its onset, and subjects that are lasmiditan-naïve.

As these differences in protocol procedures are not anticipated to effect safety or efficacy endpoints, for all analyses, these subjects will be incorporated into the previously defined subject populations. Additionally, a listing of randomized subjects that were added to the study based on Addendum 1 or Addendum 2 will be provided.

The database lock in May 2018 will not include patients added to the study through these addenda.

5.4 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 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. Analyses based on the second dose will be done for both the rescue and recurrence subpopulations.

5.5 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 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 for each treated migraine

will be assumed to have not achieved headache pain-free status, and (2) subjects who fail to record the absence of a symptom at 2 hours at each treated migraine that was considered their MBS at baseline will be assumed to have not achieved MBS-free status. This will be considered for data presented for each treated migraine attack.

5.6 Analysis for Final Database Lock

All the analysis for the final database lock will be similar to the interim analysis lock (May 2018), such that the same tables, listings and figures will be provided. Analyses for the pre-administrative hold population were conducted for the interim analysis lock (May 2018) and therefore will not be included in the final lock. Apart from those all patients including addendum 1 and 2 will be included in the final analysis.

5.7 Derivation of Diary Assessment Times for Efficacy and Exploratory Analysis

The secondary and additional exploratory endpoints along with second-dose exploratory analysis endpoints will be summarized at various elapsed times following dosing for each treated migraine attack. 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 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 indicate 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. 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.

1. 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.

5. 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.

Efficacy analysis: Below assumptions will be considered for determining the start and end dates for treatment exposure.

a. If CRF dates data is matched with e-diary dates and times: The start and end of treatment exposure for analysis will always be identified from the first and last dates of dosing entered in the CRF, when available and appear to match the e-diary dosing data.

b. If CRF dates data is NOT matched with e-diary dates and times: The e-diary 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 ITT populations of efficacy analysis when there is a confirmation of such dosing on CRF, within a reasonable matching timeframe with e-diary. Such as CRF treatment start dates

(+12 hours) will be matched if they are minimally within 24 hours of e-diary first or second dose dates.

c. If CRF dosing dates are available but e-diary dosing information is missing: 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 will not be included in ITT efficacy analysis due to unavailability of efficacy assessment data.

d. If CRF dosing dates are missing but e-diary dosing information is available: It will be determined that these subjects have not visited at sites (or even they have lot of follow-up) and there is no confirmation on exact dosing on CRF. These subjects will be excluded from Efficacy analysis.

6 DISPOSITION OF SUBJECTS AND DISCONTINUATIONS

The following will be summarized for all subjects by treatment arm, as counts and percentages of all subjects. Disposition data will be also presented for Safety Population and Pre-administrative Hold Population Subjects.

- Subjects randomized
- Subjects with confirmed eligibility
- Subjects treated with second dose
  - For Rescue and with Recurrence
- Overall number of attacks treated
  - Number of attacks treated with 1 dose
  - Number of attacks treated with 2 doses
- Average number of attacks treated in a 30 day period over participation in the study.
- Subjects in each of the analysis populations:
  - Randomized population
  - ITT population
  - ITT 2nd Dose Population
    - Rescue Population
    - Recurrence Population
  - mITT population
  - Safety population
  - 3-Month Safety Population
  - 6-Month Safety Population

  - 12-Month Safety Population
- Duration of time in study for Safety, 6-Month Safety and 12- Month Safety Population (Mean, Median, 25th Quartile, 75th Quartile, SD, Minimum and Maximum)
- Subjects who completed the study for 12 month
  - Treated
  - Not treated
- Discontinued subjects before 12 months
  - 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
  - Missing
- Discontinuations within 48 hours of last dose, by reason for discontinuation.

The number and percentage of subjects in each disposition category will be presented; percentages will be based on the number of all 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 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 a separate listing.

7 PROTOCOL DEVIATIONS

The number and percentage of subjects with protocol deviations will be presented by categories for the randomized population. Additionally, all deviations will be presented in a listing.

