Biohaven Pharmaceuticals

Protocol BHV3000-301

A Phase III, Double-Blind, Randomized, Placebo-Controlled, Safety and Efficacy Trial of BHV-3000 (rimegepant) for the Acute Treatment of Migraine

Statistical Analysis Plan

Final Version 2.0

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SIGNATURE PAGE

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Sponsor Approval

By signing this document, I acknowledge that I have read the document and approve of the planned statistical analyses described herein. I agree that the planned statistical analyses are appropriate for this study, are in accordance with the study objectives, and are consistent with the statistical methodology described in the protocol, clinical development plan, and all applicable regulatory guidances and guidelines.

I have discussed any questions I have regarding the contents of this document with the biostatistical author.

I also understand that any subsequent changes to the planned statistical analyses, as described herein, may have a regulatory impact and/or result in timeline adjustments. All changes to the planned analyses will be described in the clinical study report (CSR).

Sponsor Signatories:

PPD

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ABBREVIATIONS

Abbreviation	Definition
AE	Adverse event
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
ASE	Asymptotic standard error
AST	Aspartate aminotransferase
AT	Aminotransferases
ATC	Anatomic therapeutic class
BOCF	Baseline observation carried forward
BUN	Blood urine nitrogen
CI	Confidence interval
CPK	Creatinine phosphokinase
CMH	Cochran-Mantel-Haenszel
CRF	Case report form
CSR	Clinical study report
DILI	Drug-induced liver injury
ECG	Electrocardiogram
EDC	Electronic data capture
eGFR	Estimated glomerular filtration rate
FCS	Fully conditional method
HDL	High-density lipoprotein
ICH	International Conference on Harmonization
IP	Investigational product
IRB/EC	Institutional Review Board/Ethics Committee
IWRS	Interactive web response system
LDH	Lactate dehydrogenase
LDL	Low-density lipoprotein
LOCF	Last observation carried forward
MBS	Most bothersome symptom
MDRD	Modification of diet in renal disease
MedDRA	Medical Dictionary for Regulatory Activities
MI	Multiple imputation
mITT	Modified Intent-to-Treat
MQoLQ	Migraine Specific Quality of Life Questionnaire

Abbreviation	**Definition**
NC=F	Non-Completer Equals Failure
NC1=F	Non-Completer with more than 1 missing data point equals Failure
NC=M	Non-Completer Equals Missing
NRS	Numeric rating scale
PID	Patient identifier
POM	Preference of medication
PP	Per protocol set
PT	Preferred term
QD	Quaque Die (one daily)
RM=F	Rescue Medication = Failure
S-STS	Sheehan-Suicidality Tracking Scale
SAE	Serious adverse event
SAP	Statistical analysis plan
SD	Standard deviation
SDS	Sheehan Disability Scale
SOC	System Organ Class
TBL	Total bilirubin
WHO-DD	World Health Organization-Drug Dictionary

1 INTRODUCTION AND OBJECTIVES OF ANALYSIS

1.1 Introduction

This document presents the statistical analysis plan (SAP) for Biohaven Pharmaceuticals, Protocol BHV3000-301: A Phase III, Double-Blind, Randomized, Placebo-Controlled, Safety and Efficacy Trial of BHV-3000 (rimegepant) for the Acute Treatment of Migraine.

This SAP is based on Amendment 4 of the BHV3000-301 protocol dated 23-JAN-2018. It contains the analysis details and methodology to answer the study objectives, including planned summary tables, by-subject listings, and figures, which will provide the basis for the results section of the clinical study report (CSR). Operational aspects related to collection and timing of planned clinical assessments are not repeated in this SAP unless relevant to the planned analyses.

1.2 Study Objectives

1.2.1 Primary Objectives

To evaluate the efficacy of rimegepant (75 mg tablet) compared with placebo in the acute treatment of migraine as measured by:

- Pain freedom at two hours post-dose.
- Freedom from the most bothersome symptom (MBS), associated with migraine, at two hours post-dose.

1.2.2 Secondary Objectives

- To evaluate rimegepant (75 mg tablet) compared to placebo on freedom from photophobia at 2 hours post-dose.
- To evaluate rimegepant (75 mg tablet) compared to placebo on freedom from phonophobia at 2 hours post-dose.
- To evaluate rimegepant (75 mg tablet) compared to placebo on pain relief at 2 hours post-dose.
- To evaluate rimegepant (75 mg tablet) compared to placebo on freedom from nausea at 2 hours post-dose.
- To evaluate rimegepant (75 mg tablet) compared to placebo on the probability of requiring rescue medication within 24 hours of initial treatment.
- To evaluate rimegepant (75 mg tablet) compared to placebo on sustained pain freedom from 2 to 24 hours post-dose.

- To evaluate rimegepant (75 mg tablet) compared to placebo on sustained pain relief from 2 to 24 hours post-dose.

- To evaluate rimegepant (75 mg tablet) compared to placebo on sustained pain freedom from 2 to 48 hours post-dose.

- To evaluate rimegepant (75 mg tablet) compared to placebo on sustained pain relief from 2 to 48 hours post-dose.To evaluate rimegepant (75 mg tablet) compared to placebo for the incidence of pain relapse from 2 to 48 hours post-dose.

- To evaluate rimegepant (75 mg tablet) compared to placebo on the subjects' ability to function "normal" at 2 hours post-dose according to the Functional Disability Scale.

1.2.3 Exploratory Objectives

- To evaluate the effect of rimegepant (75 mg tablet) relative to placebo on the subjects' ability to work or function at 24 hours post-dose according to the Functional Disability Scale.

- To evaluate the effect of rimegepant (75 mg tablet) relative to placebo on pain relief at 90 minutes post-dose.

- To evaluate the effect of rimegepant (75 mg tablet) relative to placebo on pain relief at 60 minutes post-dose.

- To evaluate the effect of rimegepant (75 mg tablet) relative to placebo on pain relief at 30 minutes post-dose.

- To evaluate the effect of rimegepant (75 mg tablet) relative to placebo on the Migraine Preference of Medication (PoM) at 24 hours post-dose.

- To evaluate the effect of rimegepant (75 mg tablet) relative to placebo on pain relief on the 4-point scale at all scheduled time points post-dose.

- To evaluate the effect of rimegepant (75 mg tablet) relative to placebo on the Migraine Quality of Life Questionnaire (MQoLQ) at 24 hours post-dose.

- To evaluate the tolerability and safety of rimegepant (75 mg tablet) in the acute treatment of migraine as measured by the frequency of adverse events of at least moderate intensity, serious adverse events, and clinically relevant laboratory abnormalities.

- To evaluate the effect of rimegepant (75 mg tablet) relative to placebo on the Sheehan Suicidality Tracking Scale (S-STS) at end of treatment.

2 STUDY DESIGN

2.1 Synopsis of Study Design

BHV3000-301 is a Phase III, multicenter, randomized, double-blind, 2-arm placebo-controlled parallel-group study designed to assess safety and efficacy in the treatment of moderate to severe migraine.

After providing informed consent, subjects will first participate in the screening phase (3-28 day period) to determine eligibility for the study.

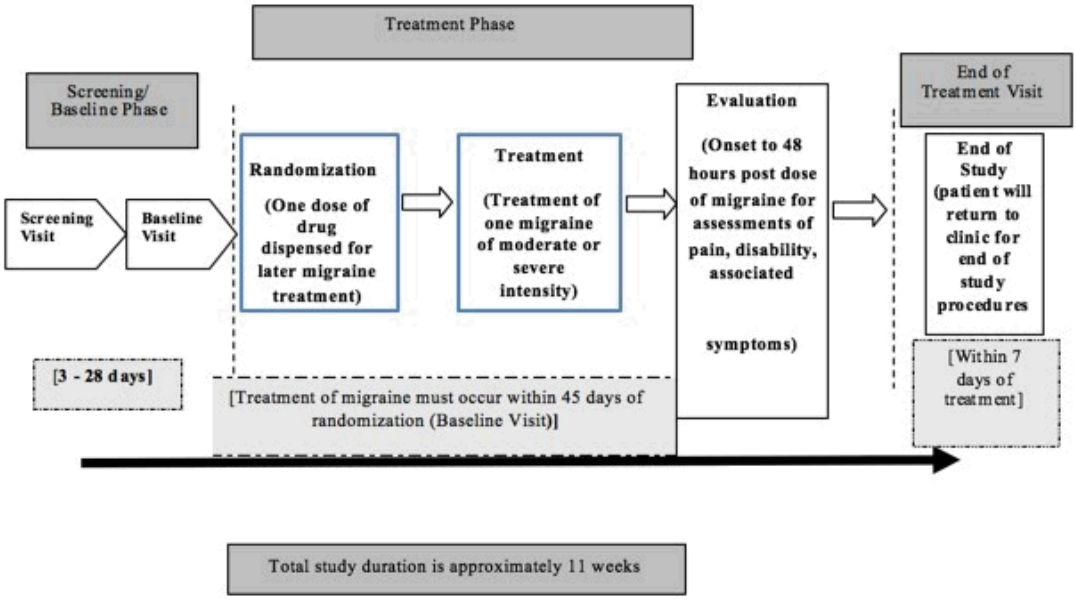
After randomization, the subject will be dispensed a single dose of the double-blind study medication to take home for up to 45 days. This study medication is to be taken when a migraine attack reaches moderate or severe intensity on the numeric rating scale (NRS) as indicated in the electronic diary (eDiary). The subject will complete an eDiary for up to 48 hours after taking the study medication. Subjects will record efficacy data in their eDiary and will telephone the study center immediately if a severe or serious adverse event occurs.

Subjects will return to the study site within 7 days of study treatment for review of the eDiary, assessment of medication compliance, and monitoring of tolerability and safety. If a subject has NOT experienced a migraine headache of sufficient severity within the 45 days after randomization, he or she will be withdrawn from the trial.

2.2 Randomization Methodology

The study will randomize approximately 1,200 subjects. The subjects will be randomized in a 1:1 ratio to receive rimegepant in a 75 mg tablet or matching placebo (see Figure 1). The randomization will be stratified by the use of prophylactic migraine medications (yes or no).

Figure 1: Study Schematic



2.3 Study Estimands

The tables that follow lay out the estimands corresponding to the study objectives. In these tables, the following abbreviations are used to describe the handling of intercurrent events for efficacy estimands:

NC=F: Non-Completers = Failure.

A subject with any missing data for an endpoint is classified as a treatment failure.

NC1=F: Non-Completers with more than 1 missing data point = Failure.

Subjects with more than 1 missing data point, other than at the 2, 24 or 48 hour data points, are classified as treatment failures. This applies to endpoints that are based on data from multiple time points. For example, for the durability endpoint of sustained pain freedom from 2 to 24 hours, the subjects should provide data at 2, 3, 4, 6, 8, and 24 hours. For NC1=F imputation, the data at 2 and 24 hour time points must be present or the subject is classified as a failure. However, any single data point may be missing at 3, 4, 6 or 8 hours without penalty. For sustained pain freedom from 2 to 48 hours, the data at 2, 24, and 48 hours are required to be present.

RM=F: Rescue Medication = Failure.

Subjects that take rescue medication before, or at, the time of the event of interest are classified as failures. If the time of rescue medication is missing, all events on or after the date of rescue medication are classified as failures.

2.3.1 Primary Estimands

The estimands corresponding to the co-primary endpoints for this study are shown in Table 1.

The population summary for all primary estimands is the difference in the percentage of subjects with a positive result ('risk difference') between the BHV-3000 and the Placebo treatment groups. This summary is computed using the modified Intent-to-Treat (mITT) population as defined in Section 4.1.

Table 1: Estimands for the Co-Primary Objectives

Objective	**Pain Freedom at 2 hours post-dose**
Population	mITT
Variable	Percent of subjects reporting no pain at 2 hours post-dose
Intercurrent Events	NC=F; RM=F;
Objective	**Freedom from Most Bothersome Symptom (MBS)**
Population	mITT
Variable	Percent of subjects reporting absence of their MBS at 2 hours post dose
Intercurrent Events	NC=F; RM=F; Failure to report MBS = F; Study medication taken before reporting MBS=F.

2.3.2 Secondary Estimands

The estimands corresponding to the secondary objectives are shown in Table 2.

The population summary for all secondary estimands is the difference in the percentage of subjects with a positive result ('risk difference') between the BHV-3000 and the Placebo treatment groups.

Table 2: Estimands for the Secondary Objectives

Objective	**Photophobia Freedom at 2 hours post-dose**
Population	mITT subjects with photophobia reported as present at migraine onset
Variable	Percent of subjects reporting no photophobia at 2 hours post-dose
Intercurrent Events	NC=F; RM=F
Objective	**Phonophobia Freedom at 2 hours post-dose**
Population	mITT subjects with phonophobia reported as present at migraine onset
Variable	Percent of subjects reporting no phonophobia at 2 hours post-dose
Intercurrent Events	NC=F; RM=F
Objective	**Pain Relief at 2 hours post-dose**
Population	mITT
Variable	Percent of subjects who report mild or no pain at 2 hours post-dose
Intercurrent Events	NC=F; RM=F
Objective	**Nausea Freedom at 2 hours post-dose**
Population	mITT subjects with nausea reported as present at migraine onset
Variable	Percent of subjects reporting no nausea at 2 hours post-dose
Intercurrent Events	NC=F; RM=F
Objective	**Probability of Rescue Medication**
Population	mITT
Variable	Percent of subjects taking rescue medication
Intercurrent Events	None
Objective	**Functional Disability at 2 hours**
Population	mITT
Variable	Percent of subjects with a response of "normal" at 2 hours post-dose
Intercurrent Events	NC=F; RM=F
Objective	**Sustained Pain Freedom (2 to 24 hours; or 2 to 48 hours)**
Population	mITT
Variable	Percent of subjects pain free during the period of interest
Intercurrent Events	NC1=F; RM=F
Objective	**Sustained Pain Relief (2 to 24 hours; or 2 to 48 hours)**
Population	mITT
Variable	Percent of subjects who report no pain, or mild pain, during the period of interest
Intercurrent Events	NC1=F; RM=F
Objective	**Pain Relapse (2 to 48 hours)**
Population	mITT subjects who report pain freedom at 2 hours post-dose
Variable	Percent of subjects who report any pain during the period of interest
Intercurrent Events	NC1=F; RM=F

2.3.3 Exploratory Estimands

The estimands corresponding to the exploratory objectives are shown in Table 3.