8 DEMOGRAPHICS AND BASELINE CHARACTERISTICS

8.1 Demographics

The following will be summarized by treatment group and overall for the Randomized, ITT, 6-Month Population, 12- Month Population, Pre-administrative Hold Population and Safety 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)
- Body Mass index (BMI) (kg/m^2)
- Smoking history
    - Never
    - Former
    - Currently
- Family history of coronary artery disease (CAD)
    - Yes
    - No
- Subjects >=1 cardiovascular risk factors
- Subjects >=2 cardiovascular risk factors
- Parent study
    - COL MIG-301/H8H-CD-LAHJ
    - COL MIG-302/H8H-CD-LAHK
    - Addendum 2 Subjects (This information will not be presented for the Interim Analysis Submission Tables)

- Duration of migraine history (This data will be used from parent study for rollover patients)
- Average migraines/Month in past three months (This data will be used from parent study for rollover patients)
- IHS Diagnostic Criteria: Migraine with Aura- Subjects with Aura consisting of at least one of the following (This data will be used from parent study for rollover patients):

- Use of medications reducing migraines (This data will be used from current 305 study IVRS report)

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

BMI will be calculated as:
Weight (lb) / height $(in)^2$ * 703

All demographic data will be presented in a listing.

8.2 MIDAS

Migraine Disability Assessment (MIDAS) total scores, number of days with headaches over the past 3 months, and average headache pain past three months will be summarized by treatment group for ITT population at **Visit 1/Screening**, **Month 1/ Visit 2, Month 3/Visit 3**, **Month 6/Visit 4**, **Month 9/Visit 5** and **Month 12/Visit 6 (EoS/ET)**. MIDAS total score will also be presented as change from baseline for each post-baseline visit. 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 2 of the Protocol.

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. Average days with headache part 3 months will be reported. If headache lasted for more than 1 day, each day will be counted.

8.3 Medical History

Medical history will be summarized by treatment group for the safety 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 group. The summaries will be presented for the Safety and ITT population. Migraine treatment history will be coded using the

World Health Organization (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. If the subject has any significant migraine history changes or updates from the parent 301 or 302 study then the new data will be recorded in 305 database. If there are no any changes from previous study and the "New treatment given" is answered as "No" on CRF then migraine history data will be used from parent study for analysis.

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

8.5 Characteristics of All Treated Migraine Attacks

The following will be summarized by treatment group for the mITT and ITT population for all treated migraine attacks in each treatment group. Similar information will also be presented by quarter. Quarter will be defined as time interval of 3 months between each nominal visit number recorded in the database starting from screening visit. E. g. **Screening/Visit 1** to **Month 3/Visit 3** with 3 months duration is Quarter 1.

- Time to dosing from the start of migraine attack (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
- 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 treated migraine attacks with second dose
    - Treated as Rescue
    - Treated as Recurrence
    - Missing (if any)

- Total number of treated migraine attacks during entire study
- Average number of migraine attacks treated per 30-day period.

Time to dosing from start of the each treated migraine attack (hours) will be calculated as:
date/time of dosing –
date/time of start of the acute migraine attack

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

9 CONCOMITANT MEDICATIONS

The frequency and percentage of all concomitant medications use will be presented by treatment group and summarized for the safety population with ATC medication class and WHO drug name. Medications will be coded using the WHO Drug Dictionary, version WHODDEMAR2018 and sorted by frequency of preferred name.

All concomitant medication data will be presented in a listing.

10 TREATMENT COMPLIANCE AND EXPOSURE

Treatment compliance will not be calculated in the study.

Treatment exposure will be assessed in terms of the confirmed dose based on the CRF matched doses with subject's diary entered doses. Based on the matched CRF dosing dates, migraine numbers will be assigned for exposure analysis while still considering the 48 hour interval on the available data. Each treatment will be assigned a number to form a sequence. From the sequence, unique cluster IDs are assigned to treatments if a treatment belongs to an equivalence class of treatments intersecting within 48 hours of each other. Number of treatments will be limited to the maximum number of treatments a subject should have been able to take with respect to the 48 hour rule. This programming process will be used to determine the individual migraine attack. For unmatched CRF dosing dates (e.g. partial dates and dates falling out of visit windows), each reported dose will be counted as a separate migraine attack for safety and exposure analyses. This method will be applied by the programming team for validation purposes. Refer to the analysis dataset specifications for more details.

The number of subjects who have been treated with a first dose for the treatment of at least one migraine during the 0-3 month (Quarter 1) , 3-6 month (Quarter 2), 6-9 month (Quarter 3) and 9-12 month (Quarter 4) time intervals and similarly the number of subjects who have been treated with a second dose for at least 1 migraine during the 0-3 month (Quarter 1) , 3-6 month (Quarter 2), 6-9 month (Quarter 3) and 9-12 month (Quarter 4) time intervals will be reported.

Total number of doses for each subject during the entire study will be calculated based on the number of first and second doses for each treated migraine which will be same as total treated migraine attacks. This data will be calculated for individual subject's CRF confirmed dose data.

Subjects with at least 3 months, at least 6 months (6-Month safety population) and 12 months (12-Month safety population) in the study will be presented with average of >=2 treated migraine attacks per month, >=3 treated migraine attacks per month and >=4 treated migraine attacks per month.
Additionally, for safety population, 3-Month safety population, 6- Month safety population and 12-Month safety population, summary statistics for total number of treated migraine attacks will be tabulated. This data will be presented for n, mean, median, standard deviation, quartiles and minimum and maximum for each treatment group. Total number of treated migraine attacks will also be presented by each quarter as described previously in summary statistics for safety, 6-Month safety and 12-Month safety populations.

11 EFFICACY ANALYSIS

This section details the specifications for summarizing efficacy endpoints.

This is an open-label study with no control group. Efficacy data will be summarized using descriptive statistics.

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 Efficacy analysis of secondary endpoint

For the secondary endpoint the proportion of attacks treated with lasmiditan 100 mg and with lasmiditan 200 mg which respond as headache pain-free at 2 hours will be calculated for each 3 month period based on the treated migraine-level of the mITT population.

The proportion will be calculated as number of attacks which meet the criteria for headache pain-free at 2 hours divided by total number of treated attacks in each treatment group.

This analysis will be presented by treated migraine attack for total no. of attacks in each treatment group. This data will be presented for each three month period of time such as 0 – 3 months after randomization, > 3 – 6 months after randomization, > 6 – 9 months after randomization, > 9 – 12 months after randomization as well as for the entire study.

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

Treated migraines that do not have a headache pain severity rating at baseline will be excluded from the analysis. Treated migraines that do not have an associated 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 this analysis.

Similar analysis will also be performed for Most Bothersome Symptoms Free at 2 hours post dose and Headache Pain Relief at 2 hours post dose under the same assumptions of sections 11.2.1.2 and 11.2.1.6 .

11.2 Efficacy analysis of additional endpoints

11.2.1.1 Headache Pain-Free

The endpoint of headache pain-free will be summarized in proportion at the 0.5, 1, 2, 4, 24, and 48-hour post-dose time points. This summary will be presented by treatment group for the ITT and mITT populations, based on first dose and for ITT2nd dose rescue and recurrence population based on second dose. These presentations will be summarized on ITT and mITT treated migraine level analysis.

Treated migraines with a mild, moderate, or severe headache severity at the time of dosing will be

the reference subjects for this summary. Treated migraines without a headache severity at baseline, or with a headache severity of 'none' will be excluded. Treated migraines missing a severity assessment at a post-dose time point will not be categorized as pain-free.

This data will be summarized for the 1st, 2nd, 3rd, 4th, 5th, 10th, 15th, and 20th treated migraine.

Similarly, data will presented for subjects with only moderate or severe pain at dosing for mITT Population at treated migraine level.

For subjects that treated 5 or more migraines, headache pain-free at 2 hours will be summarized across the first five treated migraines and as overall response for all treated migraines. Overall response for each subject in this subgroup is calculated by dividing the number of successful responses (responses at 2 hours) by total number of attacks treated.

Additionally, a time to headache pain-free Kaplan-Meier analysis will be conducted on the first treated migraine for the subject-level ITT population by dose.

Summary of headache pain free will be presented for all treated migraine attacks for mITT population as overall numbers and by each quarter as defined in section 8.5.

11.2.1.2 Most Bothersome Symptom Free (MBS-Free)

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.

Subjects who do not provide a symptom rating at baseline will be excluded from the analysis except following possibility:

- 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.

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

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

These analyses will be presented by treatment group, for the ITT and mITT populations, based on first dose and for ITT2nd dose rescue and recurrence population based on second dose. These presentations will be summarized on ITT and mITT migraine level analysis.