Table 3: Estimands for the Exploratory Efficacy Objectives

Objective	**Functional Disability at 24 hours**
Population	mITT
Variable	Percent of subjects with a response of "normal" at 24 hours post-dose
Intercurrent Events	NC=F; RM=F
Pop. Summary	Percentage within each treatment group (BHV3000 & Placebo)
Objectives	**Pain Relief at 30, 60 or 90 minutes post-dose**
Population	mITT
Variable	Percent of subjects who report pain as mild or none at the time point of interest
Intercurrent Events	NC=F; RM=F
Pop. Summary	Percentage within each treatment group (BHV3000 & Placebo)
Objectives	**Preference of Medication**
Population	Treated subjects who: 1) answer "yes" to the lead-in question (i.e. "Have you ever taken migraine medication?") and provide preference of medication data
Variable	Percentage of subjects who prefer study medication to previous migraine medications
Intercurrent Events	Observed analysis. No accounting for intercurrent events.
Pop. Summary	Percentage within each treatment group (BHV3000 & Placebo)
Objectives	**Pain Relief, on a 4 point scale, at all time points**
Population	mITT
Variable	Percent of subjects who report pain as none, mild, moderate or severe
Intercurrent Events	NC=F; RM=F
Pop. Summary	Percentage of each response, in each treatment group (BHV3000 & Placebo)
Objectives	**Migraine Quality of Life Questionnaire**
Population	mITT
Variable	Total score on the MQoLQ
Intercurrent Events	Observed analysis. No accounting for intercurrent events.
Pop. Summary	Average total score within each treatment group (BHV3000 & Placebo)
Objective	**Safety and Tolerability**
Population	All treated subjects
Variables	Multiple
Intercurrent Events	Subjects analyzed as treated. No accounting for intercurrent events
Pop. Summary	Multiple (discussed under Section 6, "Safety Analyses")
Objective	**Sheehan Suicidality Tracking Scale**
Population	All treated subjects
Variables	Change from baseline in the total score
Intercurrent Events	Subjects analyzed as treated. No accounting for intercurrent events
Pop. Summary	Percentage of subjects, by treatment group, in each of 5 categories (<-1, -1, no change, 1, >1)

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4 SUBJECT POPULATIONS

4.1 Population Definitions

The following subject populations will be evaluated and used for presentation and analysis of the data:

- Enrolled subjects: patients who sign an informed consent form and are assigned a subject identification number
- Randomized subjects: enrolled subjects who receive a randomization treatment assignment from the interactive web response system (IWRS), regardless of the treatment they actually received or subsequent withdrawal from treatment
- Treated subjects: enrolled subjects who take any amount of study therapy (rimegepant or placebo)
- Modified Intent-to-Treat (mITT) subjects: Randomized subjects who are randomized only once, take study medication, have a baseline migraine of moderate to severe intensity, and who provide at least one post-baseline efficacy data point. Subjects that re-enrolled in the study, and were randomized on two or more occasions are not included in the mITT population.

4.2 Protocol Deviations

A protocol deviation is any variance from the approved protocol, either intentional or unintentional. The possible categories for all protocol deviation are as follows:

- Informed Consent
- Inclusion/Exclusion Criteria (specify #)
- Concomitant Medication
- SAE Reporting
- Regulatory
- Drug Storage/Preparation
- Drug Administration
- Visit Schedule

- EPro Diary Noncomplinace
- Noncompliance (i.e., trends, missed assessments).

A significant protocol deviation is any deviation that could impact subject safety or the integrity of the trial. For the purposes of this study, significant protocol deviations will be defined as the following:

- Inadequate informed consent or initiation of study procedues prior to completing the informed consent
- Enrollment of subjects not meeting the inclusion/exclusion criteria
- Unreported SAEs
- Improper breaking of the blinding of the study
- Use of prohibited medication as defined by the protocol
- eDiary non-compliance with primary and secondary endpoints (2, 24, or 48-hour post-dose assessment
- Repeated deviations of the same nature for a given site or patient
- Initiation of rescue medication(s) prior to primary endpoint at 2-hours

The sponsor, or designee, will be responsible for producing the final protocol deviation file (formatted as a Microsoft Excel file). This file will include site, subject ID, deviation date, deviation type, and a description of the protocol deviation.

All protocol deviations (with the exception of those related to rescue medication and missed eDiary assessments) will be presented in a data listing. Handling of rescue medication and missed eDiary assessments are described in the statistical methods section of this SAP.

5 STATISTICAL METHODS

5.1 Sample Size Justification

Approximately 1415 patients will be screened to randomize 1200 subjects (approximately 600 per arm). If roughly 90% of the 600 subjects randomized to each treatment arm have a migraine treated with study medication in the allotted time period, there will be approximately 550 treated subjects per group.

Based on approximations from the Phase IIb study, 550 subjects provides more than 95% power to detect a difference between rimegepant and placebo on the subjects' freedom from their self-reported MBS. Also, based on the Phase IIb study, 550 subjects provides more than 95% power to detect a difference in freedom from pain at 2 hours post-dose. Having at least 95% power on each co-primary endpoint provides at least 90% power to detect a difference on both endpoints jointly.

5.2 General Statistical Methods and Data Handling

5.2.1 General Methods

All output will be incorporated into Microsoft Excel or Word files, sorted and labeled according to the International Conference on Harmonization (ICH) recommendations, and formatted to the appropriate page size(s). PDF versions of the output will also be produced.

Tabulations will be produced for appropriate demographic, baseline, efficacy, safety, and other parameters. For categorical variables, summary tabulations of the number and percentage within each category will be presented. If applicable, a category for missing data will also be presented. For continuous variables, n, mean, median, SD, minimum, and maximum values will be presented. The minimum and maximum values will be presented with the same precision as the data. The mean and median will be presented with the precision of the data + 1 decimal place. The SD will be presented with the precision of the data + 2 decimal places.

Formal statistical hypothesis testing and summary statistics will be presented, as well as confidence intervals (CIs) on selected endpoints, as described in the sections below.

The default tables, listings, and figures layout will be as presented in Table 4 below:

Table 4: Layout Specifications

Orientation	Portrait	Landscape
Paper Size	Letter	Letter
Margins	Top: 3.05 cm Bottom: 2.54 cm Left: 2.54 cm Right: 2.54 cm	Top: 3.05 cm Bottom: 2.2 cm Left: 1.9 cm Right: 1.9 cm
Font	Table text: Times new Roman 9 or 10 pts Table title: Times new Roman 12 pts Table legend: Times new Roman 10 pts	Table text: Times new Roman 8, 9 or 10 pts Table title: Times new Roman 12 pts Table legend: Times new Roman 9 or 10 pts

The font size may be reduced as necessary to allow additional columns to be presented, but not at the expense of clarity. Also the orientation may be changed to portrait if appropriate.

5.2.2 Computing Environment

All statistical analyses will be performed using SAS statistical software (Version 9.2 or higher). Medical history and AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA, Version 19.1). Concomitant medications will be coded using the World Health Organization Drug Dictionary (WHO-DD, Sep-2016).

5.2.3 Methods of Pooling Data

In the case of sparse data for the stratification factor (use of prophylactic medication: yes or no), the responses will be pooled in summary tables. Specific details on the procedures for pooling data are presented in the applicable sections of the document outlining the analyses.

5.2.4 Adjustments for Covariates and Stratification

The randomization of subjects was stratified by the use of prophylactic migraine medication (yes or no). Hence, most analyses are stratified by the use or prophylactic medication.

5.2.5 Multiple Comparisons

Type I error is controlled in this study by using a hierarchical gate-keeping procedure. First, the family of two co-primary endpoints is tested. If the co-primary endpoints are found to be significant, then secondary endpoints are tested in a fixed sequence. In particular, each co-primary endpoint will be tested for superiority to placebo at a two-sided alpha level of 0.05 without further adjustment for multiplicity. If the primary endpoint tests are both significant, then the following secondary endpoints will be tested in a fixed sequence, in the order shown, with each test conducted at p=0.05:

1. Photophobia Freedom at 2 hours
2. Phonophobia Freedom at 2 hours
3. Pain Relief at 2 hours
4. Nausea Freedom at 2 hours
5. Probability of Rescue Medication Use
6. Sustained Pain Freedom from 2 to 24 hours
7. Sustained Pain Relief from 2 to 24 hours
8. Sustained Pain Freedom from 2 to 48 hours
9. Sustained Pain Relief from 2 to 48 hours
10. Pain Relapse from 2 to 48 hours

11. Functional Disability at 2 hours

If a test in the hierarchy is not significant, then any further tests on endpoints in the sequence will have p-values presented only for descriptive purposes, and no conclusions will be drawn from those results.

For exploratory endpoints, no attempt will be made to adjust for multiplicity. Any exploratory endpoints for which p-values are produced will be evaluated at an unadjusted two-sided alpha level of 0.05 and presented only for descriptive purposes.

5.2.6 Subpopulations

The subgroups of interest for this study:

- Age: Categorized as < 40, ≥ 40 years
- Race: white, black or African American, and other (certain tables may be created for the Asian population only; but in the subgroup analyses, Asian subjects will generally be included in the "other" category due to low counts)
- Sex: Female/Male
- Aura: Presence/Absence
- Headaches per Month: Categorized as < median, ≥ median
- Triptan Non-Responder: Yes/No
- CV Risk Contraindicating Triptans: Yes/No

Subgroup analyses will be performed for the primary endpoints only.

Triptan non-responders are identified using the "Prior Triptan Response" Case Report Form (CRF) pages. The definition of triptan non-responder is based on the number of triptans that a subject failed for efficacy reasons. For each triptan and route of administration, the subject is asked the questions shown in Table 5. A subject is considered to have failed a drug for efficacy reasons if they indicated "most or all of the time" for any of the reasons in the table.

A triptan non-responder is defined as any subject that fails two or more molecular entities for efficacy reasons. To be considered a failure for a molecular entity, the subject must have failed on all routes of administration that the subject tried for the molecular entity.

Table 5: Questions Used to Determine Triptan Non-response

	Most or All of the Time	Some of the Time	Rarely	Never
The treatment took too long to relieve my headache pain.				
The pain returned after it was relieved within 24 hours				
The treatment did not relieve my other symptoms (nausea, sensitivity to light or sound, for example).				
I could not count on this treatment to relieve my pain and symptoms every time				

Subjects with CV risk that contraindicates triptans are identified using the "Cardiac and Other Risk Factors" CRF pages. The pages are used to identify subjects with cardiovascular conditions cited in triptan labels as contraindications. A subject is identified as someone with cardiovascular risk factors contraindicating triptans if any of the following questions are answered as "yes":

- Does the subject have ischemic coronary artery disease?
- Does the subject have coronary artery vasospasm including Prinzmetal's angina?
- Does the subject have Wolff-Parkinson-White Syndrome or arrhythmias associated with other cardiac accessory conduction pathway disorders?
- Does the subject have history of stroke or transient ischemic attack (TIA)?
- Does the subject have peripheral vascular disease (PVD)?
- Does the subject have ischemic bowel disease?
- Does the subject have uncontrolled hypertension?

5.2.7 Re-Screened and Re-Randomized Subjects

In the event a subject is re-screened, then the data from the last screening visit, and latest laboratory assessment are used for the screening data.

In the event a subject is re-randomized, the subject will not be analyzed as part of the mITT population for the efficacy analyses. For safety, all AEs that occurred after the first date of randomization will be considered on-study.

For safety analyses, the subject will have their actual treatment assigned as BHV-3000 if at least one of their treatments was with BHV-3000.

5.2.8 Missing and Partial Dates

For efficacy analyses, partial or missing dates will not be imputed. The relative study days, where determined, will be calculated for full dates only.

For rescue medication, if the time of rescue medication is missing, then all endpoints on or after the date of rescue medication will be imputed as failures.

For missing and/or partial dates regarding concomitant/prior medications, a conservative approach will be taken. The medication will be assumed to be concomitant if it cannot be definitively shown that the medication was not taken after the period beginning 14 days prior to the taking of study medication.

If the start date of an AE is partially or completely missing, then the date will be compared as far as possible with the date of the randomization. The AE will be assumed to be on-study if it cannot be definitively shown that the AE did not occur or worsen during the post-randomization period (worst case approach).

The following general rules will be used:

- If the start day is missing, but the start month and year are complete, an AE will only be excluded as being on-study if the start month/year is before the month/year of randomization or if the stop date is before randomization.

- If the start day and month are missing, but the start year is complete, an AE will only be excluded as being on-study if start year is before the year of randomization or if the stop date is before randomization.

- If the start date is completely missing, an AE will be considered on-study unless the stop date is before randomization.

5.2.9 Visit Windows

Windows for the timeframe around efficacy measurements (15, 30, 45, 60, 90 minutes, 2, 3, 4, 6, 8, 24, and 48 hours) will be automated and captured in the eDiary. Refer to Table 6 for details on the evaluation intervals and Appendix 1 for details on the schedule of assessments.

Table 6: Evaluation Intervals for Efficacy Analysis

Evaluation	Protocol-Specified Interval	Analysis-Specified Interval
Screening Phase		
Screening	Day -28 to Day -3	Day -40 to Day -3
Acute (Randomization) Phase		
Baseline (Randomization)	Day 1	Day -2 to 1
Onset of Migraine	Day 1 to 45	Day 1 to 45
15, 30, 45, 60, 90 minutes post-dose	Time of Dose + 15, 30, 45, 60, and 90 minutes	Time of Dose + 15, 30, 45, 60, and 90 minutes (as captured in eDiary)
2 hours post-dose	Time of Dose + 2 hours	Time of Dose + 2 hours (as captured in eDiary)
8 hours post-dose	Time of Dose + 8 hours	Time of Dose + 8 hours (as captured in eDiary)
24 hours post-dose	Time of Dose + 24 hours	Time of Dose + 24 hours (as captured in eDiary)
48 hours post-dose	Time of Dose + 48 hours	Time of Dose + 48 hours (as captured in eDiary)
End of Treatment Visit	Time of Dose + 7 days	Time of Dose + 2 to 21 days

5.3 Planned Analyses

The analyses planned for endpoints that use data from this study only will be conducted after the last subject completes their End of Treatment Visit or discontinues from the study, and the database has been locked.

A meta-analysis of the durability endpoints will be conducted after the last subject in BHV3000-301 and BHV3000-302 completes their End of Treatment Visit or discontinues from the study, and both databases have been locked.

5.4 Subject Disposition

A summary of subject disposition will be tabulated for all subjects by treatment group and overall. The disposition table will support the creation of a consort diagram, similar to that shown in Figure 1. The categories in the table will include:

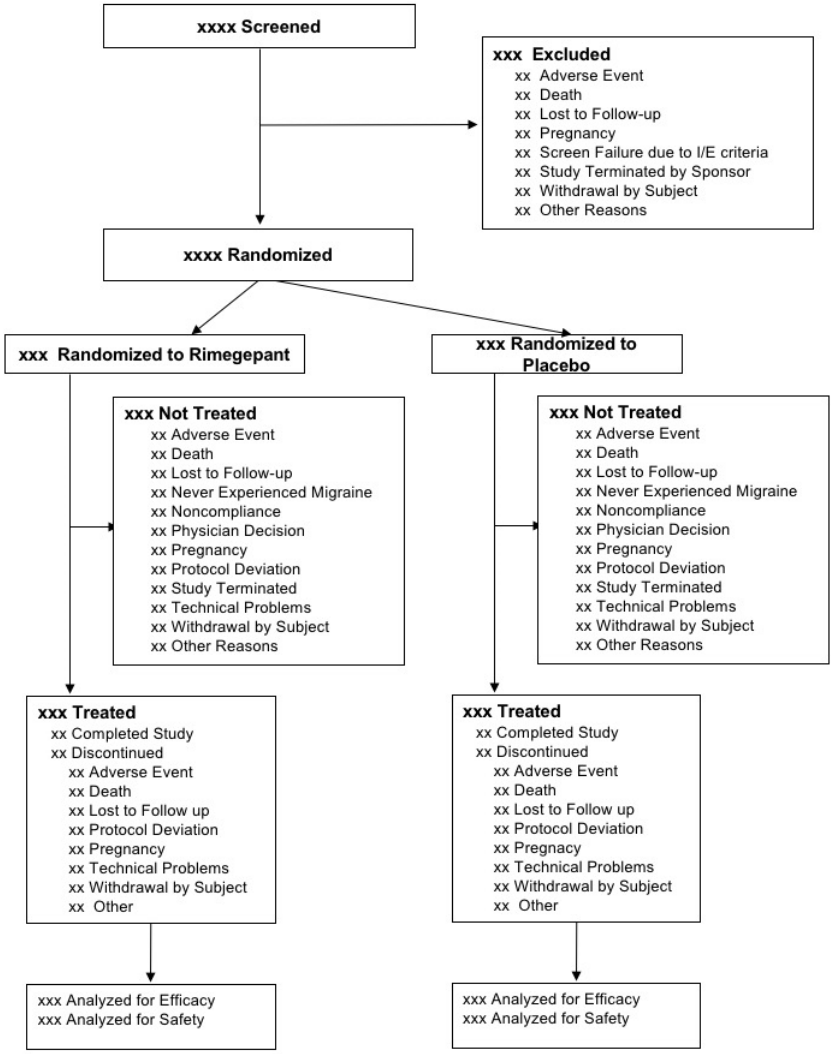
- Number of subjects screened
    - Number of screened subjects excluded from the study and reason for exclusion
- Number of subjects randomized
    - Number of subjects not treated, and the reasons for not being treated

- Number of subjects treated, and their status
  - Completed Study
  - Discontinued, and reasons for discontinuation
- Number of subjects in each analysis population

- Number of subjects who intend to continue on to the BHV-3000-201 study.