The endpoint of MBS-free will be summarized at the 0.5, 1, 2, 4, 24, and 48-hour post-dose time points. This summary will be repeated separately for each symptom (nausea, phonophobia, and photophobia) on the mITT and ITT population at treated migraine level.

This data will be summarized for the 1st, 2nd, 3rd, 4th, 5th, 10th, 15th, and 20th treated migraine.

For subjects that treated 5 or more migraines, MBS-free at 2 hours will be summarized across the first five treated migraines and as overall response for all treated migraines. Overall response for each subject in this subgroup is calculated by dividing the number of successful responses (responses at 2 hours) by total number of attacks treated.
Additionally, a time to MBS Free Kaplan-Meier analysis will be conducted on the first treated migraine for the subject-level ITT population by dose.

Summary of MBS free will be presented for all treated migraine attacks for mITT population as overall numbers and by each quarter as defined in section 8.5.

11.2.1.3 Sustained Headache Pain Free

Sustained pain-free response will also be summarized at the 24 and 48-hour post-dose time points in the same tables of Headache pain free for listed populations in section 11.2.1.1

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 for each treated migraine.

This data will be summarized for the 1st, 2nd, 3rd, 4th, 5th, 10th, 15th, and 20th treated migraine.

11.2.1.4 Consistency Analyses

This analysis will be performed on ITT subject level population.

For subjects that treated 3 or more migraines, headache pain-free at 2 hours, headache relief at 2 hours and MBS free at 2 hours will be summarized across the first three treated migraines with headache severity assessments. The number and percentage of subjects reaching pain-freedom and pain relief will be reported for the following categories: 0 of 3 migraines meeting the criteria, 1 of 3 migraines meeting the criteria, 2 of 3 migraines meeting the criteria, 3 of 3 migraines meeting the criteria, and 2 or 3 of 3 migraines meeting the criteria.

11.2.1.5 Presence of Migraine Symptoms

Counts and percentages of the presence of associated symptoms will be presented at the 0.5, 1, 2, 4, 24, and 48-hour post-dose time points. These will be summarized by treatment group for the ITT population and ITT-2nd dose rescue and recurrence populations based on second dose at treated migraine level for each treated migraine attack.

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

- Nausea
- Phonophobia
- Photophobia
- Vomiting

This data will be summarized overall and for the 1st, 2nd, 3rd, 4th, 5th, 10th, 15th, and 20th treated migraine.

11.2.1.6 Headache Pain Relief

Counts and percentages of the number of subjects with headache relief will be presented at the 0.5, 1, 2, 4, 24, and 48-hour post-dose time points. This summary will be presented by treatment group for the ITT population, ITT-2nd dose rescue and recurrence populations based on second dose at treated migraine level for each treated migraine attack.

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 (1) headache at baseline which becomes none (0) at the summarized time point for each treated migraine.

Treated migraines without a headache severity at baseline will be excluded. Treated migraines missing a severity assessment at a post-dose time point will not be categorized as pain relief.

This data will be summarized for the 1st, 2nd, 3rd, 4th, 5th, 10th, 15th, and 20th treated migraine.

For subjects that treated 5 or more migraines, headache pain relief at 2 hours will be summarized across the first five treated migraines and as overall response for all treated migraines.. Overall response for each subject in this subgroup is calculated by dividing the number of successful responses (responses at 2 hours) by total number of attacks treated.

Additionally, a time to headache pain relief Kaplan-Meier analysis will be conducted on the first treated migraine for the subject-level ITT population by dose.

Summary of headache pain relief will be presented for all treated migraine attacks for ITT population as overall numbers and by each quarter as defined in section 8.5.

11.2.1.7 Disability

Counts and percentages of the level of disability will be presented at baseline and at the 0.5, 1, 2, 4, 24, and 48-hour post-dose time points. These will be summarized for the ITT population, at treated migraine level each treated migraine attack by treatment group.

Disability is measured on a four-point scale.

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

Data will be presented based on the 4 levels of the scale, as 'Not at all' versus all other categories, and as 'Not at all' or 'Mild interference' versus 'Marked interference' or 'Completely, needs bed rest'. Additionally, a shift table of baseline disability versus 2 hour post-dose disability will be presented

This data will be summarized for the 1st, 2nd, 3rd, 4th, 5th, 10th, 15th, and 20th treated migraine.

11.2.1.8 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. These will be summarized for the ITT population, at treated migraine level each treated migraine attack by treatment group.

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

This data will be summarized for the 1st, 2nd, 3rd, 4th, 5th, 10th, 15th, and 20th treated migraine.

Data will also be presented in 2 categories, comparing those who indicated "Very Much Better" or "Much Better" to those who reported being "A little better" or "No change" or "A Little Worse" or "Much Worse" or "Very Much Worse".

12 SAFETY ANALYSIS

This section details the specifications for summarizing safety endpoints.

Adverse event (AE) analyses will be presented on the Safety populations.

Laboratory, vitals, ECG, Physical examination and C-SSRS analyses will be presented on the Safety population.

Safety endpoints will be summarized using descriptive statistics.
Descriptive statistics for quantitative variables will include: n, mean, median, minimum, maximum, and standard deviation. Descriptive statistics for qualitative variables will include frequency counts and percentages. Adverse events will be summarized in terms of the proportion of subjects and the proportion of treated migraine attacks associated with any adverse event and with specific adverse events.

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

12.1 Adverse Events

An AE with the date of onset on or within 48 hours after a dose of study drug, or an event that worsens in intensity within 48 hours of a dose of study drug will be considered a treatment-emergent adverse event (TEAE). Other AEs are defined as those occurring after randomization but not considered to be treatment-emergent.

Descriptive statistics for both number of subjects ever experiencing an event as well as for the total number of events will be presented. Furthermore, descriptive statistics will also be calculated for each treatment group irrespective of first or second dose for AE relationship and AE severity. If multiple intensities are reported for a given AE and subject, then the most severe intensity will be counted. A separate, similar analysis will be conducted for TEAEs.

AEs with a missing start date will be assumed to be treatment-emergent, except in situations 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 presented by treatment groups and 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 21.0.

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), preferred term (PT), and frequency. For the overall summary of AEs, both total subjects ever experiencing an event as well as total number of 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 by treatment arm in the following tables:

- Overall summary of AEs for Safety Population, 6-month, and 12-month population including: Add
    - All AEs
    - TEAEs
    - Other AEs
    - Related TEAEs
    - AEs leading to study discontinuation
    - Serious AEs
    - Related serious AEs
    - Deaths

- Incidence of All AEs and Other AEs by SOC for the Safety Population and Pre-administrative hold Population.
- Incidence of TEAEs by SOC for the Safety Population, 6 month and 12 month Safety Population.
- Incidence of TEAEs by decreasing frequency of PT for the Safety Population and Pre-administrative hold Population.
- Incidence of TEAEs occurring in more than 2% of subjects by quarter for Safety Population.
- Incidence of TEAEs and SAEs by SOC, PT and Doses for the Safety Population, 6-month and 12-month Safety Population.
- Summary of TEAEs by SOC, PT,and migraine attack sequence for the Safety Population.
- Summary of TEAEs by PT and migraine attack sequence for subjects that treated 5 or more migraine attacks in the Safety Population
- Summary of TEAEs occurring in more than 2% of subjects by PT for the Safety Population.
- Incidence of all SAEs by SOC for the Safety Population, 6 month and 12 month Safety Population.
- Incidence of All AEs leading to study discontinuation for Safety Population, 6-month and 12-month Population.
- Listing of All AEs leading to study discontinuation or death.
- Incidence of serious TEAEs for Safety Population, 6-month and 12-month Population. In addition, listings of these will be presented for Pre-Administrative Hold Population.
- Listing of Serious AEs.
- Time to onset and duration of TEAEs occurring in more than 2% of subjects relative to dosing regardless of second dose. If the time of adverse event is missing, no imputation will be performed for this presentation. The most frequent TEAE list will be finalized before interim soft lock and final database lock.
- Subgroup analysis will be presented for subject with cardiovascular risk factors. TEAE will be compared among subjects with and without CVRF for individual event for Safety population. They will be tested with chi-squared test or fisher's exact test as appropriate with respect to sample size and all comparisons will be done at level of significance of 0.05.

Above tables will be presented for various types of AE criteria as below:

1. Incidence of TEAE table will be provided by-subject analysis. For this analysis, the adverse events will be reported out of total number of subjects in each treatment group regardless of whether a second dose is taken.
2. Similar events as Point #1 will be reported when only 1 dose was taken and additionally when 2 doses were taken.