A by-subject listing of subject disposition information, including the reason for withdrawal, if applicable, will be presented.

Figure 2: Consort Diagram



5.5 Demographic and Baseline Characteristics

Demographic information, medical history, migraine history, cardiovascular risk factors, and prior/current triptan response will be summarized by treatment group and overall for the mITT population. A similar set of tables will be made for the treated population.

A separate set of demographic tabulations, including demographic information and migraine history, will be made for subjects enrolled but not randomized (overall only) and subjects randomized but not treated (by randomized treatment and overall).

Demographic and other baseline data will also be provided in by-subject data listings.

5.6 Missing Data Description

Descriptions and tabulations of missing data will only be concerned with the post-baseline time points required for computation of the primary and secondary endpoints. These include the time points measured from 2 hours through 48 hours post-dose (e.g.: 2, 3, 4, 6, 8, 24 and 48 hours). The other time points: 15, 30, 45, 60 and 90 minutes are only required for the exploratory endpoints. Also, some tabulations focus on the pain endpoint as that should be generally descriptive of the other efficacy endpoints.

The number and percentage of randomized subjects that were randomized but not treated will be tabulated by treatment group.

For the mITT population, the items below will be tabulated by treatment group and overall, and sub-tabulated by date of migraine onset relative to September 13, 2017 (date ≤ 13-Sep-2017; date > 13-Sep-2017; overall). Hence, there are three subcategories tabulated within each of two treatment groups and overall.

- Number and percentage of subjects with missing pain data at each time point from 2 through 48 hours post-dose. The categories in this tabulation are not mutually exclusive as subjects may have missing data at multiple time points.

- Number and percentage of subjects with: no missing pain data; 1 missing time point, 2 missing time points, 3 missing time points, 4 missing time points, 5 missing time points, 6 missing time points, or 7 missing time points. The categories in this tabulation are mutually exclusive.

- The number and percentage of subjects with missing data on the following endpoints measured at 2-hours post-dose: pain, MBS, photophobia, phonophobia, nausea, and functional disability.

In addition, the number and percentage of mITT subjects with missing pain data at 2 hours post-dose will be displayed by treatment group and overall within the categories of each of the following subgroups:

- Age: Categorized as < 40 or ≥ 40 years

- Race: white; black or African American; all other races combined (including Asian); Asian only
- Sex: Female or Male
- Aura for study migraine: Presence or Absence
- Headaches per Month: Categorized as < median or ≥ median
- Triptan Non-Responder: Yes/No
- Rescue medication taken at anytime during the study: Yes/No
- MBS at migraine onset: photophobia, phonophobia, nausea, and not reported

5.7 Efficacy Evaluation

Unless otherwise noted, all efficacy analyses will be conducted using the mITT population as outlined below. All efficacy data will be included in listings by subject, study medication, and time point (as applicable). For efficacy analyses, baseline is considered as the assessment at the onset of the treated migraine. Subjects who were randomized twice will not be included in the efficacy evaluation.

5.7.1 Rescue Medication

Subjects who take rescue medication as recorded on the CRF or any medication used for headaches as recorded anywhere on the CRF or eDiary will be considered as failures for any efficacy evaluations that are coincident or follow the administration of the rescue medication/other headache medication. If the time of rescue medication is missing, subjects will be considered as failures for any efficacy evaluations are on or after the date of administration of the rescue medication/other headache medication.

5.7.2 MBS Recored After IP is Taken

Subjects that record their MBS after taking the investigation product (IP) are considered failures for the analysis of MBS.

5.7.3 Primary Efficacy Endpoints

In addition to the analyses described below, data regarding the co-primary efficacy endpoints, pain freedom and freedom from MBS at 2 hours post-dose, will be presented in a listing that includes treatment group, historical MBS, MBS at time of onset of study migraine, initial migraine severity, gender, presence or absence of aura, and use of prophylactic migraine medication.

5.7.3.1 Pain Freedom at 2 Hours Post-Dose

Pain freedom is assessed using the number of mITT subjects that report pain levels of "none" at 2 hours post-dose on a 4-point Likert scale (0=none, 1=mild, 2=moderate, 3=severe). The information from the 4-point scale is directly summarized as follows:

- A table showing descriptive statistics for the observed data, which includes the number and percentage of subjects reporting each of the 4 pain levels at 2 hours post-dose, and the percentage of subjects with missing data, for each treatment group. The table will include exact (Clopper-Pearson) 95% CIs for each percentage.
    - This table will be repeated for Asian subjects only.

The estimand for the primary analysis is the percentage of pain free subjects. In statistical terms, this percentage is arrived at by estimating the probability or the "risk" that a subject is pain free.

The population summary, the between group difference in the percentage of pain free subjects is assessed by computing the "risk difference" between treatment groups. This is evaluated by computing the common risk difference, using Cochran-Mantel-Haenszel (CMH) weights (sample size weights), stratified by the use of prophylactic migraine medication (yes or no). The risk difference is tested at a two-sided alpha level of 0.05. Missing data at 2 hours post-dose will be imputed as failures (NC=F). If a stratum (prophylactic medication use: yes or no) has sparse data (less than 5 subjects), then the strata will be pooled.

Results presented for the primary analysis include the following:

- The number and percentage of subjects who are pain free, and those not pain free, at 2 hours post-dose. These are presented by stratum and treatment group, with asymptotic standard errors (ASE), and 95% asymptotic CIs.
- Common risk difference with sample size, p-value, asymptotic standard error (ASE), and 95% asymptotic CIs.
- Risk difference within each strata with sample size, p-value, asymptotic standard error (ASE), and 95% asymptotic CIs.
- A plot of the risk differences within each strata, and common risk difference (similar to the risk difference plot produced by SAS Proc Freq).
- Common risk for each treatment with sample size, ASE, and 95% asymptotic CIs.

The primary analysis will be repeated for the subgroups described in Section 5.2.6.

Sensitivity analyses will be conducted as follows:

1. The primary analysis is repeated, once using the mITT subjects that had a qualifying migraine before the last relevant software fix was applied to the eDiaries (onset on or before 13-Sep-2017), and once for mITT subjects with migraine onset dates after the software fix was applied (onset after 13-Sep-2017).

2. The primary analysis is repeated, using the mITT population, with missing data at 2 hours post-dose imputed using Last Observation Carried Forward (LOCF). Baseline Observation Carried Forward (BOCF) is permitted.

3. The primary analysis is repeated using only data from complete cases (data present at baseline and 2 hours).

4. The primary analysis is executed using the mITT population, and multiple imputation (with 20 imputations; m=20) methods to impute missing data at 2 hours post-dose using the copy from reference approach. The fully conditional specification (FCS) method is used with a generalized logit distribution. Covariates may include use of prophylactic medication (yes or no), sex, migraine intensity at onset (severe or other), migraines per month (< median, ≥ median), date of migraine onset (on or before 13-Sep-2017 or after 13-Sep-2017), and the subject's MBS at time of study migraine onset (nausea, photophobia, or phonophobia).

5. A series of "what if" analyses are conducted that show what the analysis results would look like if the missing data in each treatment group were replaced with data from subjects having success rates that vary over the range of 0, 10, 20 and 30 percent. This analysis is presented in a 4x4 matrix, with the rows representing the success rates for the placebo group and the columns representing the success rates for the BHV-3000 group. For example, the "30,0" cell shows the hypothetical results when a responder rate of 30% replaces the missing placebo data, and a responder rate of 0% replaces the missing BHV-3000 data. Each cell in this table will show the common risk difference, asymptotic 95% CI and uncorrected p-value. The table will be accompanied by a forest plot that displays the 16 CIs.

5.7.3.2 Freedom from MBS at 2 Hours Post-Dose

Freedom from each subject's MBS is assessed using the number of mITT subjects who report that their MBS (reported at migraine onset) is absent at 2 hours post-dose. The symptoms that can be nominated as the MBS (phonophobia, photophobia or nausea) are measured using a binary scale (0=absent, 1=present).

Subjects who reported their MBS before taking IP, or who did not provide an MBS are considered failures in this analysis.

Tabulations will be presented as follows:

- The number and percentage of subjects reporting each of the migraine associated symptoms (phonophobia, photophobia or nausea) as most bothersome, subjects with a missing MBS, and subjects who reported their MBS after taking study medication.

- A cross tabulation of the historical MBS (reported at screening) as rows, and the MBS reported at the onset of the treated migraine as columns. This tabulation only includes subjects with both assessments. P-value from a chi-square test will be reported along with the values and confidence limits for both Asymmetric Lambda and Symmetric Lambda.

The estimand, difference in percentage of MBS free subjects ("risk difference") between treatment groups, is evaluated by computing the common risk difference, using CMH weights (sample size weights), stratified by the use of prophylactic migraine medication (yes or no). The risk difference will be tested at a two-sided alpha level of 0.05. Missing data at 2 hours post-dose will be imputed as failure (NC=F). Also the use of rescue medication prior to providing data at the 2 hour assessment, taking IP prior to reporting the MBS, or failure to report a MBS are events that are imputed as treatment failures. If a stratum (prophylactic medication use: yes or no) has sparse data (less than 5 subjects) then the strata will be pooled.

The results to be presented for the primary analysis of MBS include those described in items (a) through (e) for the primary analysis of pain freedom (Section 5.7.3.1). In this case, the "risk" is now the probability of being MBS free at two-hours post-dose.

The primary analysis of MBS will be repeated for the subgroups described in Section 5.2.6.

Sensitivity analyses will be conducted as follows:

1. The primary analysis is repeated, once using the mITT subjects that had a qualifying migraine before the last relevant software fix was applied to the eDiaries (onset on or before 13-Sep-2017), and once for mITT subjects with migraine onset dates after the software fix was applied (onset after 13-Sep-2017).

2. The primary analysis is repeated, using the mITT population, with missing data at 2 hours post-dose imputed using Last Observation Carried Forward (LOCF). Baseline Observation Carried forward is permitted.

3. The primary analysis is repeated, using only data from complete cases (data present at baseline and 2 hours).

4. The primary analysis is executed using the mITT analysis set, and multiple imputation (with 20 imputations; m=20) methods to impute missing data at 2 hours post-dose using the copy from reference approach. The FCS method is used with a generalized logit distribution. Covariates may include use of prophylactic medication (yes or no), sex, migraine intensity at onset (severe or other), migraines per month (< median, ≥ median), date of migraine onset (on or before 13-Sep-2017 or after 13-Sep-2017), and the subject's MBS at time of study migraine onset (nausea, photophobia, or phonophobia).

5. A matrix of "what if" analyses, similar to that created for the co-primary endpoint of pain freedom, is created for freedom from the MBS.

6. The primary analysis will be repeated, using the mITT population, with the addition of a strata that reflects the subject's self-reported MBS at the time of study migraine onset (nausea, phonophobia, or photophobia).

5.7.4 Secondary Efficacy Endpoints Evaluated with Data from the Current Study

If the co-primary endpoint tests are both significant, then the secondary endpoints are evaluated using a fixed sequence approach, with each test in the hierarchy conducted at p=0.05. See Section 5.2.5 for the testing order.

5.7.4.1 Freedom from Photophobia, Phonophobia or Nausea at 2 Hours

Freedom from photophobia, phonophobia, and nausea are assessed, by treatment group, by tabulating the number of mITT subjects who reported the presence of the symptom at migraine onset who then report the absence of the symptom at 2 hours post-dose. Subjects who report the symptom at baseline, but have missing data at 2 hours post-dose will be imputed as failures (NC=F). Also, subjects in the analysis set that take rescue medications on or before providing their 2 hours post-dose data are imputed as failures.

The principal measurement for the associated symptoms (phonophobia, photophobia, and nausea) is made on a binary scale (0 = absent; 1 = present). An exploratory measurement of these symptoms was also made on a 4 point Likert scale (0=none, 1=mild, 2=moderate, 3=severe).

For these three endpoints, the difference between treatment groups, is evaluated by computing the common risk difference, using CMH weights (sample size weights), stratified by the use of prophylactic migraine medication (yes or no). The risk difference is tested at a two-sided alpha level of 0.05. If a stratum (prophylactic medication use: yes or no) has sparse data (less than 5 subjects) then the strata are pooled.

The results presented for the analysis of each symptom include those described in items (a) through (e) for the primary analysis of pain freedom (Section 5.7.3.1). In this case, the "risk" is the probability of being free from the symptom of interest at 2 hours post-dose. In addition, the following display will be created for each of the 3 symptoms:

- A table showing descriptive statistics for the 4-point scale, which includes the number and percentage of subjects reporting each of the 4 symptom levels at 2 hours post-dose, and the percentage of subjects with missing data, for each treatment group. The table will include exact (Clopper-Pearson) 95% CIs for each percentage.

5.7.4.2 Pain Relief at 2 Hours

Pain relief at 2 hours post-dose is assessed by tabulating the number of mITT subjects that report a pain level of none or mild (responses of 0 or 1 on the 4-point Likert scale) at 2 hours post-dose, by treatment group. Subjects with missing data at 2 hours post-dose will be imputed as failures (NC=F).

The results to be presented for the analysis include those described in items (a) through (e) for the primary analysis of pain freedom (Section 5.7.3.1). In this case, the "risk" is the probability of pain relief at 2 hours post-dose.

5.7.4.3 Probability of Requiring Rescue Medication within 24 Hours

Whether or not a subject took rescue medication within 24 hours after the initial dose of study medication is tabulated, using mITT subjects, and the percentages are compared between treatment groups.

The results are presented for the analysis include those described in items (a) through (e) for the primary analysis of pain freedom (Section 5.7.3.1). In this case, the "risk" is the probability of not requiring rescue medication within 24 hours post-dose.

Rescue medications are tabulated by treatment group and overall.

Information regarding the rescue medication, including the type, date and time taken, dose, route and form of administration, and frequency, is presented in a listing by treatment group and subject.