3. Incidence of serious adverse events table will be reported by-subject analysis for each treatment group regardless of whether a second dose is taken.
4. Similarly, to Point # 2, serious events will be reported when only 1 dose was taken and additionally when 2 doses were taken.
5. TEAEs summary will be provided by each treated migraine analysis. For this analysis, the adverse events will be reported out of total number of treated migraines for each treatment group regardless of second dose.
6. Additionally TEAE by-subject analysis will be provided for treated 1st migraine attack, 2nd migraine attack, 3rd migraine attack, 4^{th} migraine attack, 5^{th} migraine attack, 10^{th} migraine attack, 15^{th} migraine attack, 20^{th} migraine attack
7. Specific most common TEAEs will be reported in descriptive statistics (n, mean, median, SD, Minimum and maximum) by proportion of treated migraines attacksin subjects experiencing the TEAE at least once. This data will be presented out of total number of subjects in each treatment group. TEAEs will be reported if 2% or more of subjects any any treatment group report the event.

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 (SAEs) 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 standards international (SI) units.

Shift tables describing out-of-reference range shifts will be provided for clinical laboratory test results, as appropriate by treatment group and dose based on the laboratory parameters as described below.

For each parameter, the out-of-reference range shifts will be classified as:

- Low
- Normal
- High

Shifts will be presented for lowest post baseline results and for highest post baseline results for all described laboratory parameters.

Laboratory blood data and urine data will be collected during **Screening/Visit 1** (**ONLY** if more

than two weeks since **EoS/Visit 2** of COL MIG-301 or COL MIG-302) and at visit **Month 1/Visit 2**, **Month 6/Visit 4**, and **Month 12/Visit 6/EoS/ET.** If **Screening/Visit 1** is the same day the data will be used for both parent and Gladiator studies. In that case the baseline for this data will be considered from parent study (301 or 302) where subject was randomized previously, and respective lab parameters will be mapped by subject for new study for analysis. If Screening/Visit is within 2 weeks of **EoS/Visit 2** of COL MIG-301 or COL MIG-302 the data obtained will be used for both studies except a urine pregnancy test for WOCBP will be performed separately. In that case data for urine analysis will be used from current study. The question "When did the subject enter 305?" from CRF will be used to determine when the screening/Visit 1 for each subject was performed.

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

Additionally, plots of ALT and AST vs. Total bilirubin by treatment group will also be produced, with reference lines at 3xULN for ALT, AST, and 2XULN for Total bilirubin. In each plot, Total bilirubin will be in the vertical axis.

The following laboratory parameters will be summarized:

- Hematology
    - White blood cell (WBC) count with differential (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,
    - phosphate,
    - potassium,

  - sodium,
  - total bilirubin,
  - total protein,
  - total cholesterol,
  - zHDL,
  - triglycerides.
- Urinalysis
  - Protein,
  - glucose,
  - nitrite,
  - ketones,
  - blood (hemoglobin),
  - pH,
  - specific gravity,
  - RBCs,
  - WBCs.

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)
- Weight (lb)

Vital signs data will be collected during **Screening/Visit 1** and at visits **Month 1/Visit 2**, **Month 6/Visit 4**, and **Month 12/Visit 6/EoS/ET.** If **Screening/Visit 1** is the same day the data will be used for both parent and Gladiator studies. In that case the baseline for this data will be considered from parent study (301 or 302) where subject was randomized previously, and respective vitals parameters will be mapped by subject for new study for analysis. The question "When did the subject enter 305?" from CRF will be used to determine when the screening/Visit 1 for each subject was performed.

Additionally subjects with categorical changes of interest in SBP, DBP, weight and heart rate will be summarized in frequencies and percentages based on the baseline categories in the same table of Appendix 16.3.