5.7.4.4 Functional Disability Scale at 2 Hours

Impact of treatment on subject disability is assessed using a single-question, functional disability scale. Subjects rate the level of disability they perceive as a result of their migraine in performing normal actions using a 4-point scale: Normal Function, Mild Impairment, Severe Impairment, or Required Bedrest. The proportion of mITT subjects who have a response of "normal" at 2-hours post dose will be evaluated as the endpoint of interest.

The information from the 4-point scale will be directly summarized as follows:

- A table showing descriptive statistics for the 4-point scale, which includes the number and percentage of subjects reporting each of the 4 disability levels at 2 hours post-dose, and the percentage of subjects with missing data, for each treatment group, using the observed data. The table will include exact (Clopper-Pearson) 95% CIs for each percentage.

The results to be presented for the analysis include those described in items (a) through (e) for the primary analysis of pain freedom (Section 5.7.3.1). In this case, the "risk" is now the probability of a functional disability level of "normal" at 2 hours post-dose.

5.7.4.5 Sustained Pain Freedom from 2 to 24 Hours

Sustained pain freedom is assessed using the number of mITT subjects that experienced no headache pain (response of 0 on Likert scale) at all time points from 2 through 24 hours post-dose. Subjects with missing pain scores at 1 or fewer time points, given that they have responses of no pain (response of 0 on 4-point Likert scale) at all other time points including the 2 and 24 hour post-dose time points will be considered as successes. Subjects with responses missing at greater than 1 post-dose time point, missing data at the 2 or 24 hour time point, or with any pain score greater than 0 will be considered as failures.

The results to be presented for the analysis include those described in items (a) through (e) for the primary analysis of pain freedom (Section 5.7.3.1). In this case, the "risk" is the probability of sustained pain freedom from 2 to 24 hours.

5.7.4.6 Sustained Pain Freedom from 2 to 48 Hours

Sustained pain freedom is assessed using the number of mITT subjects that experienced no headache pain (response of 0 on Likert scale) at all time points from 2 through 48 hours post-dose. Subjects with missing pain scores at no more than 1 time point, given that they have responses of no pain (response of 0 on Likert scale) at the 2, 24, and 48 hour time points will be considered as successes. Subjects with responses missing at greater than 1 time point; missing data at the 2, 24, or 48 hour time point; or with any pain score greater than 0 will be considered as failures.

The results to be presented for the analysis include those described in items (a) through (e) for the primary analysis of pain freedom (Section 5.7.3.1). In this case, the "risk" is the probability of sustained pain freedom from 2 to 48 hours.

5.7.4.7 Sustained Pain Relief from 2 to 24 Hours

Sustained pain relief is assessed using the number of mITT subjects who experience no or mild headache pain (responses of either 0 or 1 on 4-point Likert scale) at all time points from 2 through 24 hours post-dose. Subjects with missing pain scores at no more than 1 time point, given that they have responses of no or mild pain at the 2 and 24 hour time points will be considered as successes. Subjects with responses missing at more than 1 time point, with missing data at the 2 or 24 hour time points, or with any pain score greater than 1 will be considered as failures.

The results to be presented for the analysis include those described in items (a) through (e) for the primary analysis of pain freedom (Section 5.7.3.1). In this case, the "risk" is the probability of sustained pain relief from 2 to 24 hours.

5.7.4.8 Sustained Pain Relief from 2 to 48 Hours

Sustained pain relief will be assessed using the number of subjects that experience no or mild headache pain (response of 0 or 1 on the 4-point Likert scale) at all time points from 2 through 48 hours post-dose. Subjects with missing pain scores at no more than 1 time point, given that they have responses of no or mild pain at all other time points including the 2, 24, and 48 hour time points will be considered as successes. Subjects with responses missing at more than 1 time point; with missing data at the 2, 24, or 48 hour time point; or with any pain score greater than 1 will be considered as failures.

The results to be presented for the analysis include those described in items (a) through (e) for the primary analysis of pain freedom (Section 5.7.3.1). In this case, the "risk" is the probability of sustained pain relief from 2 to 48 hours.

5.7.4.9 Pain Relapse from 2 to 48 Hours

Pain relapse is assessed using the number of mITT subjects that are pain free at 2 hours post-dose as the denominator. The numerator is the number of these subjects that then have a relapse of pain at any severity (response of 1, 2, or 3 on the 4-point Likert scale) within 48 hours after administration of study medication. Subjects with more than 1 time point with missing data or with missing data at the 2, 24, or 48 hour time point are classified as relapsers.

The results to be presented for the analysis include those described in items (a) through (e) for the primary analysis of pain freedom (Section 5.7.3.1). In this case, the "risk" is the probability of sustained pain relapse from 2 to 48 hours.

5.7.5 Durability Endpoints Evaluated by Meta-Analysis

The durability endpoints (e.g., pain freedom from 2 to 24 hours) will be analyzed in a meta-analysis that uses the data from both BHV3000-301 and BHV3000-302. These endpoints will be tested in a fix sequence, in the order shown below, with each test conducted at a two-sided alpha level of 0.05.

1. Sustained Pain Freedom from 2 to 24 hours
2. Sustained Pain Relief from 2 to 24 hours
3. Sustained Pain Freedom from 2 to 48 hours
4. Sustained Pain Relief from 2 to 48 hours
5. Pain Relapse from 2 to 48 hours

For the durability endpoints, the meta-analysis will mirror the primary analysis, with the addition of strata to represent each study. The common risk difference is computed using CMH weights, stratified by the use of prophylactic migraine medication (yes or no) and study (BHV3000-301 or BHV3000-302). For each endpoint, the risk difference is tested at a two-sided alpha level of 0.05. If a stratum (prophylactic medication use: yes or no) has sparse data (less than 5 subjects) then the strata will be pooled.

Results presented for each analysis include the following:

- The number and percentage of subjects who are successes or not successes on the endpoint of interest. These are presented by strata and treatment group, with ASE, and 95% asymptotic CIs.
- Common risk difference with sample size, p-value, ASE, and 95% asymptotic CIs.
- Risk difference within each strata with sample size, p-value, ASE, and 95% asymptotic CIs.
- A plot of the risk differences within each strata and common risk difference.
- Common risk for each treatment with sample size, ASE, and 95% asymptotic CIs.
- The common risk difference, with ASE, is also computed separately for each of the two studies.

5.7.6 Exploratory Efficacy Endpoints

Any p-values presented for exploratory efficacy endpoints are for descriptive purposes only.

5.7.6.1 Functional Disability Scale at 24 Hours

Data will be analyzed in the same manner as described in Section 5.7.4.4. However, in this case the analysis uses the data from the 24 hour post-dose time point.

5.7.6.2 Pain Relief at 30, 60 and 90 Minutes Post-Dose

Pain relief at 30, 60, and 90 minutes post-dose will be assessed by tabulating the number of mITT subjects that report a pain level of none or mild (responses of 0 or 1 on the 4-point Likert scale) at the specified post-dose time point by treatment group. Subjects with missing data at the specified post-dose time point will be imputed as failures (NC=F).

First, the data will be evaluated at each time point for each time point, using the first analysis methods described in Section 5.7.3.1.

Pain relief over time up to 2 hours will be analyzed using Kaplan-Meier methods. Kaplan-Meier estimates will be tabulated using the following time periods (0 through 30 minutes, > 30 through 60 minutes, > 60 through 90 minutes, > 90 through 135 minutes, and >135 minutes).

For each time period, the number of subjects at risk, with an event (pain relief), censored, and survival probability estimate (with 95% CI), will be presented by treatment group. Subjects who never reach mild or no pain by 135 minutes, will be censored at 136 minutes. Additionally, subjects who take rescue medication prior to 135 minutes will be censored at the date/time associated with their rescue medication. Note that the probability of survival corresponds to the probability of NOT having pain relief. Survival estimates are calculated using the Kaplan-Meier product-limit method and median survival (time to pain relief), and will be presented along with 95% CIs calculated using the method of Brookmeyer and Crowley.

To support the analysis, a Kaplan-Meier plot, with time in minutes on the x-axis and probability of survival on the y-axis, will be presented by treatment group. The number at risk at each time point (0, 15, 30, 45, 60, 90, and 135) minutes will be presented below the figure. In this analysis, being at risk corresponds to not yet having had pain relief; therefore, the subject is still "at risk" of having pain relief. Once a subject has pain relief or is censored, then the subject is no longer in the risk pool. If a subject has missing data at an earlier time point, then the time point with missing data is not considered. The subject is still considered at risk of failure at a future time point if data are available. Subjects are censored as described above.

5.7.6.3 Preference of Medication (PoM)

The PoM is a brief scale that captures the subjects' perception of whether the medication they are taking has had a greater benefit compared with previous medications to treat their pain. Responses at 24 hours post-dose for all subjects who provided a response, and answered "yes" to the lead-in question (i.e. "Have you ever taken migraine medication") will be tabulated. The number and percentage of subjects preferring the study medication, along with 95% asymptotic CIs, are presented by treatment group. The tabulations will be repeated for the subset of subjects considered as responders and non-responders by treatment group without imputation. Responders are those subjects who reported a pain score of 0 or 1 at 2 hours post-dose and who did not require rescue medication at or prior to 2 hours post-dose.

5.7.6.4 Migraine Quality of Life Questionnaire (MQoLQ)

Impact of treatment on patient-reported quality of life is assessed using the MQoLQ, which is a 15-item instrument that has been validated in migraine patients to measure the short-term impact of treatment (within 24 hours). The MQoLQ consists of 15 items across the following five domains: (1) work functioning, (2) social functioning, (3) energy/vitality, (4) migraine symptoms, and (5) feelings/concerns. There are three items within each domain. Response options for each of the items are on a 7-point scale where 1 indicates maximum impairment of QoL and 7 indicates no impairment. Each domain has a maximum score of 21 and a minimum score of 3. The items in the work functioning domain are: (1) ability to do normal everyday work, (2) ability to operate machinery or a motor vehicle, and (3) ability to stay alert. The items in the social functioning domain are: (1) interactions with people who are close to you, (2) interactions with other people, and (3) ability to enjoy life. The items in the energy/vitality domain are: (1) energy level, (2) ability to have a good night's sleep, and (3) mood. The items in the migraine symptoms domain are: (1) have throbbing head pain, (2) have increased sensitivity to light and/or noise, and (3) have nausea. Lastly, the items in the feelings/concerns domain are:

(1) feel upset about having migraine headaches, (2) feel physically uncomfortable, and (3) feel concern that your migraine medication wouldn't relieve your migraine headache symptoms.

The observed responses at 24 hours post-dose will be presented for each item, each domain, and as a total score, by treatment group. The observed responses at 24 hours will also be summarized as a continuous response for each item, domain, and for the total score. Responses will also be presented in a by-subject listing along with treatment group, historical MBS collected at screening, MBS reported at migraine onset, migraine severity just prior to study medication, and migraine severity at 24 hours post-dose.

5.7.6.5 Additional Tabulations

Pain freedom, pain relief, freedom from MBS, and functional disability score will be tabulated by treatment group at each post-dose time point. Success for each of these endpoints will be tabulated using the mITT subjects.

Freedom from nausea, freedom from phonophobia, freedom from photophobia, and functional disability scale response will be tabulated by treatment group at each post-dose time point. The tabulation will include: the total number of subjects reporting each of the above symptoms at baseline, success as the percentage of the total number of subjects reporting the symptoms at baseline, and the number of subjects that reported the symptom but with missing data at the post-dose time point as a percentage of the number reporting the symptom at baseline.

5.7.6.6 Sheehan-Suicidality Tracking Scale (S-STS)

The S-STS is a prospective, self-reported rating scale that contains 16 questions to track both treatment-emergent suicidal ideation and behaviors. In the event the subject is unavailable, the S-STS clinician-administered rating scale will be completed that contains 6 yes/no questions.

Self-reported S-STS scores are calculated as follows:

- Ideation subscale score: Sum of scores (0 – 4) for Questions 2 – 11
- Behavior subscale score: Sum of scores (0 – 4) for Questions 1a, (highest of 12 or any row of 16), (highest of 14 or any row of 15), 17, and 20
- Total score: Sum of the ideation and behavior subscale scores

The self-reported S-STS ideation subscale, behavior subscale, and total score will be summarized at baseline and the change from baseline (i.e., <-1, -1, no change, 1, >1) will be summarized at the end of treatment visit.

5.7.6.7 Pain Freedom to 8 Hours Post-Dose

Pain freedom over time up to 8 hours will be analyzed using Kaplan-Meier methods. Kaplan-Meier estimates will be tabulated using the following time periods (0 through 30 minutes, > 30 through 60 minutes, > 60 through 90 minutes, > 90 through 120 minutes, >120 minutes through 180 minutes, >180 minutes though 240 minutes, >240 minutes though 360 minutes, >360 minutes though 495 minutes, and > 495 minutes). For each time period, the number of subjects at risk, with an event (pain freedom), censored, and survival probability estimate (with 95% CI), will be presented by treatment group. Subjects who fail to reach no pain by 495 minutes, will be censored at 495 minutes. Additionally, subjects who take rescue medication prior to 495 minutes will be censored at the date/time associated with their rescue medication. Note that the probability of survival corresponds to the probability of NOT having pain freedom. Survival estimates are calculated using the Kaplan-Meier product-limit method and median survival (time to pain freedom), and will be presented along with 95% CIs calculated using the method of Brookmeyer and Crowley.

To support the analysis, a Kaplan-Meier plot, with time in minutes on the x-axis and probability of survival on the y-axis, will be presented by treatment group. The number at risk at each time point (0, 15, 30, 45, 60, 90, 120, 180, 240, 360, and 495) minutes will be presented below the figure. In this analysis, being at risk corresponds to not yet having achieved pain freedom; therefore, the subject is still “at risk” of having pain freedom. Once a subject has pain freedom or is censored, then the subject is no longer in the risk pool. If a subject has missing data at an earlier time point, then the time point with missing data is not considered. The subject is still considered at risk of failure at a future time point if data are available. Subjects are censored as described above.

5.8 Pharmacokinetic Evaluations

No pharmacokinetic data were collected in this study.

6 SAFETY ANALYSIS

Safety analyses will be conducted on the treated population. All safety and other data will be listed. Subjects who were re-randomized will be considered as two individual subjects for the safety analyses. If such a subject is treated at least once with rimegepant, then their as-treated group assignment is rimegepant for all treatment occasions.

Safety outcome measures include: adverse events, laboratory assessments including liver toxicity, physical examinations, vital signs, physical measurements, ECGs, and concomitant medications.

Unless otherwise noted, baseline is considered as last assessment prior to study drug randomization.

6.1 Extent of Exposure

Extent of exposure is measured by subjects providing self-repored drug exposure information in their eDiaries. As a check on this exposure data, drug accountability data are provided by the study center on the "Drug Accountabilty" CRF page.

The self-reported exposure data will be tabulated by treatment group, and will include:

- The number (and percentage) of randomized subjects that took study medication
    - The number and percentage who took the medication prior to providing baseline study migraine migraine characteristics
    - The number and percentage that took study medication after providing baseline study migraine characteristics
- The number and percentage of randomized subjects who reported not taking study medication
- The number and percentage of randomized subjects for whom no expossure data was reported

The drug accountability will be tabulated by treatment and overall, and will include:

- The number and percentage of randomized subjects to whom kits were dispensed
- The number and percentage of kits returned
    - The number and percentage of kits returned from which the IP was used
    - The number and percentage of kits returned from which the IP was not used
- The number and percentage of kits not returned

A cross tabulation of exposure and accountability data will be prepared. This will be done overall. For the exposure data the categories are: Took IP, Did not Take IP, and Unknown. For the accountability data, the categories will be: IP Used, IP not Used, and Unknown.

A listing will be prepared that indicates the exposure and accountabilty status of all randomized subjects. A patient identifier (PID) lisiting will be prepared if subjects had unknown exposure data, unknown accountability data, or for whom the exposure and accountability data did not match.

6.2 Adverse Events

Adverse events (AEs) will be coded using MedDRA and displayed in tables and listings by system organ class (SOC) and preferred term (PT).

Analyses of AEs will be performed for those events that are considered on-study AEs with a start date prior to 30 days after the last dose of study medication. On-study is defined as any AE that developed, worsened, or became serious after study randomization.

Adverse events are summarized by subject incidence rates; therefore, in any tabulation, a subject contributes only once to the count for a given AE (SOC or PT).

The number and percentage of subjects with any on-study AE, with any on-study AE related to treatment (definite, probable, or possible relationship), with any on-study SAE, with any on-study severe AE, and with any on-study AE leading to discontinuation will be summarized by treatment group and overall. In these tabulations, each subject will contribute only once (i.e., the most related occurrence or the most intense occurrence) to each of the incidence rates in the descriptive analysis, regardless of the number of episodes.

No formal hypothesis-testing of AE incidence rates will be performed.

All AEs occurring pre-randomization and on-study will be listed. Additional listings will be provided including: deaths; SAEs; and AEs leading to discontinuation.

6.3 Laboratory Data

Clinical laboratory evaluations include:

- Hematology: hemoglobin, hematocrit, red blood cell count, white blood cell count with differential, and platelets
- Serum Chemistry: sodium, potassium, chloride, bicarbonate, calcium, glucose, BUN (urea), serum creatinine, uric acid, ALT, AST, alkaline phosphatase, LDH, total protein, albumin, total bilirubin, direct bilirubin, indirect bilirubin, CPK (with fractionation, if available)
- Lipid Panel: Cholesterol, LDL, HDL, triglycerides (screening only)
- Estimated glomerular filtration rate (eGFR) using the estimated MDRD formula will be calculated and reported by the central lab at each visit that the clinical laboratory test is collected.
- Urinalysis: pH, specific gravity, protein, ketones, nitrites, urobilinogen, leukocyte esterase, protein, glucose, microalbuminuria, and blood. If blood, protein, or leukocytes are positive, reflex to microscopic examination.
- Urine drug screen: for drugs of abuse

Clinical laboratory values will be expressed using both Standard US units and SI units. Tabulations, listings, and graphics will be provided to show the data in both systems. The observed value and change from baseline will be summarized for select continuous laboratory parameters. In addition, shift tables (low, normal, high) will be presented. For AST and ALT, the shift tables will use the categories: Normal, >ULN, >3x ULN, and >5x ULN. In the event of repeat values from the same visit, the non-missing value closest to the target date for the visit will be used. In the case of a tie, the latest record will be used.

All laboratory data will be provided in data listings. Additional listings will be presented for all abnormal laboratory values.

On-study laboratory abnormalities are those with an assessment date after the date/time of first dose of study drug and within 30 days after the last dose of study drug.

6.3.1 Liver Toxicity Evaluation

Potential drug induced liver injury are those events meeting Hy's Law, defined as:

1. Aminotransferases (AT) ALT or AST elevation > 3 times the upper limit of normal (ULN);

2. Total bilirubin (TBL) > 2 times ULN, without initial findings of cholestasis (elevated serum alkaline phosphatase); and

3. No other immediately apparent possible causes of AT elevation and hyperbilirubinemia, included but not limited to: viral hepatitis, pre-existing chronic or acute liver disease, or the administration of other drug(s) known to be hepatotoxic.

Any potential drug-induced liver injuries (DILIs), meeting the above defined criteria, will be reported as SAEs and tabulated by treatment group. A listing will be prepared that shows the AT and TBL values for all subjects that experience either AT > 3 times the upper limit of normal or TBL > 2 times the upper limit of normal at any time during the study.

Additionally, a table will be created that summarizes the incidence (as the number of subjects experiencing the given measurement post-randomization) of the following:

- >3x, >5x, >10x, and >20x ULN elevations of AST, ALT, and either ALT or AST

- Any elevations of bilirubin >1x ULN and >2x ULN

- Any elevations of ALP > 1.5x ULN

- Elevation of AST or ALT (>3x ULN) accompanied by elevated bilirubin (>1.5x ULN and >2x ULN)

- Elevation of AST or ALT along with an on-study AE of nausea, vomiting, anorexia, abdominal pain, or fatigue

An evaluation of Drug-Induced Serious Hepatotoxicity (eDISH) plot will be created by plotting the maximum total bilirubin against maximum ALT and presenting these data points by treatment group. The maximum values for each subject during the study will be identified as the maximum values that occur post-baseline, but not necessarily concurrently. Maximum total bilirubin (presented as xULN) will be plotted on a log scale on the y-axis and maximum ALT (presented as xULN) will be plotted on a log scale on the x-axis. A horizontal reference line will be placed at 2x ULN for maximum total bilirubin and a vertical reference line will be placed at 3x ULN for maximum ALT. The lower left quadrant will be labeled "Normal Range". The upper left quadrant will be labeled "Hyperbilirubinemia". The lower right quadrant will be labeled "Temple's Corollary". The upper right quadrant will be labeled "Possible Hy's Law Range".

6.4 Physical Examinations

For each body system, the shift from screening will be summarized as the number and percentage of subjects with each result (normal, abnormal, or physical examination not done) at the end of treatment visit.

6.4.1 Vital Signs and Physical Measurements

The observed value and change from baseline in vital signs will be summarized at baseline and end of treatment.

6.4.2 Electrocardiogram

The shift from baseline in ECG parameters will be summarized as the number and percentage of subjects with normal, abnormal, and clinically significant abnormal results at the screening and end of treatment visits. Descriptive statistics for ECG interval data (e.g., RR, QRS, PR, QT, QTcF), and ventricular heart rate will also be reported for the screening and end of treatment visits.

6.5 Concomitant Medications

Concomitant medications will be coded using the WHO-DD. Results will be tabulated by Anatomic Therapeutic Class (ATC) and PT.

7 CHANGES TO PLANNED ANALYSES IN THE PROTOCOL

Supportive analyses were conducted in addition to the planned analyses specified in the protocol. All additional analyses are described in Appendix 3 and corresponding tables and figures are listed in Appendix 4 of this document.

Appendix 1. Tables, Listings, And Figures

14.1.1	Subject Disposition	All Subjects	Y
14.1.2.1	Demographic and Baseline Characteristics	mITT Subjects	Y
14.1.2.2	Demographic and Baseline Characteristics	Subjects Enrolled but Not Randomized	
14.1.2.3	Demographic and Baseline Characteristics	Subjects Randomized but Not Treated	
14.1.2.4	Demographic and Baseline Characteristics	Treated Subjects	
14.1.3	Medical History	Treated Subjects	
14.1.4.1	Migraine Disease History	mITT Subjects	Y
14.1.4.2	Migraine Disease History	Subjects Enrolled but Not Randomized	
14.1.4.3	Migraine Disease History	Subjects Randomized but Not Treated	
14.1.5	Cardiac and Other Risk Factors	Treated Subjects	
14.1.6	Prior Triptan Response	mITT Subjects	
14.1.7	Current Triptan Response	mITT Subjects	
14.1.8	Subgroup Summary	mITT Subjects	Y
14.1.9.1	Missing Data Summary	Randomized Subjects	
14.1.9.2	Missing Pain Data Summary by Subgroup	mITT Subjects	
14.2.1	Pain Freedom at 2 Hours Post Dose: Observed Data	mITT Subjects	
14.2.1.1	Pain Freedom at 2 Hours Post Dose: Asian Subjects Only	mITT Subjects	
14.2.1.2	Pain Freedom at 2 Hours Post Dose: Primary Analysis	mITT Subjects	Y
14.2.1.2.1	Pain Freedom at 2 Hours Post Dose: Subgroup Analysis by Age	mITT Subjects	
14.2.1.2.2	Pain Freedom at 2 Hours Post Dose: Subgroup Analysis by Race	mITT Subjects	
14.2.1.2.3	Pain Freedom at 2 Hours Post Dose: Subgroup Analysis by Sex	mITT Subjects	
14.2.1.2.4	Pain Freedom at 2 Hours Post Dose: Subgroup Analysis by Aura	mITT Subjects	
14.2.1.2.5	Pain Freedom at 2 Hours Post Dose: Subgroup Analysis by Headaches per Month	mITT Subjects	
14.2.1.2.6	Pain Freedom at 2 Hours Post Dose: Subgroup Analysis by Prior Triptan Response	mITT Subjects	
14.2.1.2.7	Pain Freedom at 2 Hours Post Dose: Subgroup Analysis by Cardiovascular Risk	mITT Subjects	
14.2.1.3.1	Pain Freedom at 2 Hours Post Dose: Sensitivity Analysis 1	mITT Subjects	
14.2.1.3.2	Pain Freedom at 2 Hours Post Dose: Sensitivity Analysis 2	mITT Subjects	
14.2.1.3.3	Pain Freedom at 2 Hours Post Dose: Sensitivity Analysis 3	mITT Subjects	
14.2.1.3.4	Pain Freedom at 2 Hours Post Dose: Sensitivity Analysis 4	mITT Subjects	
14.2.1.3.5	Pain Freedom at 2 Hours Post Dose: Sensitivity Analysis 5	mITT Subjects	
14.2.2	Most Bothersome Symptom at Migraine Onset: Observed Data	mITT Subjects	
14.2.2.1	Historically Most Bothersome Symptom versus Most Bothersome Symptom at Migraine Onset	mITT Subjects	

Table Number	Title	Population	Topline
14.2.2.2	Freedom from Most Bothersome Symptom at 2 Hours Post Dose: Primary Analysis	mITT Subjects	Y
14.2.2.2.1	Freedom from Most Bothersome Symptom at 2 Hours Post Dose: Subgroup Analysis by Age	mITT Subjects	
14.2.2.2.2	Freedom from Most Bothersome Symptom at 2 Hours Post Dose: Subgroup Analysis by Race	mITT Subjects	
14.2.2.2.3	Freedom from Most Bothersome Symptom at 2 Hours Post Dose: Subgroup Analysis by Sex	mITT Subjects	
14.2.2.2.4	Freedom from Most Bothersome Symptom at 2 Hours Post Dose: Subgroup Analysis by Aura	mITT Subjects	
14.2.2.2.5	Freedom from Most Bothersome Symptom at 2 Hours Post Dose: Subgroup Analysis by Headaches per Month	mITT Subjects	
14.2.2.2.6	Freedom from Most Bothersome Symptom at 2 Hours Post Dose: Subgroup Analysis by Prior Triptan Response	mITT Subjects	
14.2.2.2.7	Freedom from Most Bothersome Symptom at 2 Hours Post Dose: Subgroup Analysis by Cardiovascular Risk	mITT Subjects	
14.2.2.3.1	Freedom from Most Bothersome Symptom at 2 Hours Post Dose: Sensitivity Analysis 1	mITT Subjects	
14.2.2.3.2	Freedom from Most Bothersome Symptom at 2 Hours Post Dose: Sensitivity Analysis 2	mITT Subjects	
14.2.2.3.3	Freedom from Most Bothersome Symptom at 2 Hours Post Dose: Sensitivity Analysis 3	mITT Subjects	
14.2.2.3.4	Freedom from Most Bothersome Symptom at 2 Hours Post Dose: Sensitivity Analysis 4	mITT Subjects	
14.2.2.3.5	Freedom from Most Bothersome Symptom at 2 Hours Post Dose: Sensitivity Analysis 5	mITT Subjects	
14.2.2.3.6	Freedom from Most Bothersome Symptom at 2 Hours Post Dose: Sensitivity Analysis 6	mITT Subjects	
14.2.3.1	Most Bothersome Symptom Score at 2 Hours Post Dose: Observed Data	mITT Subjects	
14.2.3.1.1	Freedom from Photophobia at 2 Hours Post Dose in Subjects who Reported Photophobia at Study Migraine Onset: Observed Data	mITT Subjects	
14.2.3.1.2	Freedom from Photophobia at 2 Hours Post Dose in Subjects who Reported Photophobia at Study Migraine Onset: Secondary Analysis	mITT Subjects	Y
14.2.3.2.1	Freedom from Phonophobia at 2 Hours Post Dose in Subjects who Reported Phonophobia at Study Migraine Onset: Observed Data	mITT Subjects	

Table Number	Title	Population	Topline
14.2.3.2.2	Freedom from Phonophobia at 2 Hours Post Dose in Subjects who Reported Phonophobia at Study Migraine Onset: Secondary Analysis	mITT Subjects	Y
14.2.3.3.1	Pain Relief at 2 Hours Post Dose: Observed Data	mITT Subjects	
14.2.3.3.2	Pain Relief at 2 Hours Post Dose: Secondary Analysis	mITT Subjects	Y
14.2.3.4.1	Freedom from Nausea at 2 Hours Post Dose in Subjects who Reported Nausea at Study Migraine Onset: Observed Data	mITT Subjects	
14.2.3.4.2	Freedom from Nausea at 2 Hours Post Dose in Subjects who Reported Nausea at Study Migraine Onset: Secondary Analysis	mITT Subjects	Y
14.2.3.5	Rescue Medication within 24 Hours Post Dose: Secondary Analysis	mITT Subjects	
14.2.3.6.1	Functional Disability Scale at 2 Hours Post Dose: Observed Data	mITT Subjects	
14.2.3.6.2	Functional Disability Scale at 2 Hours Post Dose: Secondary Analysis	mITT Subjects	
14.2.3.7.1	Sustained Pain Freedom from 2 to 24 Hours Post Dose: Secondary Analysis	mITT Subjects	
14.2.3.7.2	Sustained Pain Relief from 2 to 24 Hours Post Dose: Secondary Analysis	mITT Subjects	
14.2.3.7.3	Sustained Pain Freedom from 2 to 48 Hours Post Dose: Secondary Analysis	mITT Subjects	
14.2.3.7.4	Sustained Pain Relief from 2 to 48 Hours Post Dose: Secondary Analysis	mITT Subjects	
14.2.3.7.5	Pain Relapse from 2 to 48 Hours Post Dose: Secondary Analysis	mITT Subjects	
14.2.3.8.1	Functional Disability Scale at 24 Hours Post Dose: Exploratory Analysis	mITT Subjects	
14.2.3.8.2	Pain Relief at 30, 60, and 90 Minutes Post Dose: Exploratory Analysis	mITT Subjects	
14.2.3.8.3	Kaplan-Meier Time to Pain Relief: Exploratory Analysis	mITT Subjects	Y
14.2.3.8.4	Median Time to Pain Relief	mITT Subjects	Y
14.2.3.8.5	Preference of Medication at 24 Hours Post Dose: Exploratory Analysis	mITT Subjects	
14.2.3.8.6.1	Migraine Quality of Life Questionnaire at 24 Hours Post Dose: Continuous Exploratory Analysis	mITT Subjects	
14.2.3.8.6.2	Migraine Quality of Life Questionnaire at 24 Hours Post Dose: Frequency Exploratory Analysis	mITT Subjects	
14.2.3.8.7	Pain Freedom at Every Timepoint Post Dose: Exploratory Analysis	mITT Subjects	
14.2.3.8.8	Pain Relief at Every Timepoint Post Dose: Exploratory Analysis	mITT Subjects	
14.2.3.8.9	Freedom from Most Bothersome Symptom at Every Timepoint Post Dose: Exploratory Analysis	mITT Subjects	