12.4 12-lead Electrocardiograms (ECGs)

The 12-lead ECG assessments will be performed during **Screening/Visit 1** (**ONLY** if more than two weeks since **EoS/Visit 2** of COL MIG-301 or COL MIG-302) and at visit **Month 1/Visit 2**, **Month 6/Visit 4**, and **Month 12/Visit 6/EoS/ET.** If **Screening/Visit 1** is the same day or within 2 weeks of **EoS/Visit 2** of COL MIG-301 or COL MIG-302 the data will be used for both parent and Gladiator studies. In that case the baseline for this data will be considered from parent study (301 or 302) where subject was randomized previously, and respective ECG parameters will be mapped by subject for new study for analysis. The question "When did the subject enter 305?" from CRF will be used to determine when the screening/Visit 1 for each subject was performed.

Shift tables describing abnormal shifts will be provided for ECG results, as appropriate by treatment group and dose, and will be classified as either:

- Normal
- Abnormal, Insignificant
- Abnormal, Significant

Worst value at any post baseline visit will be considered for the shift. Abnormal significant will be considered worse than Abnormal Insignificant and Abnormal Insignificant will be considered as worse than Normal.

Observed and change from baseline summaries will be presented for quantitative measurements using descriptive statistics.

The following ECG parameters will be summarized by each visit.

- Mean Heart rate
- PR interval, Aggregate
- QRS Duration, Aggregate
- QT Interval, Aggregate
- QTcB Interval, Aggregate
- QTcF Interval, Aggregate

Rhythm assessments will be presented in a listing.

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

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

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

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

Categorical changes in ECG intervals will be summarized in frequencies and percentages based

on the categories as described in Appendix 16.4.

12.5 Physical Examination

If **EoS/Visit 2** of COL MIG-301 or COL MIG-302 is the same day as **Screening/Visit 1**, only a brief physical examination if indicated by an AE will be performed (as required by the earlier studies). In that case, the data will be used for both parent and Gladiator studies. The baseline for this data will be considered from parent study (301 or 302) where subject was randomized previously, and respective physical examination parameters will be mapped by subject for new study for analysis. The question "When did the subject enter 305?" from CRF will be used to determine when the screening/Visit 1 for each subject was performed.

If the subject is not enrolling in COL MIG-305 the same day they are completing COL MIG-301 or COL MIG-302, a complete physical examination will be performed during **Screening/Visit 1** A complete physical examination of all body systems will include the following: general appearance, skin, HEENT, heart, lymph nodes, lungs, abdomen, extremities/joints, neurological systems, and mental status. At each visit, **Month 1/Visit 2, Month 3/Visit 3**, **Month 6/Visit 4**, **Month 9/Visit 5** and **Month 12/Visit 6/EoS/ET,** a brief symptom related physical examination will be performed if indicated by an AE. In this case, the baseline data will be used from current study for analysis.

Weight will be measured at **Screening/Visit 1**. BMI will be calculated by the database using the subject's height recorded for COL MIG-301 or COL MIG-302 in specific parent study. Weight will also be measured at **Month 12/Visit 6/EoS/ET.**

The shift in physical examination evaluations will be summarized for each system for subjects who had a physical examination at each visit up to **EoS/Visit 6** 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

Worst value at any post baseline visit will be considered for the shift. Not Done will be considered worse than Abnormal and Abnormal will be considered as worse than Normal.

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

The C-SSRS will be used to assess suicidal ideation and behavior. Listings will present all C-SSRS data for subjects with at least one positive response to any C-SSRS question at any time during the study.

If **Screening/Visit 1** is the same day or within 2 weeks of **EoS/Visit 2** of COL MIG-301 or COL MIG-302 the data obtained will be used for both studies. The baseline for this data will be considered from parent study (301 or 302) where subject was randomized previously, and respective C-SSRS parameters will be mapped by subject for new study for analysis. The question "When did the subject enter 305?" from CRF will be used to determine when the screening/Visit 1 for each subject was performed.

The "since last visit" version of questionnaire will be administered at **Screening/Visit 1** (**ONLY** if more than two weeks since **EoS/Visit 2** of COL MIG-301 or COL MIG-302) and at visit **Month 1Visit 2**, **Month 3/Visit 3**, **Month 6/Visit 4**, **Month 9/Visit 5** and **Month 12/Visit 6/ EoS/ET.** In this case, the baseline data will be used from current study for analysis.

12.7 Cardiovascular Medication Use

A summary of baseline cardiovascular medication use (e.g. anti-anginal, anti-hypertensive, anti-arrhythmic, etc.) will be provided for the safety population. In addition, a summary of patients with changes to cardiovascular medication use post-baseline, including initiation of a new cardiovascular medication and an increase in dose in current cardiovascular medications, will be provided for the safety population.