Table Number	Title	Population	Topline
14.2.3.8.9.1	Freedom from Photophobia at Every Timepoint Post Dose: Exploratory Analysis	mITT Subjects	
14.2.3.8.9.2	Freedom from Phonophobia at Every Timepoint Post Dose: Exploratory Analysis	mITT Subjects	
14.2.3.8.9.3	Freedom from Nausea at Every Timepoint Post Dose: Exploratory Analysis	mITT Subjects	
14.2.3.8.10	Functional Disability Scale at Every Timepoint Post Dose: Exploratory Analysis	mITT Subjects	
14.2.3.8.11	Sheehan-Suicidality Tracking Scale: Exploratory Analysis	mITT Subjects	
14.2.3.9.1	Kaplan-Meier Time to Pain Freedom: Exploratory Analysis	mITT Subjects	Y
14.2.3.9.2	Median Time to Pain Freedom	mITT Subjects	Y
14.3.1.1	Self-Reported Exposure Data Summary	All Randomized Subjects	
14.3.1.2	Drug Accountability Data Summary	All Randomized Subjects	
14.3.1.3	Cross Tabulation of Exposure and Accountability Data	All Randomized Subjects	
14.3.2.1	Summary of On-Study Adverse Events	Treated Subjects	Y
14.3.2.2	Incidence of On-study Adverse Events by System Organ Class and Preferred Term	Treated Subjects	Y
14.3.2.3	Incidence of On-study Adverse Events Related to Study Drug by System Organ Class and Preferred Term	Treated Subjects	
14.3.2.4	Incidence of On-study Serious Adverse Events by System Organ Class and Preferred Term	Treated Subjects	Y
14.3.2.5	Incidence of On-study Adverse Events with Severe Grade by System Organ Class and Preferred Term	Treated Subjects	
14.4.1.1	Hematology (SI Units): Observed and Change From Baseline Values by Visit	Treated Subjects	
14.4.1.2	Hematology (UI Units): Observed and Change From Baseline Values by Visit	Treated Subjects	
14.4.2.1	Serum Chemistry (SI Units): Observed and Change From Baseline Values by Visit	Treated Subjects	
14.4.2.2	Serum Chemistry (US Units): Observed and Change From Baseline Values by Visit	Treated Subjects	
14.4.3.1	Hematology (SI Units): Shift from Baseline by Visit	Treated Subjects	Y
14.4.3.2	Hematology (US Units): Shift from Baseline by Visit	Treated Subjects	Y
14.4.4.1	Serum Chemistry (SI Units): Shift from Baseline by Visit	Treated Subjects	Y
14.4.4.2.	Serum Chemistry (US Units): Shift from Baseline by Visit	Treated Subjects	Y
14.4.5.1	Urinalysis (SI Units): Shift from Baseline by Visit	Treated Subjects	
14.4.5.2	Urinalysis (SI Units): Shift from Baseline by Visit	Treated Subjects	

Table Number	Title	Population	Topline
14.4.6.1	Transaminases (SI Units): Shift from Baseline by Visit	Treated Subjects	Y
14.4.6.2	Transaminases (SI Units): Shift from Baseline by Visit	Treated Subjects	Y
14.4.7	Summary of On-Study Liver Toxicity	Treated Subjects	Y
14.5.1	Vital Signs and Physical Measurements: Observed and Change from Baseline Values by Visit	Treated Subjects	
14.5.2.1	Electrocardiogram: Observed and Change from Baseline Values by Visit	Treated Subjects	
14.5.2.2	Electrocardiogram: Shift from Baseline by Visit	Treated Subjects	
14.5.3.1	Concomitant Medications by Therapeutic Class and Preferred Term	Treated Subjects	
14.5.3.2	Rescue Medications by Therapeutic Class and Preferred Term	Treated Subjects	

Listing Number	Title	Population	Topline
16.2.1	Subject Disposition	All Subjects	
16.2.2	Subject Eligibility	All Subjects	
16.2.3	Protocol Deviations	All Subjects	
16.2.4.1	Demographic and Baseline Characteristics	All Subjects	
16.2.4.2	Significant Medical History	All Subjects	
16.2.4.3	General Migrain Disease History	All Subjects	
16.2.4.3.1	Migraine Symptom History	All Subjects	
16.2.4.3.1	Migraine Aura Symptom History	All Subjects	
16.2.5	Batch Numbers	All Subjects	
16.2.6	Subpopulations and Subgroups	All Subjects	
16.2.7.1	Observed Pain and MBS Efficacy Measurements	mITT Subjects	
16.2.7.2	Observed Primary Efficacy Measurements at 2 Hours Post Dose	mITT Subjects	
16.2.7.3	Fucntional Disability Scale	mITT Subjects	
16.2.7.4	Preference of Medication at 24 Hours Post Dose	mITT Subjects	
16.2.7.5	Migraine Quality of Life Questionnaire at 24 Hours Post Dose	mITT Subjects	
16.2.8	Exposure and Accountability Data	mITT Subjects	
16.2.9.1	Pre-Randomization Adverse Events	All Subjects	
16.2.9.2	On-Study Advserse Events	All Subjects	
16.2.9.3	Serious On-Study Adverse Events	All Subjects	
16.2.9.4	Deaths	All Subjects	
16.2.10.1.1	Hematology Results (SI Units)	All Subjects	
16.2.10.1.2	Hematology Results (US Units)	All Subjects	
16.2.10.2.1	Serum Chemistry Results (SI Units)	All Subjects	
16.2.10.2.2	Serum Chemistry Results (US Units)	All Subjects	

Listing Number	Title	Population	Topline
16.2.10.3.1	Urinalysis Results (SI Units)	All Subjects	
16.2.10.3.2	Urinalysis Results (US Units)	All Subjects	
16.2.10.4.1	Endocrine Results (SI Units)	All Subjects	
16.2.10.4.2	Endocrine Results (US Units)	All Subjects	
16.2.10.5.1	Pregnancy Results (SI Units)	All Subjects	
16.2.10.5.2	Pregnancy Results (US Units)	All Subjects	
16.2.10.6	GC/MS Results	All Subjects	
16.2.10.7.1	All Abnormal Laboratory Results (SI Units)	All Subjects	
16.2.10.7.2	All Abnormal Laboratory Results (US Units)	All Subjects	
16.2.10.8.1	Potential Drug Induced Liver Injury (SI Units)	All Subjects	Y
16.2.10.8.2	Potential Drug Induced Liver Injury (US Units)	All Subjects	Y
16.2.11.1	Vital Signs and Physical Measurements	All Subjects	
16.2.11.2	Electocardiogram Results	All Subjects	
16.2.11.3.1	Comcomitant Medications	All Subjects	
16.2.11.3.2	Prophylactic Migraine Medications	All Subjects	
16.2.11.3.3	Rescue Medications	All Subjects	
16.2.11.4.1	Prior Triptan Response	All Subjects	
16.2.11.4.2	Current Triptan Response	All Subjects	
16.2.11.5	Procedures	All Subjects	
16.2.11.6	Sheehan-Suicidality Tracking Scale Results	All Subjects	
16.2.11.7	Cardiac and all Other Risk Factors	All Subjects	

Figure Number	Title	Population	Topline
14.2.1	Forest Plot of Pain Freedom at 2 Hours Post Dose	mITT Subjects	
14.2.1.1	Forest Plot of Pain Freedom at 2 Hours Post Dose: Sensitivity Analysis 1	mITT Subjects	
14.2.1.2	Forest Plot of Pain Freedom at 2 Hours Post Dose: Sensitivity Analysis 2	mITT Subjects	
14.2.1.3	Forest Plot of Pain Freedom at 2 Hours Post Dose: Sensitivity Analysis 3	mITT Subjects	
14.2.1.4	Forest Plot of Pain Freedom at 2 Hours Post Dose: Sensitivity Analysis 4	mITT Subjects	
14.2.1.5	Forest Plot of Pain Freedom at 2 Hours Post Dose: Sensitivity Analysis 5	mITT Subjects	
14.2.1.6	Forest Plot of Pain Freedom at 2 Hours Post Dose by Subgroup	mITT Subjects	

Figure Number	Title	Population	Topline
14.2.2	Forest Plot of Freedom from Most Bothersome Symptom at 2 Hours Post Dose	mITT Subjects	
14.2.2.1	Forest Plot of Freedom from Most Bothersome Symptom at 2 Hours Post Dose: Sensitivity Analysis 1	mITT Subjects	
14.2.2.2	Forest Plot of Freedom from Most Bothersome Symptom at 2 Hours Post Dose: Sensitivity Analysis 2	mITT Subjects	
14.2.2.3	Forest Plot of Freedom from Most Bothersome Symptom at 2 Hours Post Dose: Sensitivity Analysis 3	mITT Subjects	
14.2.2.4	Forest Plot of Freedom from Most Bothersome Symptom at 2 Hours Post Dose: Sensitivity Analysis 4	mITT Subjects	
14.2.2.5	Forest Plot of Freedom from Most Bothersome Symptom at 2 Hours Post Dose: Sensitivity Analysis 5	mITT Subjects	
14.2.2.6	Forest Plot of Freedom from Most Bothersome Symptom at 2 Hours Post Dose: Sensitivity Analysis 6	mITT Subjects	
14.2.2.7	Forest Plot of Freedom from Most Bothersome Symptom at 2 Hours Post Dose by Subgroup	mITT Subjects	
14.2.3	Forest Plot of Freedom from Photophobia, Phonophobia, and Nausea at 2 Hours Post Dose	mITT Subjects	
14.2.4	Forest Plot of Pain Relief at 2 Hours Post Dose	mITT Subjects	
14.2.5	Forest Plost of Probability of Requiring Rescue Medication within 24 Hour Post Dose	mITT Subjects	
14.2.6	Forest Plot of Probability of Functioning Normally According to the Functional Disability Scale at 2 Hour Post Dose	mITT Subjects	
14.2.7	Forest Plot of Durability of Pain Relief or Pain Freedom	mITT Subjects	
14.2.8	Forest Plot of Probability of Pain Relapse	mITT Subjects	
14.2.9	Forest Plot of Probability of Functioning Normally According to the Functional Disability Scale at 24 Hour Post Dose	mITT Subjects	
14.2.10	Forest Plot of Pain Relief at 30, 60, and 90 Minutes Post Dose	mITT Subjects	
14.2.11	Kaplan-Meier Plot of Time to Pain Relief to Two Hours Post Dose	mITT Subjects	Y
14.2.12	Kaplan-Meier Plot of Time to Pain Freedom to Eight Hours Post Dose	mITT Subjects	Y
14.3.1	Evaluation of Drug-Induced Hepatotoxicity (eDISH)	Treated Subjects	Y

Appendix 2. Schedule Of Assessments

Procedure	Screening Visit (3-28 days)[1]	Baseline Visit (Randomization)[1]	Onset of moderate or severe migraine[2]	During Treatment 15, 30, 45, 60 and 90 minutes Post-Dose	During Treatment 2, 3, 4, 6, 8 hours Post- Dose	During Treatment 24 hours Post-Dose	During Treatment 48 hours Post- Dose	End of Treatment Visit
Eligibility Assessments								
Informed Consent	X							
Inclusion/Exclusion Criteria	X	X						
Medical History	X							
Prophylactic Migraine Medication/ Concomitant Medication[3]	X	X						X
Assessment of Migraine History (Signs and symptoms) paper source[14]	X							
Safety Assessments								
Physical Examination	X							X
Vital Signs/Physical Measurements[4]	X	X						X
Clinical Safety Laboratory Testing[5]	X							X

Procedure	Screening Visit (3-28 days)[1]	Baseline Visit (Randomization)[1]	Onset of moderate or severe migraine[2]	During Treatment 15, 30, 45, 60 and 90 minutes Post-Dose	During Treatment 2, 3, 4, 6, 8 hours Post- Dose	During Treatment 24 hours Post-Dose	During Treatment 48 hours Post- Dose	End of Treatment Visit
ECG	X							X
Pregnancy Test[6]	X	X	X					X
Adverse Event and Serious Adverse Event Assessment[7]	X	X	X	X	X	X	X	X
Sheehan Suicidality Tracking Scale[8]	X	X						X
Clinical Drug Supplies/Study Supplies								
Randomize[9]		X						
Dispense Study Medication		X						
Administer 1 dose of study medication[10]			X					
Return unused study medication								X
eDiary returned/reviewed for completeness[11]								X
Efficacy Assessments[12]								
Assessment of migraine pain[13]			X	X	X	X	X	

Procedure	Screening Visit (3-28 days)[1]	Baseline Visit (Randomization)[1]	Onset of moderate or severe migraine[2]	During Treatment 15, 30, 45, 60 and 90 minutes Post-Dose	During Treatment 2, 3, 4, 6, 8 hours Post- Dose	During Treatment 24 hours Post-Dose	During Treatment 48 hours Post- Dose	End of Treatment Visit
Assessment of Migraine Symptoms (photophobia, phonophobia, and nausea - eDiary)[13]			X	X	X	X	X	
Functional Disability Scale[13]			X	X	X	X	X	
MQoLQ (Migraine Specified Quality of Life Questionnaire)[13]						X		
Preference of Medication[13]						X		

[1] **Screening/Baseline Phase** will be 3 - 28 days. The **Baseline Visit** may be scheduled but should only occur *after* all screening procedures are complete, patient meets inclusion/exclusion criteria, and lab test results have been received by the site.

[2] Patients will use eDiary to answer questions about their migraine symptoms upon experiencing a moderate/severe migraine headache. The patient will administer pre-dispensed study drug if 1) the headache remains moderate or severe; 2) the patient has completed all required migraine assessment questions in the eDiary, including their current most bothersome migraine symptom, and 3) the patient has not already taken prohibited medications (see protocol section 5.4).

[3] Patients should keep track of their concomitant medications throughout the study and report them to the study personnel at the End of Treatment Visit. Any medication taken for recurrent headache should be documented. Use of concomitant medications after randomization, including rescue medications, will be recorded by the patient on a paper diary and reported to the site.

[4] Height will only be captured at the Screening Visit. Weight body temperature, respiratory rate, blood pressure and heart rate will be collected at all time points where indicated. Sitting arterial systolic and diastolic blood pressure and pulse rate will be measured.

[5] All Screening Visit laboratory test results must be received prior to Baseline Visit.

[6] A serum pregnancy test will be completed at Screening and End of Treatment Visits as part of the standard laboratory tests (if appropriate). Confirmatory urine pregnancy test for WOCBP should be completed on site at Baseline Visit and any subsequent visits for confirmation at the Investigator's discretion. Home pregnancy test will be provided to WOCBP after completion of baseline visit.

[7] SAEs are reported from the time of informed consent and non-serious AEs are reported from baseline. All ongoing non-serious AEs and SAEs will be followed to resolution or until investigator deems there will be no further status change. SAE and AE's that occur during the treatment period should be reported to the site.

[8] This scale will be clinician administered, completed on site, and will be in paper. The source document will be provided by Biohaven. The assessment period for completing the scale will be 30 days prior to Screening, and since the last visit for the remainder of the study.

[9] Patients will be randomized in the IWRS system at the Baseline Visit (Randomization Day 01)

[10] Patient should be instructed that the dose should be taken once the migraine attack reaches moderate or severe pain.

[11] Site staff to review and confirm entries with patients and confirm all data points are transferred to the system and reset eDiary for future patient use, PRIOR to the patient leaving the clinic.

[12] ± Windows for timeframe around efficacy assessments (15, 30, 45, 60, 90 min, 2, 3, 4, 6, 8, 24 and 48 hours) will be automated and captured in the eDiary.

[13] These scales will be captured in the eDiary. Patients will also be asked about their most bothersome symptom at the time of reporting and treating a qualifying migraine.

[14] Paper source document will be used to capture Migraine History. Patients will also be asked about their typical most bothersome symptom when having a migraine.

Appendix 3. Supportive Analyses

1 DURABILITY ENDPOINTS

New durability endpoints were defined for pain freedom, pain relief, most bothersome symptom, functional disability, nausea, photophobia, and phonophobia. For each of these endpoints, durability was measured during six time periods:

- 2 to 24 hours
- 3 to 24 hours
- 4 to 24 hours
- 2 to 48 hours
- 3 to 48 hours
- 4 to 48 hours

For pain freedom and pain relief, the 2 to 24 hour and 2 to 48 hour durability endpoints were previously defined in the SAP in Sections 5.7.4.5 – 5.7.4.8.

Pain freedom, pain relief, most bothersome symptom, and functional disability were assessed using the mITT population. Nausea, photophobia, and phonophobia were assessed using mITT subjects who reported the given symptom as present at the start of their treated migraine.

For all ad-hoc durability endpoints, the following were presented:

- The number and percentage of subjects who are successful. These are presented by stratum and treatment group, with ASE and 95% asymptotic CIs.
- Common risk difference with sample size, p-value, ASE, and 95% asymptotic CIs.
- Risk difference within each strata with sample size, p-value, ASE and 95% asymptotic CIs.
- A plot of the risk differences within each strata, and common risk difference (similar to the risk difference plot produced by SAS Proc Freq).
- Common risk for each treatment with sample size, ASE, and 95% asymptotic CIs.

The “risk” is the probability of the given endpoint (success) through the given durability period.

1.1 Sustained Pain Freedom

The ad-hoc sustained pain freedom endpoints were:

- Sustained Pain Freedom 3 to 24 hours
- Sustained Pain Freedom 4 to 24 hours
- Sustained Pain Freedom 3 to 48 hours
- Sustained Pain Freedom 4 to 48 hours

Sustained pain freedom for the above time periods were defined in a manner similar to that used for sustained pain freedom from 2 to 24 hours and 2 to 48 hours.

Sustained pain freedom was assessed using the number of mITT subjects who experienced no headache pain (response of 0 on the Likert scale) at all time points from the starting time point (3 or 4 hours post-dose) through the ending time point (24 or 48 hours post-dose). Subjects with missing pain scores at 1 or fewer time points, given that they had responses of no pain at all other time points including the starting and ending time points (and 24 hours for periods through 48 hours), were considered as successes. Subjects with missing data at greater than 1 post-dose time point, missing data at either the starting or ending time point (or 24 hours for periods through 48 hours), or with any pain score greater than 0 were considered as failures.

1.2 Sustained Pain Relief

The ad-hoc sustained pain relief endpoints were:

- Sustained Pain Relief 3 to 24 hours
- Sustained Pain Relief 4 to 24 hours
- Sustained Pain Relief 3 to 48 hours
- Sustained Pain Relief 4 to 48 hours

Sustained pain relief for the above time periods were defined in a manner similar to that used previously for sustained pain relief from 2 to 24 hours and 2 to 48 hours.

Sustained pain relief was assessed using the number of mITT subjects who experienced no or mild headache pain (response of 0 or 1 on the Likert scale) at all time points from the starting time point (3 or 4 hours post-dose) through the ending time point (24 or 48 hours post-dose). Subjects with missing pain scores at 1 or fewer time points, given that they had responses of no or mild pain at all other time points including the starting and ending time points (and 24 hours for periods through 48 hours), were considered as successes. Subjects with missing data at greater than 1 post-dose time point, missing data at either the starting or ending time point (or

24 hours for periods through 48 hours), or with any pain score greater than 1 were considered as failures.

1.3 Sustained Freedom from Most Bothersome Symptom

The ad-hoc sustained freedom from the MBS endpoints were:

- Sustained Freedom from MBS 2 to 24 hours
- Sustained Freedom from MBS 3 to 24 hours
- Sustained Freedom from MBS 4 to 24 hours
- Sustained Freedom from MBS 2 to 48 hours
- Sustained Freedom from MBS 3 to 48 hours
- Sustained Freedom from MBS 4 to 48 hours

Sustained freedom from MBS for these time periods is defined in a manner similar to that used for sustained pain freedom from 2 to 24 hours and 2 to 48 hours.

Sustained MBS freedom was assessed using the number of mITT subjects who did not have their MBS (response of absent) at all time points from the starting time point (2, 3 or 4 hours post-dose) through the ending time point (24 or 48 hours post-dose). Subjects with missing MBS scores at 1 or fewer time points, given that they had responses of absent MBS at all other time points including the starting and ending time points (and 24 hours for periods through 48 hours), were considered as successes. Subjects with missing data at greater than 1 post-dose time point, missing data at either the starting or ending time point (or 24 hours for periods through 48 hours), or with any MBS present at any time point in the period were considered as failures.

1.4 Sustained Freedom from Functional Disability

The ad-hoc sustained freedom from functional disability endpoints were:

- Sustained Freedom from Functional Disability 2 to 24 hours
- Sustained Freedom from Functional Disability 3 to 24 hours
- Sustained Freedom from Functional Disability 4 to 24 hours
- Sustained Freedom from Functional Disability 2 to 48 hours
- Sustained Freedom from Functional Disability 3 to 48 hours
- Sustained Freedom from Functional Disability 4 to 48 hours

Sustained freedom from functional disability for these time periods is defined in a manner similar to that used for sustained pain freedom from 2 to 24 hours and 2 to 48 hours.

Sustained freedom from functional disability was assessed using the number of mITT subjects who experienced normal functioning at all time points from the starting time point (2, 3 or 4 hours post-dose) through the ending time point (24 or 48 hours post-dose). Subjects with missing disability scores at 1 or fewer time points, given that they have responses of no disability at all other time points including the starting and ending time points (and 24 hours for periods through 48 hours), were considered as successes. Subjects with missing data at greater than 1 post-dose time point, missing data at either the starting or ending time point (or 24 hours for periods through 48 hours), or with any reported disability in the time period were classified as failures.

1.5 Sustained Freedom from Nausea

The ad-hoc sustained freedom from nausea endpoints were:

- Sustained Freedom from Nausea 2 to 24 hours
- Sustained Freedom from Nausea 3 to 24 hours
- Sustained Freedom from Nausea 4 to 24 hours
- Sustained Freedom from Nausea 2 to 48 hours
- Sustained Freedom from Nausea 3 to 48 hours
- Sustained Freedom from Nausea 4 to 48 hours

Sustained freedom from nausea for these time periods was defined in a manner similar to that used for sustained pain freedom from 2 to 24 hours and 2 to 48 hours. However, the analysis population was restricted to those subjects with nausea reported as present at the start of their treated migraine.

Sustained nausea freedom was assessed using the number of mITT subjects who had nausea present at baseline and did not report nausea (response of absent) at any time point from the starting time point (2, 3 or 4 hours post-dose) through the ending time point (24 or 48 hours post-dose). Subjects with missing nausea scores at 1 or fewer time points, given that they had responses of no nausea at all other time points including the starting and ending time points (and 24 hours for periods through 48 hours), were considered as successes. Subjects with missing data at greater than 1 post-dose time point, missing data at either the starting or ending time point (or 24 hours for periods through 48 hours), or with any nausea present at any time point in the period were considered as failures.

1.6 Sustained Freedom from Photophobia

The ad-hoc sustained freedom from photophobia endpoints are:

- Sustained Freedom from Photophobia 2 to 24 hours
- Sustained Freedom from Photophobia 3 to 24 hours
- Sustained Freedom from Photophobia 4 to 24 hours
- Sustained Freedom from Photophobia 2 to 48 hours
- Sustained Freedom from Photophobia 3 to 48 hours
- Sustained Freedom from Photophobia 4 to 48 hours

Sustained freedom from photophobia for these time periods was defined in a manner similar to that used for sustained freedom from nausea. The analysis population was restricted to those mITT subjects with photophobia reported as present at the start of their treated migraine.

Sustained photophobia freedom was assessed using the number of mITT subjects who had photophobia present at baseline and that did not report photophobia (response of absent) at any time point from the starting time point (2, 3 or 4 hours post-dose) through the ending time point (24 or 48 hours post-dose). Subjects with missing photophobia scores at 1 or fewer time points, given that they had responses of no photophobia at all other time points including the starting and ending time points (and 24 hours for periods through 48 hours), were considered as successes. Subjects with missing data at greater than 1 post-dose time point, missing data at either the starting or ending time point (or 24 hours for periods through 48 hours), or with any photophobia present at any time point in the period were considered as failures.

1.7 Sustained Freedom from Phonophobia

The ad-hoc sustained freedom from phonophobia endpoints are:

- Sustained Freedom from Phonophobia 2 to 24 hours
- Sustained Freedom from Phonophobia 3 to 24 hours
- Sustained Freedom from Phonophobia 4 to 24 hours
- Sustained Freedom from Phonophobia 2 to 48 hours
- Sustained Freedom from Phonophobia 3 to 48 hours
- Sustained Freedom from Phonophobia 4 to 48 hours

Sustained freedom from phonophobia for these time periods was defined in a manner similar to that used for sustained freedom from nausea. The analysis population was restricted to those mITT subjects with phonophobia reported as present at the start of their treated migraine.

Sustained phonophobia freedom was assessed using the number of mITT subjects who had phonophobia present at baseline and that did not report phonophobia (response of absent) at any time point from the starting time point (2, 3 or 4 hours post-dose) through the ending time point (24 or 48 hours post-dose). Subjects with missing phonophobia scores at 1 or fewer time points, given that they had responses of no phonophobia at all other time points including the starting and ending time points (and 24 hours for periods through 48 hours), were considered as successes. Subjects with missing data at greater than 1 post-dose time point, missing data at either the starting or ending time point (or 24 hours for periods through 48 hours), or with any phonophobia present at any time point in the period were considered as failures.

2 TIME TO EVENT ANALYSES

2.1 Time to Rescue Medication

Kaplan-Meier plots were created for the time to first use of rescue medication. The K-M plot covered the 24 hour period after dosing. Subjects who did not take rescue medication within 24 hours of dosing were censored at 24 hours and 1 minute. Regardless of pain or MBS response, subjects were considered at risk until the first use of rescue medication, loss to follow-up (last contact date), or the end of the 24 hour period, whichever came first. The analysis population consisted of mITT subjects.

Two tables were created to support the plot. The first table presented the median time to rescue medication along with 95% CIs calculated using the method of Brookmeyer and Crowley and the log-rank p-value. The second table presented the number of subjects at risk, with an event, censored, and the survival probability estimate (with 95% CI) for each period by treatment group.

2.2 Time to First Report of Absence of Various Symptoms

For each of the following variables, two sets of Kaplan-Meier plots and tables were created:

- Time to First Report of Absence of Most Bothersome Symptom
- Time to First Report of Absence of Nausea
- Time to First Report of Absence of Photophobia
- Time to First Report of Absence of Phonophobia
- Time to First Report of Return to Normal Functioning

The first set of plots and tables was similar to those created for the time to rescue medication (using actual time). For the second set of plots, nominal (planned time point) as opposed to actual time was used for clinical event times. Censoring was measured using actual time as in all previous plots.

For both sets of analyses, the analysis population for MBS and functional disability was the set of mITT subjects. The analysis population for nausea, phonophobia, and photophobia was the subset of mITT subjects that reported the symptom as present at the onset of their study migraine. The y-axis for all plots represents the probability of the occurrence of the event of interest, and therefore are increasing from left to right.

2.2.1 Kaplan-Meier Plots and Tables: Actual Time for Event of Interest

The first set of K-M plots and tables were created using actual time of censoring and actual time for the clinical event of interest. Subjects were censored at the actual time of their first use of rescue medication or last reported data point if lost to follow-up. Subjects who did not have the clinical event of interest by 8 hours post dose were censored at 496 minutes (480 minutes + 15 minute window + 1 minute).

2.2.2 Kaplan-Meier Plots and Tables: Nominal Time for Event of Interest

The second set of K-M plots and tables were created for the above variables with nominal time (planned time of collection, e.g., 2 hours, 3 hours, etc.) used for clinical events of interest and actual time used for censoring events. Subjects were censored at the actual time of their first use of rescue medication or last reported data point if lost to follow-up. Subjects who did not have the clinical event of interest by 8 hours post dose were censored at 496 minutes (480 minutes + 15 minute window + 1 minute).

3 PAIN AND MBS AT 3 HOURS POST DOSE

3.1 Pain Freedom at 3 Hours Post Dose

The between group difference in the percentage of subjects with pain freedom at 3 hours post-dose was assessed by computing the “risk difference” between treatment groups. This was evaluated by computing the common risk difference, using CMH weights (sample size weights), stratified by the use of prophylactic migraine medication (yes or no). The risk difference was tested at a two-sided alpha level of 0.05. Missing data at 2 hours post-dose were imputed as failures (NC=F).

Results presented for this analysis included the following:

- Common risk difference with sample size, p-value, ASE, and 95% asymptotic CIs.
- Risk difference within each strata with sample size, p-value, ASE, and 95% asymptotic CIs.
- A plot of the risk differences within each strata, and common risk difference (similar to the risk difference plot produced by SAS Proc Freq).
- Common risk for each treatment with sample size, ASE, and 95% asymptotic CIs.

3.2 Freedom from MBS at 3 Hours Post Dose

The estimand, difference in percentage of subjects with freedom from MBS at 3 hours between treatment groups was evaluated by computing the common risk difference using CMH weights (sample size weights), stratified by the use of prophylactic migraine medication (yes or no). The risk difference was tested at a two-sided alpha level of 0.05. Missing data at 3 hours post-dose was imputed as failure (NC=F). Also the use of rescue medication prior to providing data at the 3 hour assessment, taking IP prior to reporting the MBS, or failure to report a MBS are events that were imputed as treatment failures.

Results presented for this analysis included the following:

- Common risk difference with sample size, p-value, ASE, and 95% asymptotic CIs.
- Risk difference within each strata with sample size, p-value, ASE, and 95% asymptotic CIs.
- A plot of the risk differences within each strata, and common risk difference (similar to the risk difference plot produced by SAS Proc Freq).
- Common risk for each treatment with sample size, ASE, and 95% asymptotic CIs.