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 since the parent study. Counts and percentages of subjects with emergency room or urgent care visits for migraines since parent study will be presented. Data on CV related events at different visits as **Month 1Visit 2**, **Month 3/Visit 3**, **Month 6/Visit 4**, **Month 9/Visit 5** and **Month 12/Visit 6/ EoS/ET** will be also presented for subjects in frequencies and percentages. This data will include different providers (cardiologist, primary care, emergency room, other), hospitalizations, performed procedures and changes in cardiovascular medications in last 6 months. This summary will be presented on the Safety population by treatment groups.

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

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	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	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: 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	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.
Partial	Known	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: 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	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: 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	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: 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	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	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: 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	If start date/time < dose date/time, then not TEAE. If start date/time >= dose date/time and < (dose date/time + 48 hours (or 2 days)), then TEAE
	Partial	If start date/time < dose date/time, then not TEAE. If start date/time >= dose date/time and < (dose date/time + 48 hours (or 2 days)), then TEAE.
	Missing	If start date/time < dose date/time, then not TEAE. If start date/time >= 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	If stop date/time < dose date/time, then not TEAE. If stop date/time >= dose date/time, then TEAE.
	Partial	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: If stop date/time < dose date/time, then not TEAE. If stop date/time >= dose date/time, then TEAE.
	Missing	Assumed TEAE.
Missing	Known	If stop date/time < dose date/time, then not TEAE.

START DATE/TIME	STOP DATE/TIME	ACTION
		If stop date/time >= dose date/time, then TEAE.
	Partial	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: If stop date/time < dose date/time, then not TEAE. If stop date/time >= dose date/time, then TEAE.
	Missing	Assumed TEAE.

16.3 CRITERIA FOR CATEGOROCAL CHANGES IF INTEREST IN VITAL SIGNS (SBP, DBP, PULSE, WEIGHT)

Parameter	Direction	Criteria	Subjects Population defined by Baseline Categories
Systolic BP (mm Hg)(sitting)	Low	≤90 and decrease ≥20	All Subjects; >90; ≤90
	High	≥140 and increase ≥20	All Subjects; <140; ≥140
	PCS High	≥180 and increase ≥20	All Subjects; <180; ≥180
	Sustained Elevation	≥140 and increase ≥20 at 2 consecutive visits	All Subjects; <140; ≥140
Diastolic BP (mm Hg) (sitting)	Low	≤50 and decrease ≥10	All Subjects; >50; ≤50
	High	≥90 and increase ≥10	All Subjects; <90; ≥90
	PCS High	≥105 and increase ≥15	All Subjects;<105; ≥105
	Sustained Elevation	≥90 and increase ≥10 at 2 consecutive visits	All Subjects; < 90; ≥90
Systolic BP or Diastolic BP (mm Hg) (sitting)	Sustained Elevation	Meeting criteria for systolic BP for 2 consecutive visits or meeting criteria for diastolic BP for 2 consecutive visits or both	All Subjects
Pulse (bpm) (sitting)	Low	<50 and decrease ≥15	All Subjects; ≥50; <50

	High	>100 and increase ≥15	All Subjects; ≤100; >100
	Sustained Elevation	>100 and increase ≥15 at 2 consecutive visits	All Subjects; ≤100; >100
Weight (lb)	Low	(Loss) decrease ≥7%	All Subjects
	High	(Gain) increase ≥7%	All Subjects

Abbreviations: BP = blood pressure; PCS = potentially clinically significant; mm Hg = millimeters of mercury; bpm = beats per minute.
Note, "all subjects" include all subjects in safety population with at least 1 non-missing baseline and at least 1 postbaseline measure.

16.4

Parameter	Direction	Criteria
PR Interval	Low	<120
	High	≥220
QRS Interval	Low	Low <60
	High	High ≥120
QT (msec) uncorrected	High	>500
QTcF (msec)	Low	Males: <330; Females: <340
	High	Males: >450; Females: >470
	High	>500
	Increase	Increase >30
		Increase >60
		Increase >75

Abbreviations: bpm = beats per minute; ECG = electrocardiogram; msec = milliseconds; QTcF = Fridericiacorrected.

16.5 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.