4 OTHER ENDPOINTS AT 3 HOURS POST DOSE

4.1 Freedom from Photophobia, Phonophobia, or Nausea at 3 Hours

Freedom from photophobia, phonophobia, and nausea were assessed, by treatment group, by tabulating the number of mITT subjects who reported the presence of the symptom at migraine onset, and later reported the absence of the symptom at 3 hours post-dose. Subjects who reported the symptom at baseline, but have missing data at 3 hours post-dose were imputed as failures (NC=F). Also, subjects in the analysis set who took rescue medications on or before providing their 3 hour post-dose data were imputed as failures.

The principal measurement for the associated symptoms (phonophobia, photophobia, and nausea) is made on a binary scale (0 = absent; 1 = present). An exploratory measurement of these symptoms was also made on a 4-point Likert scale (0=none, 1=mild, 2=moderate, 3=severe).

For these three endpoints, the difference between treatment groups, was evaluated by computing the common risk difference using CMH weights (sample size weights), stratified by the use of prophylactic migraine medication (yes or no). The risk difference was tested at a two-sided alpha level of 0.05.

Results presented for these analyses included the following:

- Common risk difference with sample size, p-value, ASE, and 95% asymptotic CIs.
- Risk difference within each strata with sample size, p-value, ASE, and 95% asymptotic CIs.

- A plot of the risk differences within each strata, and common risk difference (similar to the risk difference plot produced by SAS Proc Freq).
- Common risk for each treatment with sample size, ASE, and 95% asymptotic CIs.

4.2 Pain Relief at 3 Hours Post Dose

Pain relief at 3 hours post-dose was assessed by tabulating the number of mITT subjects that reported a pain level of none or mild (responses of 0 or 1 on the 4-point Likert scale) at 3 hours post-dose by treatment group. Subjects with missing data at 3 hours post-dose were imputed as failures (NC=F). Also, subjects in the analysis set who took rescue medications on or before providing their 3 hour post-dose data were imputed as failures.

Results presented for this analysis included the following:

- Common risk difference with sample size, p-value, ASE, and 95% asymptotic CIs.
- Risk difference within each strata with sample size, p-value, ASE, and 95% asymptotic CIs.
- A plot of the risk differences within each strata, and common risk difference (similar to the risk difference plot produced by SAS Proc Freq).
- Common risk for each treatment with sample size, ASE, and 95% asymptotic CIs.

4.3 Functional Disability Scale at 3 Hours Post Dose

Impact of treatment on subject disability was assessed using a single-question, functional disability scale. Subjects rated the level of disability they perceived as a result of their migraine in performing normal actions using a 4-point scale: Normal Function, Mild Impairment, Severe Impairment, or Required Bedrest. The proportion of mITT subjects who had a response of "normal" at 3-hours post dose was evaluated as the endpoint of interest.

Results presented for this analysis included the following:

- Common risk difference with sample size, p-value, ASE, and 95% asymptotic CIs.
- Risk difference within each strata with sample size, p-value, ASE, and 95% asymptotic CIs.
- A plot of the risk differences within each strata, and common risk difference (similar to the risk difference plot produced by SAS Proc Freq).
- Common risk for each treatment with sample size, ASE, and 95% asymptotic CIs.

5 ADDITIONAL SAFETY ANALYSES

5.1 Adverse Events Leading to Study Discontinuation

Adverse events leading to study discontinuation were summarized for the treated subjects by system organ class and preferred term.

5.2 Prophylactic Medications

Prophylactic medications were summarized for the treated subjects by system organ class and preferred term.

Appendix 4. Tables And Figures For Supportive Analyses

Table Number	Title	Population
14.2.3.7.1.2	Sustained Pain Freedom from 3 to 24 Hours Post Dose: Ad-hoc Analysis	mITT Subjects
14.2.3.7.1.3	Sustained Pain Freedom from 4 to 24 Hours Post Dose: Ad-hoc Analysis	mITT Subjects
14.2.3.7.2.2	Sustained Pain Relief from 3 to 24 Hours Post Dose: Ad-hoc Analysis	mITT Subjects
14.2.3.7.2.3	Sustained Pain Relief from 4 to 24 Hours Post Dose: Ad-hoc Analysis	mITT Subjects
14.2.3.7.3.2	Sustained Pain Freedom from 3 to 48 Hours Post Dose: Ad-hoc Analysis	mITT Subjects
14.2.3.7.3.3	Sustained Pain Freedom from 4 to 48 Hours Post Dose: Ad-hoc Analysis	mITT Subjects
14.2.3.7.4.2	Sustained Pain Relief from 3 to 48 Hours Post Dose: Ad-hoc Analysis	mITT Subjects
14.2.3.7.4.3	Sustained Pain Relief from 4 to 48 Hours Post Dose: Ad-hoc Analysis	mITT Subjects
14.2.3.7.5.1	Sustained MBS Freedom from 2 to 24 Hours Post Dose: Ad-hoc Analysis	mITT Subjects
14.2.3.7.5.2	Sustained MBS Freedom from 3 to 24 Hours Post Dose: Ad-hoc Analysis	mITT Subjects
14.2.3.7.5.3	Sustained MBS Freedom from 4 to 24 Hours Post Dose: Ad-hoc Analysis	mITT Subjects
14.2.3.7.6.1	Sustained MBS Freedom from 2 to 48 Hours Post Dose: Ad-hoc Analysis	mITT Subjects
14.2.3.7.6.2	Sustained MBS Freedom from 3 to 48 Hours Post Dose: Ad-hoc Analysis	mITT Subjects
14.2.3.7.6.3	Sustained MBS Freedom from 4 to 48 Hours Post Dose: Ad-hoc Analysis	mITT Subjects
14.2.3.7.7.1	Sustained Nausea Freedom from 2 to 24 Hours Post Dose: Ad-hoc Analysis	mITT Subjects
14.2.3.7.7.2	Sustained Nausea Freedom from 3 to 24 Hours Post Dose: Ad-hoc Analysis	mITT Subjects
14.2.3.7.7.3	Sustained Nausea Freedom from 4 to 24 Hours Post Dose: Ad-hoc Analysis	mITT Subjects
14.2.3.7.8.1	Sustained Nausea Freedom from 2 to 48 Hours Post Dose: Ad-hoc Analysis	mITT Subjects
14.2.3.7.8.2	Sustained Nausea Freedom from 3 to 48 Hours Post Dose: Ad-hoc Analysis	mITT Subjects
14.2.3.7.8.3	Sustained Nausea Freedom from 4 to 48 Hours Post Dose: Ad-hoc Analysis	mITT Subjects
14.2.3.7.9.1	Sustained Photophobia Freedom from 2 to 24 Hours Post Dose: Ad-hoc Analysis	mITT Subjects
14.2.3.7.9.2	Sustained Photophobia Freedom from 3 to 24 Hours Post Dose: Ad-hoc Analysis	mITT Subjects
14.2.3.7.9.3	Sustained Photophobia Freedom from 4 to 24 Hours Post Dose: Ad-hoc Analysis	mITT Subjects
14.2.3.7.10.1	Sustained Photophobia Freedom from 2 to 48 Hours Post Dose: Ad-hoc Analysis	mITT Subjects
14.2.3.7.10.2	Sustained Photophobia Freedom from 3 to 48 Hours Post Dose: Ad-hoc Analysis	mITT Subjects
14.2.3.7.10.3	Sustained Photophobia Freedom from 4 to 48 Hours Post Dose: Ad-hoc Analysis	mITT Subjects
14.2.3.7.11.1	Sustained Phonophobia Freedom from 2 to 24 Hours Post Dose: Ad-hoc Analysis	mITT Subjects
14.2.3.7.11.2	Sustained Phonophobia Freedom from 3 to 24 Hours Post Dose: Ad-hoc Analysis	mITT Subjects
14.2.3.7.11.3	Sustained Phonophobia Freedom from 4 to 24 Hours Post Dose: Ad-hoc Analysis	mITT Subjects
14.2.3.7.12.1	Sustained Phonophobia Freedom from 2 to 48 Hours Post Dose: Ad-hoc Analysis	mITT Subjects
14.2.3.7.12.2	Sustained Phonophobia Freedom from 3 to 48 Hours Post Dose: Ad-hoc Analysis	mITT Subjects
14.2.3.7.12.3	Sustained Phonophobia Freedom from 4 to 48 Hours Post Dose: Ad-hoc Analysis	mITT Subjects
14.2.3.7.13.1	Sustained Functional Disability Freedom from 2 to 24 Hours Post Dose: Ad-hoc Analysis	mITT Subjects
14.2.3.7.13.2	Sustained Functional Disability Freedom from 3 to 24 Hours Post Dose: Ad-hoc Analysis	mITT Subjects
14.2.3.7.13.3	Sustained Functional Disability Freedom from 4 to 24 Hours Post Dose: Ad-hoc Analysis	mITT Subjects

Table Number	Title	Population
14.2.3.7.13.1	Sustained Functional Disability Freedom from 2 to 48 Hours Post Dose: Ad-hoc Analysis	mITT Subjects
14.2.3.7.13.2	Sustained Functional Disability Freedom from 3 to 48 Hours Post Dose: Ad-hoc Analysis	mITT Subjects
14.2.3.7.13.3	Sustained Functional Disability Freedom from 4 to 48 Hours Post Dose: Ad-hoc Analysis	mITT Subjects
14.2.3.12.1	Kaplan-Meier Time to Rescue Medication up to 24 hours Post Dose: Ad-hoc Analysis	mITT Subjects
14.2.3.12.2	Median Time to Rescue Medication: Ad-hoc Analysis	mITT Subjects
14.2.3.13.1	Kaplan-Meier Time to First Report of Absence of MBS up to 8 hours Post Dose: Ad-hoc Analysis	mITT Subjects
14.2.3.13.2	Median Time to First Report of Absence of MBS: Ad-hoc Analysis	mITT Subjects
14.2.3.13.3	Kaplan-Meier Nominal Time to First Report of Absence of MBS up to 8 hours Post Dose: Ad-hoc Analysis	mITT Subjects
14.2.3.13.4	Median Nominal Time to First Report of Absence of MBS: Ad-hoc Analysis	mITT Subjects
14.2.3.14.1	Kaplan-Meier Time to First Report of Absence of Nausea up to 8 hours Post Dose: Ad-hoc Analysis	mITT Subjects
14.2.3.14.2	Median Time to First Report of Absence of Nausea: Ad-hoc Analysis	mITT Subjects
14.2.3.14.3	Kaplan-Meier Nominal Time to First Report of Absence of Nausea up to 8 hours Post Dose: Ad-hoc Analysis	mITT Subjects
14.2.3.14.4	Median Nominal Time to First Report of Absence of Nausea: Ad-hoc Analysis	mITT Subjects
14.2.3.15.1	Kaplan-Meier Time to First Report of Absence of Photophobia up to 8 hours Post Dose: Ad-hoc Analysis	mITT Subjects
14.2.3.15.2	Median Time to First Report of Absence of Photophobia: Ad-hoc Analysis	mITT Subjects
14.2.3.15.3	Kaplan-Meier Nominal Time to First Report of Absence of Photophobia up to 8 hours Post Dose: Ad-hoc Analysis	mITT Subjects
14.2.3.15.4	Median Nominal Time to First Report of Absence of Photophobia: Ad-hoc Analysis	mITT Subjects
14.2.3.16.1	Kaplan-Meier Time to First Report of Absence of Phonophobia up to 8 hours Post Dose: Ad-hoc Analysis	mITT Subjects
14.2.3.16.2	Median Time to First Report of Absence of Photophonia: Ad-hoc Analysis	mITT Subjects
14.2.3.16.3	Kaplan-Meier Nominal Time to First Report of Absence of Phonophobia up to 8 hours Post Dose: Ad-hoc Analysis	mITT Subjects
14.2.3.16.4	Median Nominal Time to First Report of Absence of Photophonia: Ad-hoc Analysis	mITT Subjects
14.2.3.17.1	Kaplan-Meier Time to First Report of Return to Normal Functioning up to 8 hours Post Dose: Ad-hoc Analysis	mITT Subjects
14.2.3.17.2	Median Time to First Report of Return to Normal Functioning: Ad-hoc Analysis	mITT Subjects
14.2.3.17.3	Kaplan-Meier Nominal Time to First Report of Return to Normal Functioning up to 8 hours Post Dose: Ad-hoc Analysis	mITT Subjects
14.2.3.17.4	Median Nominal Time to First Report of Return to Normal Functioning: Ad-hoc Analysis	mITT Subjects
14.2.3.18.1	Pain Freedom at 3 Hours Post Dose: Ad-hoc Analysis	mITT Subjects
14.2.3.18.2	Freedom from Most Bothersome Symptom at 3 Hours Post Dose: Ad-hoc Analysis	mITT Subjects
14.2.3.18.3	Freedom from Photophobia at 3 Hours Post Dose: Ad-hoc Analysis	mITT Subjects
14.2.3.18.4	Freedom from Phonophobia at 3 Hours Post Dose: Ad-hoc Analysis	mITT Subjects
14.2.3.18.5	Pain Relief at 3 Hours Post Dose: Ad-hoc Analysis	mITT Subjects

Table Number	Title	Population
14.2.3.18.6	Freedom from Nausea at 3 Hours Post Dose: Ad-hoc Analysis	mITT Subjects
14.2.3.18.7	Functional Disability Scale at 3 Hours Post Dose: Ad-hoc Analysis	mITT Subjects
14.3.2.6	Incidence of On-study Adverse Events Leading to Study Discontinuation by System Organ Class and Preferred Term	Treated Subjects
14.5.3.3	Prophylactic Medications by Therapeutic Class and Preferred Term	Treated Subjects

Figure Number	Title	Population
14.2.17	Kaplan Meier Survival Plot of Time to Rescue Medication up to 24 Hours Post Dose	mITT Subjects
14.2.18	Kaplan Meier Survival Plot of Time to First Report of Absence of MBS up to 8 Hours Post Dose	mITT Subjects
14.2.19	Kaplan Meier Survival Plot of Time to First Report of Absence of Nausea up to 8 Hours Post Dose	mITT Subjects
14.2.20	Kaplan Meier Survival Plot of Time to First Report of Absence of Photophobia up to 8 Hours Post Dose	mITT Subjects
14.2.21	Kaplan Meier Survival Plot of Time to First Report of Absence of Phonophobia up to 8 Hours Post Dose	mITT Subjects
14.2.22	Kaplan Meier Survival Plot of Time to First Report of Return to Normal Functioning up to 8 Hours Post Dose	mITT Subjects
14.2.23	Kaplan Meier Survival Plot of Time to First Report of Absence of MBS up to 8 Hours Post Dose (Nominal Time)	mITT Subjects
14.2.24	Kaplan Meier Survival Plot of Time to First Report of Absence of Nausea up to 8 Hours Post Dose (Nominal Time)	mITT Subjects
14.2.25	Kaplan Meier Survival Plot of Time to First Report of Absence of Photophobia up to 8 Hours Post Dose (Nominal Time)	mITT Subjects
14.2.26	Kaplan Meier Survival Plot of Time to First Report of Absence of Phonophobia up to 8 Hours Post Dose (Nominal Time)	mITT Subjects
14.2.27	Kaplan Meier Survival Plot of Time to First Report of Return to Normal Functioning up to 8 Hours Post Dose (Nominal Time)	mITT Subjects